Hydrogen-Bonded Tapes Based on Symmetrically Substituted Diketopiperazines: A Robust Structural Motif for the Engineering of Molecular Solids

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Abstract: A series of eight symmetrically substituted diketopiperazines (DKPs) derived from 1-amino-1-carboxycycloalkanes ($n = 3-7$; 3,3,5,5-tetramethylcyclohexane; 4,4-dimethylcyclohexane; 2-indan) were synthesized and their crystal structures determined. In the solid state, all eight compounds form two pairs of hydrogen bonds with two adjacent molecules to form a one-dimensional structure that we refer to as "tapes". These molecules represent a range of volumes and shapes that contain a common molecular fragment (DKP ring). We examined this series of compounds with three objectives in mind: (i) to establish the ability of the hydrogen-bonded "tape" motif to persist through these differences in volume and shape; (ii) to provide a series of structurally related compounds to use to test computational methods of predicting crystal structure from molecular structure; (iii) to search for qualitative correlations between molecular structure and crystal packing. All compounds form tapes and with one exception, all tapes pack with their long axes parallel. When viewed down their long axis, two types of tapes emerge: *planar* and *nonplanar*. The type of tape that forms reflects the conformation adapted by the DKP ring—planar or boat. Planar tapes form when the angle (α) between the two planes defined by the *cis*-amides in the DKP ring is 180°; nonplanar tapes form when $\alpha < 180°$. Five of the eight compounds studied form planar tapes, the remaining three compounds form nonplanar tapes. Despite the variability in volume and shape represented by this series of molecules, the persistence of the tape motif in their crystalline solids suggests that the hydrogen-bonding interactions between DKPs dominate the packing arrangement of these molecules. Void space in the crystalline solid is minimized by parallel alignment of tapes that pack in a manner that permits the interdigitation of substituents on adjacent tapes.

Introduction

The formation of molecular crystals is a fundamental form of self-assembly.[1−4] An understanding of the relationship between molecular structure and crystal structure would provide insight into the design of solids with properties that depend on the arrangement of molecules in crystals (e.g., rates of dissolution, bioavailability, modulation of electromagnetic frequency). Rationalizing and predicting the structure of molecular crystals in terms of the structure of their constituent molecules has, however, proved difficult for several reasons. First, no procedures exist for sorting the many alternative packing of molecules in terms of relative stabilities.[5−8] Second, virtually no procedures exist for estimating entropies of formation of crystals. Third, the prevalence of polymorphs in organic molecular crystals suggests that either structures of similar energies (within ~1 kcal/mol)[9] are common, or the kinetics of nucleation and growth of crystals are comparable in importance to the thermodynamics of their formation,[10−13] or both.

We are developing a systematic approach to understanding the forces that dictate how molecules pack during the self-assembly of organic molecular crystals. One component of this effort is to limit the number of orientations available to molecules in crystals using noncovalent, directional interactions. To this end, we and others[14−16] have used intermolecular hydrogen bonds[17] that are oriented in a manner that permits the formation of "tapes". Tapes are a structural motif that result when each molecule forms hydrogen bonds with only two neighboring molecules, and the hydrogen bonds between *any two molecules* form a cyclic, eight-membered ring.[18] Tapes are attractive as a structural motif for crystal engineering because of the limited variations on this motif that can be generated from different combinations of NH−O interactions. In addition, we expect hydrogen-bonded tapes to pack with their long axes

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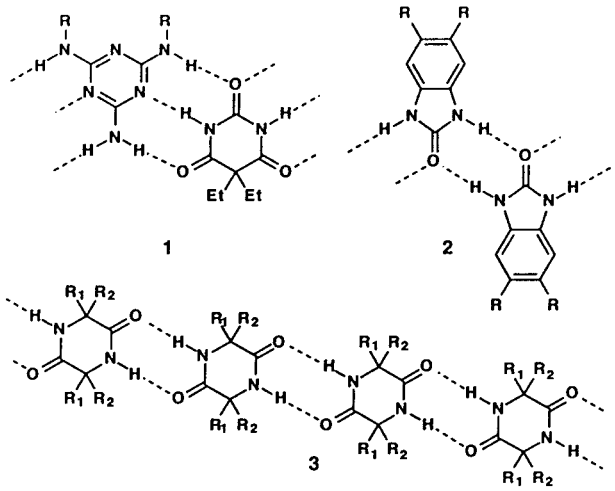
Scheme 1. Schematic View of the Tapes Based on Disubstituted Melamines and Diethylbarbital (**1**), Cyclic Ureas (**2**), and 2,5-Diketopiperazines (**3**)

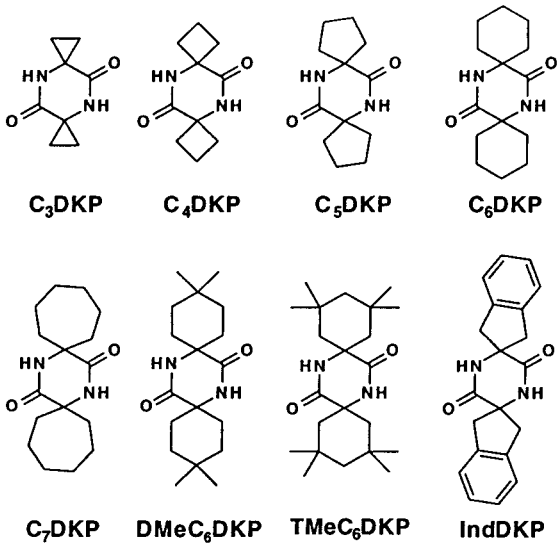


parallel; this common packing motif should further limit the number of orientations available to molecules in their crystalline solids.

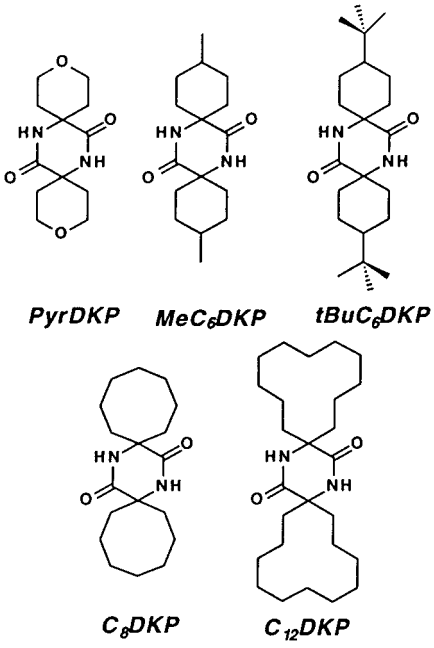
We[19−22] and others[14−16] have experimentally tested the hypothesis that appropriately structured molecules capable of forming intermolecular hydrogen bonds will form tapes in the solid state. In one set of experiments, we have demonstrated that 1:1 cocrystals of disubstituted melamines and diethylbarbital (**1**, Scheme 1) form three different hydrogen-bonded motifs: linear tapes, crinkled tapes, and rosettes (cyclic hexamers).[19−22] In this series of molecules, both linear and crinkled tapes usually packed with their long axes parallel. A systematic study of the crystal structures of the diethylbarbital−melamine cocrystals was complicated, however, by polymorphism arising from the conformational flexibility in the diphenylmelamine moiety and the $>CEt_2$ moiety of the barbital. Although this series of molecules was too complex to serve as a basis for a broad study of the physical−organic chemistry of molecular crystals, it did provide valuable information about the influence of steric effects on crystal structure. We have also examined a second system, based on 4,5-disubstituted-2-benzimidazolones (cyclic ureas, **2**, Scheme 1). Although cyclic ureas are simpler structurally, the tape motif was less robust, and a number of nontape structures formed.[23]

Among the classes of molecules able to form hydrogen-bonded tapes, the 2,5-diketopiperazines (DKPs, **3**, Scheme 1) appear especially attractive.[18] Their packing patterns are expected to be less complex than that for the cocrystals of melamine and diethylbarbital, because there is only one combination of hydrogen-bonding interactions that can form a tape. Additionally, the location of the substituents, in the plane perpendicular to the long axis of the tape, may "protect" the secondary amide groups from interactions with other amide groups. Consequently, this protection would inhibit the formation of two- or three-dimensional hydrogen-bonded networks as were observed in crystals of cyclic ureas.[23]

Scheme 2. The Eight Symmetrically Substituted DKPs That Gave Crystals Suitable for Single-Crystal X-ray Diffraction Studies



Scheme 3. The Five Symmetrically Substituted DKPs That Did Not Give Crystals Suitable for Single-Crystal X-ray Diffraction Studies



More than 40 crystal structures of DKPs have been published.[18] Only half of these structures are simple enough to be relevant to our work; the remaining structures form hydrates or hydrogen-bonded solvates or have competing hydrogen-bonding functional groups. Of the simple DKPs, almost all form tapes that pack with their long axes parallel. This observation suggests that the formation of four hydrogen bonds per DKP dominates the structure of their crystalline solids and that this class of compounds is a strong candidate for a common scaffold for physical−organic studies in the solid state. There has been, however, no systematic variation in the size, nature, and location of the substituents among this group of DKPs. Moreover, nearly all of the published crystal structures contain DKPs with at least one stereocenter. Consequently, we cannot evaluate the influence that substituents may have on the overall shape of the tapes (planar vs nonplanar) and their relationship to adjacent tapes

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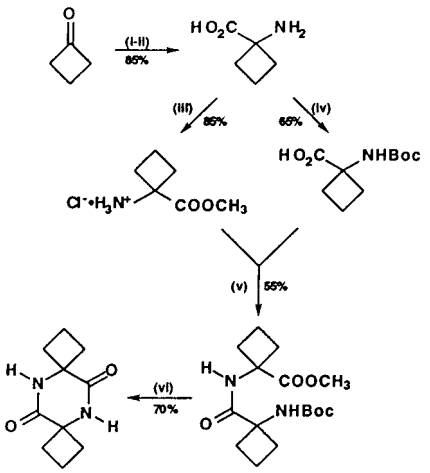
Scheme 4. Synthesis of the Symmetrically Substituted DKPs[a]



[a] (i) $KCN/(NH_4)_2CO_3$ in ethanol/water 1:1, 2 h at 60 °C; (ii) 3 N NaOH, reflux 3 days; (iii) CH_3OH saturated with gaseous HCl, reflux 4 h; (iv) 1 equiv of $(Boc)_2O$ and 2 equiv of NaOH in dioxane/water 2:1, rt for 12 h; (v) coupling performed in CH_2Cl_2 with 1 equiv of 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride and 1 equiv of 1-hydroxybenzotriazole, rt, 24 h; (vi) 98% formic acid, rt, 2 h, followed by vigorous heating in 2-butanol and xylene, 4 h.

(i.e., three-dimensional packing into centrosymmetric or noncentrosymmetric space groups).

In order to evaluate the influence of substituents on the packing of DKPs in their crystalline solids, we have examined the crystal structures of a series of symmetrically substituted DKPs in which the positions R_1 and R_2 constitute a cycloalkyl group (Scheme 2 and 3). The substituents were selected to avoid as much complexity as possible: these substituents interact with one another primarily through van der Waals interactions, they do not contain hydrogen-bonding groups that could compete for hydrogen bonds, their conformations are limited, and they are not chiral. They represent, however, a substantial range of molecular volume and shape. We will show that despite the range in size and shape represented by these substituents, all eight compounds form tapes in their crystalline solids, and the packing of these tapes is such that the substituents of adjacent tapes are always interdigitated. These results support the hypothesis that the most stable packing arrangement of molecules capable of forming hydrogen bonds is achieved when all hydrogen-bond donor and acceptor sites are satisfied, while maintaining the free volume in the crystal at a minimum.[2−4] Additionally, the data suggest that the boat conformation is adapted in the solid state both to minimize steric interference of hydrogen-bond formation between *cis*-amides of adjacent DKPs and to relieve bond angle strain at the spirocyclic carbon atom.

Results

Synthesis. Scheme 4 summarizes the synthetic methodology used to prepare symmetrically substituted DKPs. The cyclobutyl derivative is given as an example. The amino acids that were not commercially available were synthesized from the corresponding ketones via their hydantoin derivatives. The dipeptides were prepared from the N- and C-protected amino acids using DCC coupling methods. Cyclization of the dipeptide using Nitecki's method[24] gave symmetrically substituted DKPs with an average overall yield of ∼20% from the amino acid.

Crystallization. The solvents used for crystal growth include methanol, ethanol, acetic acid, butanol, pyridine, and hexafluoro-2-propanol. In general, DKPs have low solubility and dissolution required heating and large volumes of solvent. Single crystals suitable for X-ray diffraction studies were obtained by slow evaporation of solvent, vapor diffusion, or sublimation at ambient temperature. Compounds for which we obtained crystals suitable for single-crystal diffraction studies are shown in Scheme 2 and are indicated in bold type in the text. Other compounds we prepared—*PyrDKP*, *MeC6DKP*, *tBuC6DKP*, *C8DKP*, and *C12DKP*—gave crystals that were too small for single-crystal data collection (Scheme 3) and are indicated in italic type in the text. Low solubility was a major problem with **DMeC6DKP**, *MeC6DKP*, and *C8DKP*.

Crystallography. Table 1 summarizes the structural data for the eight DKPs examined including the previously characterized **MeDKP** (bis(3,6-dimethyl-2,5-diketopiperazine)) and **C3DKP** (bis(3,6-cyclopropyl-2,5-diketopiperazine)).[25] Several X-ray diffraction facilities were used to collect the structural data, and therefore, different temperatures and wavelengths of radiation were used. Each structure was determined at only one temperature. All compounds crystallized in either monoclinic or triclinic crystal systems, belong to low symmetry space groups (*P*-1, $P2_1/c$, or $C2/c$), and have values for C_k* [26] within the range expected for organic crystals (67−72%).[4] All eight DKPs form tapes despite the substantial range in volume occupied by the substituents (∼53 Å^3 for each cycloalkyl substituent of **C3DKP** to ∼290 Å^3 for each cycloalkyl substituent of **TMeC6DKP**). None of these crystals include molecules of solvent.

Summarized in Table 2 are the distances between molecules within each tape and distances between tapes for the eight DKPs structurally characterized. The length of the hydrogen bonds between the *cis*-amide functional groups on adjacent molecules (N−H- -O) range between 2.8 and 3.0 Å. The periodicity within a tape ranges from 5.9 Å for **IndDKP** to 6.3 Å for **DMeC6DKP** with an average periodicity of 6.1 Å.

Polymorphism. The crystal structure of a selected single crystal may not represent the most stable structure of a molecule or represent the bulk of solid that remains in a crystallization flask.[11,27] X-ray powder diffraction (XPD) was used to examine ground powders of crystals grown in different solvents. We performed these measurements to ensure that the structure of the crystal chosen for single-crystal X-ray diffraction studies is representative of the structure of the compound crystallized under different conditions. With the exception of **IndDKP**, XPD confirmed that only one structure formed for each DKP even though the crystals obtained from different solvents were often different in size and shape. Unfortunately, we were unable to grow a crystal of an alternate form of **IndDKP** that was suitable for single-crystal X-ray diffraction. All XPD patterns calculated from the single-crystal diffraction data were in good agreement with the experimental XPD patterns (supporting material).

Infrared Spectroscopy in Solution and in the Solid State. Infrared spectroscopy provided some useful supplemental information about hydrogen bonding in these systems. The amide group undergoes out-of-plane deformations[28] and strain is one of the factors that can affect its vibrational modes. For example, the stretching vibration of the carbonyl group occurs

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Table 1. Crystallographic Data for Symmetrically Substituted DKPs

DKP	type of tape	space group	*a* (Å)	*b* (Å)	*c* (Å)	α (deg)	*β* (deg)	*γ* (deg)	R_1[a]	R_2[b]	density[c] (g/cm^3)	solvent	crystal habit	C_k*[d]
Me[f]	planar	*P*-1	5.649	5.685	8.363	69.890	113.04	116.00	0.085	na[e]	1.261	CH_3OH	na[e]	0.681[f]
C_3	planar	$C2_1/c$	9.051	7.956	11.370	90	97.7	90	0.038	na[e]	1.36	CH_3OH	block	0.69
C_5	planar	*P*-1	6.2084(14)	8.931(2)	5.7859(13)	104.97(2)	116.84(2)	78.18(2)	0.0423	0.0577	1.342	CH_3OH	plate	0.716
C_6	planar	*P*-1	5.9280(10)	6.2640(10)	9.8200(10)	87.38	80.52	66.27	0.0573	0.0643	1.263	AcOH	block	0.684
$DMeC_6$	planar	*P*-1	6.0860(10)	6.3210(10)	11.5730(10)	90.09	101.15	109.83	0.0331	0.0346	1.242	sublim	needle	0.709
C_7	planar	*P*-1	5.9620(10)	6.127(2)	11.156(2)	85.98(0)	82.68	68.48	0.0457	0.0560	1.212	AcOH	plate	0.667
C_4	nonplanar	$P2_1/c$	6.0760(10)	17.232(2)	8.9710(10)	90	95.66	90	0.0454	0.0857	1.380	CH_3OH	plate	0.722
$TMeC_6$	nonplanar	*P*-1	6.098(3)	7.884(3)	23.070(12)	94.48(4)	94.73(4)	107.09(3)	0.0592	0.1129	1.146	BuOH/toluene	needle	0.671
Ind	nonplanar	*C*2/*c*	9.772(2)	14.046(3)	11.822(3)	90	95.93(2)	90	0.0379	0.0554	1.310	CH_3OH	block	0.68

[a] R_1 is the crystallographic reliability index, $R_1 = |F_o - F_c|/\sum F_o$ for $F_o > 2\sigma$. [b] $R_2 = |F_o^2 - F_c^2|/\sum F_o^2$ for all σ. [c] Calculated using the program Cerius2.[76] [d] $C_k^* = V_m/V_c$, where V_m is the volume of the molecules in the unit cell (calculated using molecular volumes obtained using the program Platon), V_c the total volume of the unit cell,[26] rather than from tables of incremental volumes.[20] [e] Datum not available. [f] We assigned the location of the hydrogen atoms because they are not reported in the Cambridge Structural Database.

Table 2. Inter- and Intratape Distances for Symmetrically Substituted DKPs

DKP	N−H- -O (Å)[a]	N−H- -O (deg)	shortest O- -H−C distance between two tapes within the same sheet (Å)[b]	shortest O- -H−C distance between two tapes in adjacent sheets (Å)[c]	distance between two tapes within the same sheet (Å)	distance between two tapes in adjacent sheets (Å)
C_3	2.806	178.5	3.56 (O1−C4)	3.63 (O1−C3)	17.38	4.19
C_5	2.904 (0.003)	177.29 (2.54)	4.25 (O1−C5)	3.65 (O1−C3)	9.30	4.53
C_6	2.927 (0.002)	177.48 (1.99)	6.70 (O1−C4)	4.91 (O1−C4)	9.82	4.71
$DMeC_6$	2.978 (0.002)	173.92 (1.52)	7.22 (O1−C8)	3.64 (O1−C3)	14.08	4.80
C_7	2.876 (0.004)	172.63 (2.25)	5.55 (O1−C5)	3.63 (O1−C3)	11.96	4.66
C_4	2.892 (0.004)	172.61 (2.59)[d]	3.76 (O1−C9)	4.20 (O1−C8)	9.40, 7.83	3.33, 5.32
	2.904 (0.004)	175.40 (2.48)	4.11 (O1−C4)	4.69 (O1−C10)		
$TMeC_6$	2.871 (0.006)	172.13 (5.11)[d]	6.36 (O1−C10)	3.48 (O1−C9)	11.16, 11.91	7.88
	2.875 (0.006)	168.30 (4.13)				
Ind	2.884 (0.002)	171.42 (1.41)	3.41 (O1−C8)	6.20 (O1−C5)	9.77	7.21

[a] The distance between the nitrogen and the oxygen atoms involved in the hydrogen-bonding interactions of the amide groups (hydrogen atoms were refined after location on a difference map). [b] The shortest distance observed between atoms belonging to two adjacent tapes within the same sheet [c]or between adjacent sheets. The atoms that interact are shown in parentheses. [d] The two hydrogen-bonded dimers do not have the same geometry.

at significantly higher wavenumbers in bicyclic lactams such as 2-azabicyclo[2.2.1]heptan-3-one (1690 cm^{-1}, neat film[29]), 2-azabicyclo[2.2.2]octan-3-one (1695 cm^{-1}, CCl_4 solution[30]), and 2-azabicyclo[2.2.2] octa-5,7-dien-3-one (1685 cm^{-1}, $CHCl_3$ solution[31]) than in monocyclic *δ*-valerolactam (1668 cm^{-1}, melt). The infrared absorption spectra of diketopiperazines show similar behavior in the stretching vibration of the amide I band when planar and boat conformations of 3,6-dimethyl-2,5-diketopiperazine and 3,6-bis(hydroxymethylene)-2,5-diketopiperazine[32,33] are compared. When the DKP ring is forced into a boat conformation by the ethylene bridge in 2,5-diaza-3,6-dioxobicyclo[2.2.2]octane, the carbonyl stretching frequency occurs at 1695 cm^{-1}.[34] No systematic study, however, has been conducted to determine the effect of puckering of the DKP ring on the vibrational properties of diketopiperazines.

Summarized in Table 3 are IR data for the stretching mode of the carbonyl bond for the eight DKPs structurally characterized and the five DKPs that gave crystals too small for single-crystal data collection and published data of three other DKPs. We observe a systematic difference of ca. 15 cm^{-1} between the C═O stretching bands of DKPs in the planar vs the boat conformation. The discrepancy observed for **C_3DKP** with respect to the other planar DKPs probably arises from additional strain induced into the DKP ring by the two cyclopropyl rings.

Topography and Packing of Tapes. Summarized in Table 4 are the torsion angles and geometrical data for symmetrically substituted DKPs. The torsion angles Φ and Ψ are strongly affected by the puckering of the DKP ring, while the amide groups remain nearly planar, as indicated by torsion angle *ω*. The angle *β* measures the extent of puckering in the DKP ring, and the angle α measures how this puckering affects the relative

Table 3. Infrared Analysis of Selected Derivatives of Diketopiperazine

DKP	conformation	ν_{solid} (cm^{-1})[a]	$\nu_{solution}$ (cm^{-1})[b]
C_3	planar	1670	1655, 1674[c]
C_5	planar	1658	1640, 1661[c]
C_6	planar	1658	1635, 1660[c]
$DMeC_6$	planar	1658	1636, 1660[c]
C_7	planar	1658	1635, 1660[c]
C_4	boat	1680	1644, 1671[c]
$TMeC_6$	boat	1665	1632, 1659[c]
Ind	boat	1680	1645, 1675[c]
S,R-Me	planar	1658[d]	1643[e]
R,R-Me	boat	1703[f]	not available
[2.2.2]	boat	1695[g]	not available
Pyr	not available	1658	1675
MeC_6	not available	1658	1635, 1662[c]
$tBuC_6$	not available	1658	1636, 1660[c]
C_8	not available	1658	1635, 1660[c]
C_{12}	not available	1665	1630, 1660[c]

[a] ν_{solid} is the wavenumber of the stretching mode of the carbonyl group, recorded on a KBr pellet. [b] $\nu_{solution}$ is the wavenumber of the stretching mode of the carbonyl group, recorded in a solvent given below. [c] Recorded in hexafluoro-2-propanol. [d] The value has been shown to be dependent on the crystalline form of the 3,6-D,L-dimethyl-2,5-diketopiperazine.[33] The value given here is for a powder.[30] [e] Recorded in D_2O. [f] 3,6-L,L-Dimethyl-2,5-diketopiperazine.[30] [g] 2,5-Diaza-3,6-dioxobicyclo[2.2.2]octane.[32]

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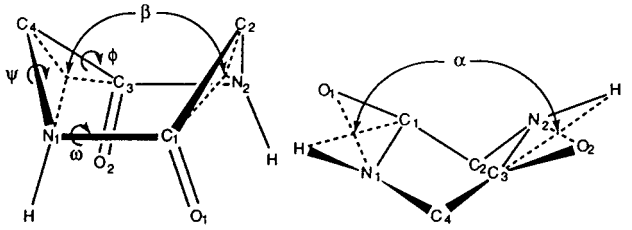
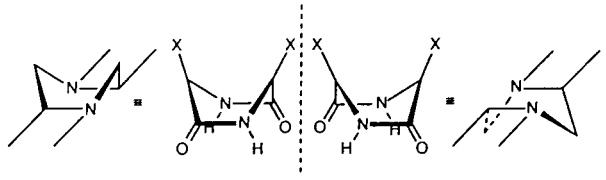
Table 4. Torsion Angles and Geometrical Data for Symmetrically Substituted DKPs



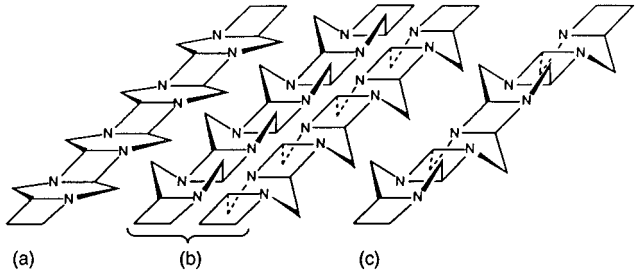
DKP	Φ (deg)[a]	Ψ (deg)[a]	ω (deg)[a]	α (deg)[b]	β (deg)[c]
Me	−5.07	5.82	6.20	180	180
C_3	1.8	2.0	−2.0	180	180
C_5	−1.4	1.5	−1.6	180	180
C_6	−0.7	0.8	−0.8	180	180
$DMeC_6$	−0.5	0.6	0.6	180	180
C_7	−5.9	−6.6	7.1	180	180
C_4	25.2, 22.7	−32.0, −29.3	−4.6, −7.1	162.8	134.1
$TMeC_6$	23.2, 32.4	−13.5, −23.9	4.3, 15.2	148.8	140.3
Ind	−31.2, −31.2	34.8, 34.8	−2.7, −2.7	149.4	124.5

[a] The dihedral angles Φ, Ψ, and ω are the torsion angles defined by the IUPAC−IUB for the conformational analysis of peptides[77] and commonly used in the conformational analysis of diketopiperazines.[43−48,78,79] When the DKP rings are planar, the torsion angles Φ, Ψ, and ω are given for one amino acid residue, the values for the other residue are of opposite sign. [b] Measured between the two planes (shown as intersection of dashed lines) defined by (−H−N_1−C_1−O_1−) and (−H−N_2−C_2−O_2−). [c] Measured between the two planes (shown as intersection of dashed lines) defined by (−C_1−C_2−N_2−) and (−C_3−C_4−N_1−). Definition of the planes and the measurement of angles were performed using SHELXTL Version 5.03 (Sheldrick, 1994).[80]

Scheme 5. Nonsuperimposable Boat Conformations That Result from the Puckering of the DKP Ring (X = C_4, $TMeC_6$, and Ind)



Scheme 6. (a) Planar Tape; (b) Nonplanar, Enantiomerically Pure Tapes; (c) Nonplanar, Racemic Tape (Substituents, Oxygen and Hydrogen Atoms Removed for Clarity)



orientations of the amide groups.[1] Both α and β should be 180° for a planar DKP ring. Puckering of the DKP ring results in two, nonsuperimposable boat conformations (i.e., *conformational* enantiomers) (Scheme 5).

Two different types of tapes emerge from the eight DKPs structurally characterized: *planar* and *nonplanar* (Scheme 6). **C_3DKP, C_5DKP, C_6DKP, $DMeC_6$DKP**, and **C_7DKP** form planar tapes where the DKP rings are themselves planar and occupy a common plane within the tape (Scheme 6a). With the exception of **C_3DKP**, these DKPs crystallize in the *P*-1 space group, reflecting the similar packing patterns of their tapes (Figure 1). Substitution of methyl groups for the hydrogen atoms at the 4-position of the cyclohexyl substituent in **C_6DKP** has little influence on the manner in which **$DMeC_6$DKP** packs in the solid state. Both **C_6DKP** and **$DMeC_6$DKP** are similarly arranged in their crystalline solids, with differences only in the size of the unit cell and the efficiency of packing (the methyl groups adjust the packing of adjacent stacks of tapes to allow for slightly better interdigitation of substituents). There are no close contacts (i.e., ≤3.0 Å) between molecules in different tapes, neither within the same sheet of tapes nor between neighboring sheets. Tapes in different sheets, however, pack closer than tapes within the same sheet (cf. Table 2).

The crystal structure of **C_3DKP** is unique in this group of solids in that not all tapes pack with their long axis parallel. Instead, parallel tapes form stacks of tapes that are "zippered" together with a diagonal tape. The presence of diagonal tapes between stacks of tapes may prevent electrostatic repulsion ("$\pi-\pi$" repulsion) that would occur between the cyclopropyl groups if stacks of tapes packed directly adjacent to each other.[35] Although the molecular structure of **C_3DKP** is similar to the molecular structure of **MeDKP**, their packing arrangements are very different (the crystal structure of **MeDKP** is similar to that of **C_5DKP**).

C_4DKP, **$TMeC_6$DKP**, and **IndDKP** form nonplanar tapes, reflecting the boat conformation adapted by the DKP ring (Scheme 6b and 6c). The consequence of the DKP ring adapting a boat conformation is that the center of mass of both cycloalkyl substituents lie on the same side of the DKP ring (i.e., inside the boat), and therefore, these solids are racemic mixtures of conformational enantiomers (Figure 2). The nonplanar tapes that form in these crystalline solids are either enantiomerically pure (Scheme 6b), as observed in the crystalline solids of **C_4DKP** and **$TMeC_6$DKP**, or racemic (Scheme 6c), as observed in the crystalline solid of **IndDKP**. Because the boat conformation is present as a racemate, all three of these DKPs crystallize in centrosymmetric space groups.

The enantiomerically pure tapes of **C_4DKP** and **$TMeC_6$DKP** pack in two different arrangements, which are best illustrated by the end-on view of tapes in Figure 2. The crystalline solid of **C_4DKP** contains enantiomerically pure tapes that pack as racemic pairs with each tape facing its opposite enantiomer (i.e., inside of boats of one enantiomeric tape face inside of boats of opposite enantiomeric tape). The result is a crystalline solid with interdigitation of substituents occurring between every other tape rather than between every tape, in contrast to what is observed in the crystal structures of the seven other DKPs characterized. The crystalline solid of **$TMeC_6$DKP** contains enantiomerically pure stacks of tapes, with tapes facing in the same direction within the same stack. Adjacent stacks are of the opposite conformational enantiomer and face in the opposite direction. van der Waals interactions between the tetramethylcyclohexyl substituents of **$TMeC_6$DKP** appear to dominate the packing of tapes relative to each other. Both **C_4DKP** and **$TMeC_6$DKP** form two-dimensional sheets of parallel tapes as a result of van der Waals contact between the cycloalkyl group on one tape and the carbonyl oxygen atom of an adjacent tape. As with **C_3DKP**, **C_5DKP**, **C_6DKP**, **$DMeC_6$DKP**, and **C_7DKP**, the tapes pack in sheets through a half-period shift along their main axes.

The crystalline solid of **IndDKP** contains racemic tapes. The tapes pack so that the phenyl rings of **IndDKP** are in van der Waals contact with the carbonyl oxygen atom on an adjacent tape. No π-stacking occurs, however, between phenyl rings, which are 3.8 Å apart and slightly tilted away from each other.

Molecular Modeling of the DKPs in Vacuum. We used molecular mechanics to help rationalize the solid state confor-

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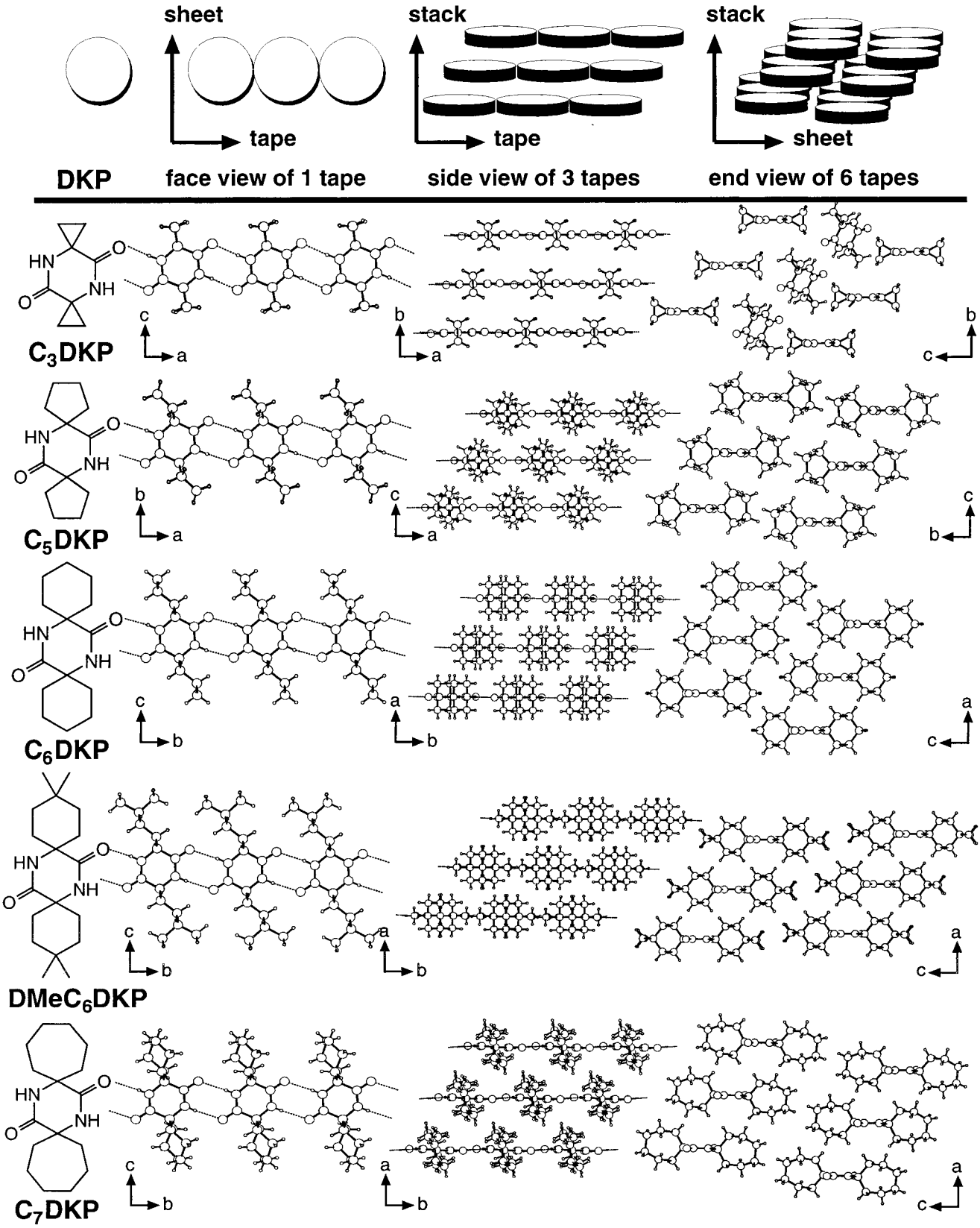

Figure 1. DKPs that form *planar* tapes and their patterns of packing. Three perspectives are shown with labeled axes to guide the eye. The labels a, b and c correspond to the tape, stack, and sheet axes, respectively. Note that these axes do not necessarily correspond to the crystallographic axes.

mations of the eight DKPs. Specifically, we examined how the substituents influenced the conformation of the DKP rings (boat or planar) in vacuum to determine whether trends observed in vacuum correlated with trends observed in the corresponding crystal structures. For this study, a model of each compound was built in Quanta 4.0,[36] and calculations in vacuum were carried out using CHARMM 22.[37] The dielectric constant was set to 1 and no cutoff distance was used in determining nonbonded interactions. Conformational analyses were per-

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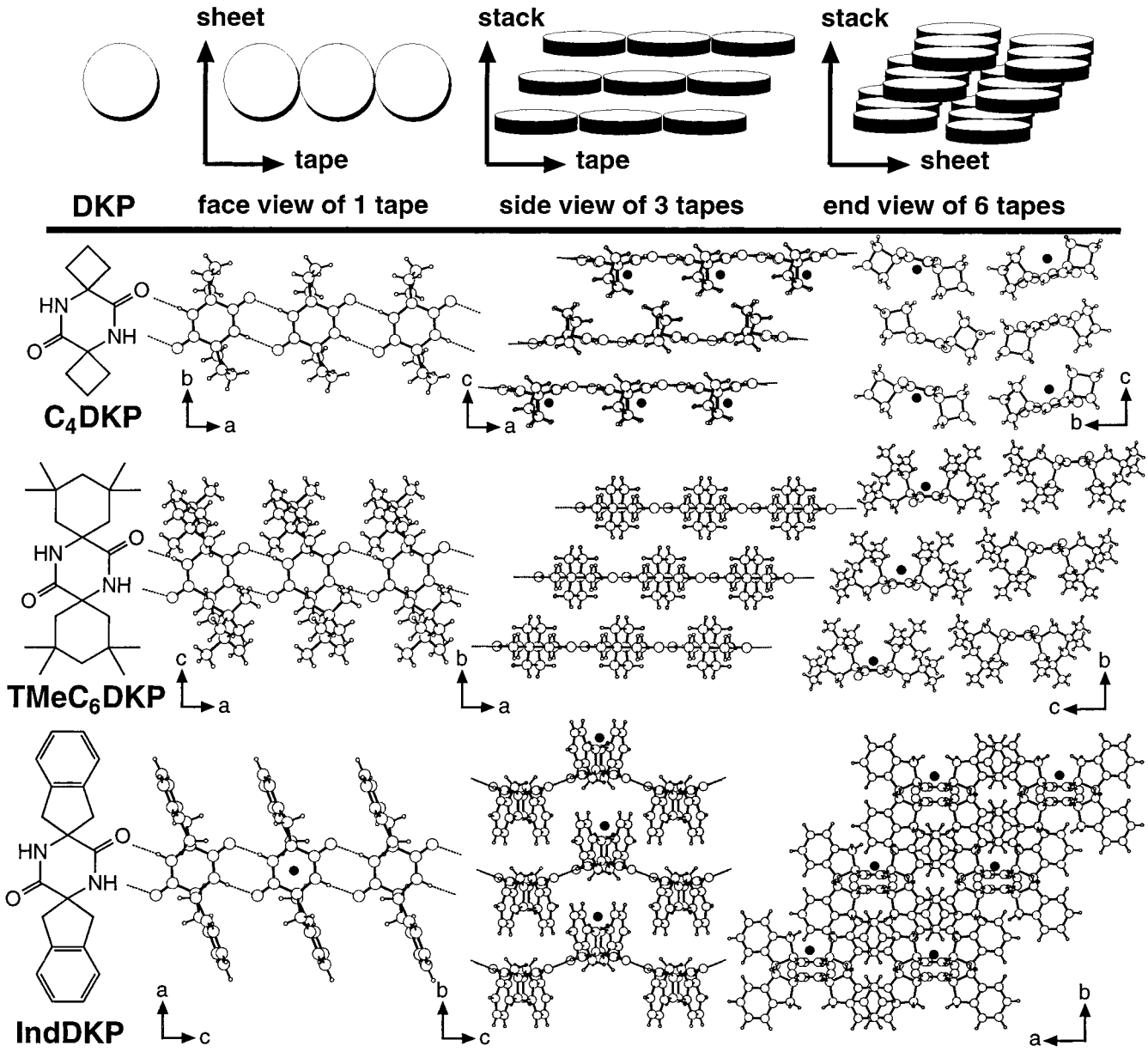

Figure 2. DKPs that form *nonplanar* tapes and their patterns of packing. Three perspectives are shown with labeled axes to guide the eye. The labels a, b, and c correspond to the tape, stack, and sheet axes, respectively. Note that these axes do not necessarily correspond to the crystallographic axes. The symbol (●) marks the location of the conformational enantiomer of the unmarked enantiomer. The crystalline solid of C_4DKP contains enantiomerically pure tapes and sheets and racemic stacks. The crystalline solid of $TMeC_6$DKP contains enantiomerically pure tapes and stacks and racemic sheets. The crystalline solid of IndDKP contains racemic tapes, stacks, and sheets.

formed by varying the angles, Φ and Ψ, over the range 0° to 35° in increments of 1° (this range includes the observed values for these angles). After each iteration of the torsion angles, the energies of the compounds were minimized using the Adopted-Basis Newton Raphson (ABNR) method[37] until the gradient in the energy fell below 0.0001 kcal/mol·Å.

The results of our calculations indicate that the predominant conformation adapted by this series of DKPs in vacuum is the boat conformation (Table 5). This result is in contrast to what is observed in the crystalline solids where the planar conformation is present in five of the eight structures studied (Figure 1). Two general trends appear: first, the difference in energy between the boat and planar conformation is small (<2 kcal mol^{-1}) for all but one of the DKPs that favor the planar over the boat conformation in the crystalline solid. Second, the compounds that most strongly favor the boat conformation in vacuum, **$TMeC_6$DKP** and **IndDKP**, adopt the boat conformation in the crystal. **C_4DKP** does not fall into these two general trends. The difference in energy between planar and boat conformation is small relative to energies associated with packing in a crystalline environment. We infer from these data

Table 5. Energy Calculations on Planar and Boat Conformations of DKPs

DKP	conformation in the crystal	lowest energy conformation in vacuum	$E_{planar} - E_{boat}$[a] (kcal/mol)
Me	planar	boat	−0.9
C_3	planar	boat	−1.2
C_5	planar	boat	−1.7
C_6	planar	boat	−1.7
$DMeC_6$	planar	boat	−1.7
C_7	planar	boat	−1.6
C_4	boat	boat	−1.7
$TMeC_6$	boat	boat	−5.2
Ind	boat	boat	−2.4

[a] The difference in energy between planar and boat conformations in gas-phase calculations.

that, with the exception of **TMeC$_6$DKP** and **IndDKP**, the planar conformation permits more efficient packing of molecules (or tapes) in the crystal than the lower energy boat conformation.

Discussion

The structure of the eight crystalline solids presented can be analyzed in terms of successive levels of organization following Kitaigorodskii's Aufbau principle:[4] DKPs reliably form one-dimensional tapes; tapes pack into two-dimensional sheets by interdigitation of substituents on adjacent tapes; sheets stack into three-dimensional crystalline structures. The fact that all eight DKPs form tapes in their crystalline solids, whether they are planar or nonplanar tapes, suggests that the location of substituents on the DKP ring limits their influence on the formation of the tapes and allows systematic variation in the structure of these substituents while preserving the common tape motif. Moreover, the tape motif is preserved even when the geometry of the DKP ring changes.

The question of conformation with regard to DKPs in solution has been examined using NMR.[38−42] For example, DKPs bearing aromatic side chains generally adapt the boat conformation in solution. Our molecular-modeling studies of DKPs in vacuum, as well as those of others, confirm that the boat conformation is generally the more stable conformation.[43−48] As shown by Ciarkowski, however, all possible conformations of the DKP ring are found within a 6 kcal mol^{-1} range.[44]

Almost half of the published crystal structures of diketopiperazines contain the DKP ring in the boat conformation.[49] Among them, 12 form nonplanar tapes similar to those observed in the crystalline solids of **C$_4$DKP** and **TMeC$_6$DKP**.[50−62] We note, however, that the high degree of puckering observed in **C$_4$DKP** and **TMeC$_6$DKP** has not been previously observed in symmetrically substituted DKPs. The nonplanarity of the DKP ring may be a way of increasing the strength of the hydrogen bonds. Further puckering of the DKP ring results in the type of nonplanar tape observed in the crystalline solid of **IndDKP**.[63]

Comparison of the carbonyl stretching frequency in DKPs suggests a difference of ∼15 cm^{-1} between the planar and boat conformations, both in solution and in the polycrystalline solid. This difference, if confirmed with more extensive data, may be useful in discriminating between the planar and boat conformation of DKPs. Modeling of the vibrational properties of the DKP ring in the boat conformation (simulations of planar DKPs are available)[64−67] may allow for unambiguous assignment of conformation. The observed increase in the vibrational frequency of the C═O stretching mode in the boat conformation is consistent with similar behavior observed in lactams.[68−70] It is doubtful that this shift in frequency is related only to the nonplanarity of the amide group, as claimed by Blaha,[68,70] since no straightforward relationship can be found in our data between the torsion angle ω and the frequency of the C═O stretch.

The filling of space appears to be the driving force behind the packing of the tapes. Adjacent tapes pack through a half-period shift along the main axis of the tape, which brings the substituent on one tape close to the amide dimer of the adjacent tape. In all eight structures, the closest contact between adjacent tapes occurs between substituents of one tape and the carbonyl oxygen of an adjacent tape.

Conclusions

We have selected derivatives of diketopiperazines, together with cyclic ureas,[23] as candidates for comparative work in the solid state on the basis of a survey of the literature.[18] In this paper we systematically tested the ability of DKPs to form tapes in the presence of nonpolar, achiral, cycloalkyl substituents that represent a substantial range of size and shape. As evident from the crystal structures presented, the hydrogen-bonded tape motif is sufficiently stable that it survives large changes in the shape and volume of the alkyl substituents. Although bulkier substituents may preclude the formation of the tapes, this effect has not yet been demonstrated experimentally. These results, along with those from previous studies, establish that DKPs reliably form tapes in the presence of a large variety of substituents: small or bulky, apolar or slightly polar, flexible or rigid, and aliphatic or aromatic.

Our results also indicate that the tape motif can accommodate either the planar or boat conformation of the DKP ring. Trends from molecular modeling in vacuum suggest that when the boat conformation is favored over the planar conformation by <2 kcal/mol, then the planar conformation may appear in the crystal; when the boat is favored over the planar conformation by >2 kcal/mol, then the boat conformation appears in the crystal. This information may be useful in predicting the conformation of new derivatives of DKPs in the solid state.

The XPD patterns of crystals grown under different conditions (see Supporting Information) provide further evidence in support of using DKPs as a basis for a systematic study of physical−organic chemistry of the solid state—only one example showed polymorphism. One explanation for the low frequency of polymorphism may be that the hydrogen-bond donor and

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acceptor sites of the secondary amide groups are "buried" by the substituents on the DKP ring, thus limiting their interactions with one another, with other substituents, and with the highly polar solvents generally used in the crystallization of DKPs (although inclusion of solvent occurs in some systems, it would further complicate these studies and therefore, is not desirable).

In summary, these studies, and nonsystematic data in the literature, reinforce the strength of the hypothesis that the DKP-derived tape will provide a structural motif in the solid state that is sufficiently robust that it will allow systematic studies of the relation between molecular structure and crystal structure. The compounds are relatively easily synthesized; crystal structure analysis poses no unusual problems. The most serious drawback of this system—as for most organic compounds—is that growing crystals suitable for single-crystal X-ray diffraction remains a slow and empirical process.

Experimental Section

General Methods. All chemicals (Aldrich) were used as received without further purification. All solvents were reagent grade and used as received except methanol, which was dried by distillation from sodium for the esterification of the amino acids. Melting points were determined on a Mel-Temp apparatus and are uncorrected. The compounds *PyrDKP*, *MeC$_6$DKP*, *tBuC$_6$DKP*, *C$_8$DKP*, and *C$_{12}$DKP* were prepared in a manner similar to the other DKPs but did not give crystals suitable for single-crystal data collection. Synthetic details and characterization of all compounds are given in the Supporting Information.

Preparation of the Cyclic Ketones. All ketones used in this work were commercially available except 4,4-dimethylcyclohexan-1-one, which was prepared in 80% yield from 4,4-dimethyl-2-cyclohexen-1-one by catalytic hydrogenation using (+)-limonene as a hydrogen donor and 10% Pd/C as catalyst.[71] The ketone was purified by chromatography with a pentane/ethyl acetate eluant. The ^{1}H NMR spectrum corresponded to data reported in the literature.[72]

General Procedure for the Preparation of Hydantoins from the Cyclic Ketones. The cyclic hydantoins (5,5-cyclo-2,4-imidazolidinedione) were prepared according to reported methods.[73] Typically, 0.1 mol of the cyclic ketone was suspended in 250 mL of 50% ethanol containing 45.5 g of ammonium carbonate and 13 g of potassium cyanide. The mixture was heated at 55−60 °C for several hours, concentrated to one-half of the volume, and cooled over ice. The precipitated hydantoin was filtered and rinsed with cold water. All hydantoins were used without further purification except the indanoyl derivative, which was recrystallized from ethanol after decolorizing with activated carbon. The IR spectra and melting points were identical with reported data.[74,75]

General Procedure for the Formation of the Cyclic Amino Acids. 1-Amino-1-cyclopropanecarboxylic acid, 1-amino-1-cyclopentanecarboxylic acid, and 1-amino-1-cyclohexanecarboxylic acid were purchased from Aldrich. The other amino acids were prepared as described from the corresponding hydantoins.[74,75] Typically, the hydantoin was refluxed for 3 days in 3 M NaOH. The reaction mixture was cooled and acidified to pH 6 with concentrated hydrochloric acid. The resulting amino acid was separated and washed with cold water. The IR spectra, NMR spectra, and melting points for 1-amino-1-cyclobutanecarboxylic acid, 1-amino-1-cycloheptane carboxylic acid, 1-amino-1-cyclooctanecarboxylic acid, and 2-aminoindan-2-carboxylic acid were identical with data reported in the literature.[74,75] The cyclobutyl derivative proved difficult to purify and was used without complete purification in subsequent steps.

General Procedure for the Esterification of the Cyclic Amino Acids. The cyclic amino acids were esterified with methanol following described methods.[74] Typically, the amino acid was suspended in freshly distilled methanol. The suspension was cooled to 0 °C, saturated with gaseous HCl, and refluxed for 4 h. The solvent was evaporated and the residue dissolved in cold saturated sodium carbonate. The esterified amino acid was extracted with diethyl ether, dried, and precipitated as an ammonium salt by bubbling gaseous HCl into the ethereal solution. The white powder was recrystallized from methanol/diethyl ether to give shiny platelets. The yield was between 75 and 90%. The IR spectra and NMR spectra for C_4, C_5, C_6, C_7, and C_8 derivatives were identical with data reported in the literature.[74]

General Procedure for the Boc-Protection of the Cyclic Amino Acids. The amino groups of the cyclic amino acids were protected following classical methods. Typically, the amino acid was suspended in a 2:1 dioxane/water mixture. Then 2.5 equiv of sodium hydroxide was added, and the solution was cooled to 0 °C. One equivalent of di-*tert*-butyl-dicarbonate (Aldrich) was added and the mixture stirred at room temperature for 12 h. The reaction mixture was concentrated to half of its initial volume, ethyl acetate was added, and the water phase acidified to pH 3 with a saturated $KHSO_4$ solution. After extraction with ethyl acetate, the organic solution was dried and evaporated. The solid *N*-Boc-amino acid was separated and purified by chromatography with THF eluant. The cyclopropyl and cyclopentyl amino acids were protected using the Cbz group (benzyloxycarbonyl) instead of Boc.

General Procedure for the Coupling of the N-Protected and the O-Protected Amino Acids. The coupling between the *N*-Boc-protected cyclic amino acids and their corresponding methyl esters was performed, unless noted otherwise, via a slight modification of Nitecki's method.[24] Equimolar amounts of the *N*-Boc-amino acid and the methyl ester hydrochloride were suspended in dry methylene chloride. One equivalent of dry triethylamine was added, and the solution was cooled to 0 °C. One equivalent of 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide·HCl and 1 equiv of 1-hydroxybenzotriazole were added, and the mixture was stirred at room temperature overnight. The reaction mixture was washed sequentially with water, 1 N citric acid solution, saturated sodium carbonate, and water. The crude dipeptide was purified by chromatography using THF as the eluant.

General Procedure for the Closure of the DKP Ring. The DKP ring was obtained, unless noted otherwise, following Nitecki's method.[24] The *N*-Boc-dipeptide methyl ester was dissolved in 98% formic acid and the solution stirred at room temperature for 2 h. After removal of the formic acid in vacuum at low temperature (<30 °C), the oily residue was dissolved in a 4:1 (vol) mixture of 2-butanol and xylene. The solution was boiled for 4 h and the solvent level maintained by addition of 2-butanol. After the solution was cooled and concentrated, the white solid was separated and recrystallized.

Crystallization of Single Crystals for X-ray Crystallography. Crystals of C_3DKP, C_4DKP, C_5DKP, C_6DKP, C_7DKP, TMeC_6DKP and IndDKP were grown in beakers covered with filter paper by slow cooling and evaporation of solvent. The crystals from DMeC_6DKP were grown by sublimation at 350 °C at ambient pressure.

Determination of Crystal Structure by X-ray Crystallography. The details of X-ray data collection, structure solution, and refinement are provided in the Supporting Information. Data on C_4DKP, C_6DKP and C_7DKP were collected at Harvard University on a Siemens P4 X-ray diffractometer using Mo Kα radiation. Data on DMeC_6DKP and TMeC_6DKP were collected at the University of California at Davis, using Cu Kα radiation on a Siemens P41RA X-ray diffractometer equipped with a rotating anode generator. Data on C_5DKP were collected by Molecular Structure Corporation, The Woodlands, TX, using Cu Kα radiation on a Rigaku AFC5R diffractometer equipped with a rotating anode generator. Data on IndDKP were collected by

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Crystallitics Company, Lincoln, NE, using Mo Kα radiation on a computer-controlled four-circle Nicolet (Siemens) Autodiffractometer.

X-ray Powder Diffraction. XPD patterns were recorded on thoroughly ground powders of the DKPs manually pressed onto a glass slide. The diffractometer used was an XDS 2000 from Scintag Inc., Sunnyvale, CA, equipped with a Cu Kα radiation source. Each XPD pattern was collected in 40 min.

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Supporting Information Available: Synthesis and characterization of all DKPs including those that did not give crystals suitable for data collection; crystallographic details including tables of atomic positional parameters and bond lengths and angles; structure diagram showing 50% probability displacement ellipsoids; packing diagrams; and X-ray powder diffraction spectra (58 pages). See any current masthead page for ordering and Internet access instructions.

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