Solid-State Structures of Hydrogen-Bonded Tapes Based on Cyclic Secondary Diamides

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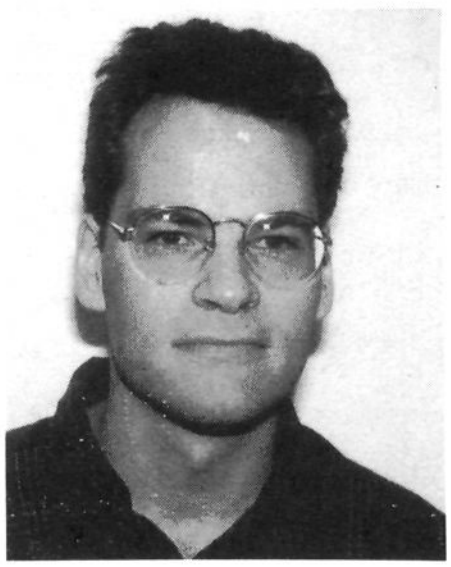

John C. MacDonald was born in Akron, OH, in 1964. He earned his A.B. degree from Bowdoin College in 1987. Working with the late Margaret C. Etter at the University of Minnesota, he received his Ph.D. in 1993 on a thesis entitled *Hydrogen-Bonded Aggregates: Imidazole as a Hydrogen-Bond Director with Applications Toward the Design of Solid-State Materials.* He is currently completing a Merck post-doctoral fellowship with George M. Whitesides at Harvard University. His research interests include molecular recognition and other aggregation phenomena, materials science, surface chemistry, and crystal chemistry.

George M. Whitesides was born in Louisville, KY, in 1939. He received his B.A. from Harvard in 1960 and his Ph.D. with John D. Roberts from the California Institute of Technology in 1964. After spending almost 20 years at the MIT, he joined the Department of Chemistry at Harvard University in 1982. His research interests include materials science, surface chemistry, rational drug design, molecular virology, and molecular recognition.

I. Introduction

The *design* of molecular organic crystals—that is, the prediction of the packing of molecules in the crystal based on the structure of the molecule, or the complete rationalization of crystalline structure based on molecular structure—is not yet possible.[1] The ability to predict crystal structure based on molecular structure would be invaluable for designing crystals that exhibit nonlinear optical properties,[2–12] ferromagnetic behavior,[13–21] electrical conductivity,[13,15–17,20–27] or solid-state reactivity.[28–39] Each of these solid-state properties is influenced by solid-state structure: the component molecules must have both the requisite molecular structure and the correct orientation with respect to one another in the crystal lattice.[24,40] The design of new solid-state materials, therefore, must be concerned with controlling both molecular and supramolecular structure.[41–43] Current levels of synthetic technology make it possible to synthesize organic molecules with a wide variety of structures and associated chemical and physical properties. Despite advances in understanding the molecular basis for the nucleation and growth of crystals,[22,44–63] predicting solid-state structure and controlling the intermolecular forces that determine molecular packing patterns in organic crystals—an enterprise that we and others refer to collectively as

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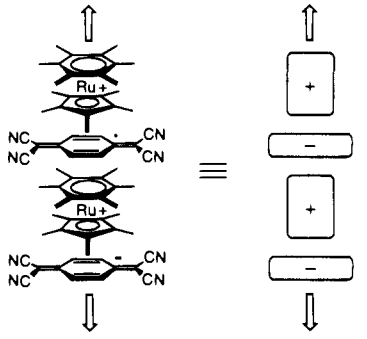
Table 1. Examples of One-, Two-, and Three-Dimensional Motifs for Organic Molecules That Influence Orientation in the Solid State (Strong intermolecular interactions—those with distances less than the sum of the van der Waals radii or clearly involved in hydrogen bonding or charge-transfer interactions—are indicated by dashed lines.)

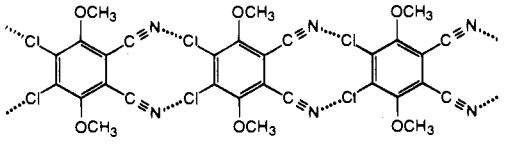
One-Dimensional Motifs

a)



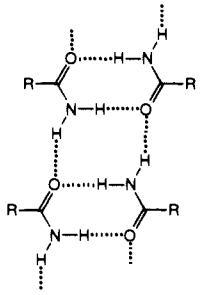
$(Cp^*)(Ru^{1+})(HMB)\cdot TCNQ^{1\cdot}$ charge-transfer complex (stack)[15, 16]

b)



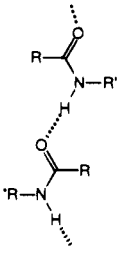
5,6-dichloro-2,3-dicyano-1,4-dimethoxybenzene (tape)[124]

c)



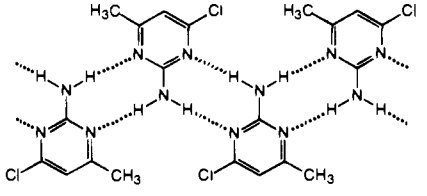
1° amides (tape)[101]

d)



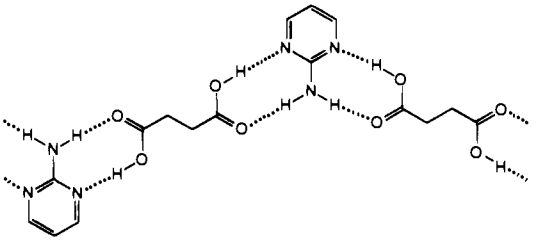
2° amides (chain)[104-106]

e)



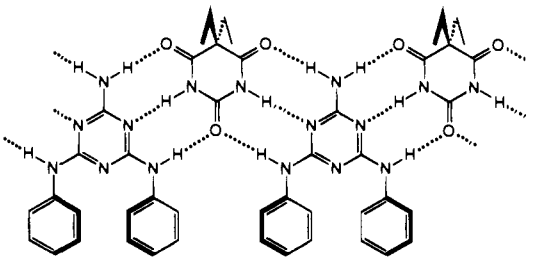
2-amino-4-chloro-6-methylpyrimidine (tape)[80]

f)



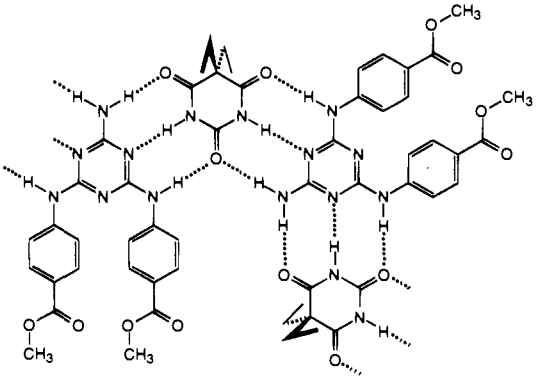
2-aminopyrimidine•succinic acid cocrystal (chain)[95]

g)



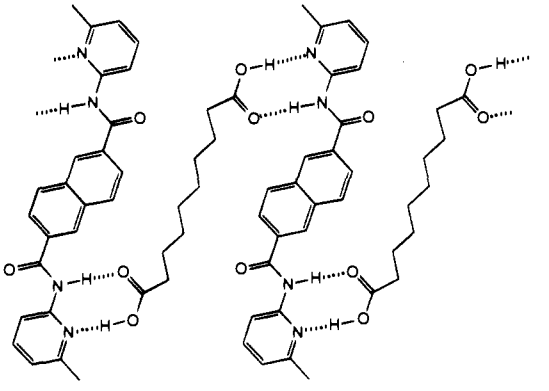
N,N'-bis(phenyl)melamine•barbital cocrystal ("linear" tape)[125-127]

h)



N,N'-bis(4-carboxymethylphenyl)melamine•barbital cocrystal ("crinkled" tape)[125, 126]

i)

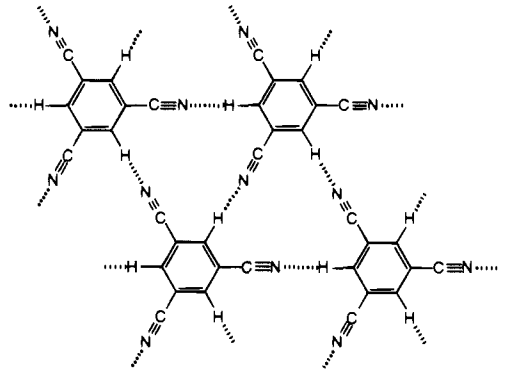


2,6-bis[[(6-methylpyrid-2-yl)amino]carbonyl]naphthalene•1,8-octanedicarboxylic acid cocrystal (chain)[128]

Table 1 (Continued)

Two-Dimensional Motifs

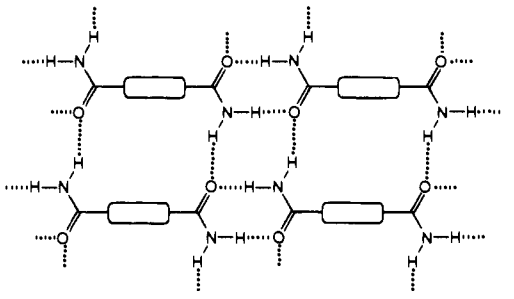
j)



1,3,5-tricyanobenzene•hexamethylbenzene (layer)[129]

[hexamethylbenzene layer is not shown]

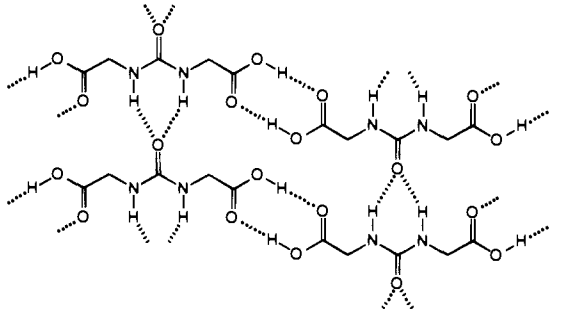
k)



1° diamides (layer)[101]

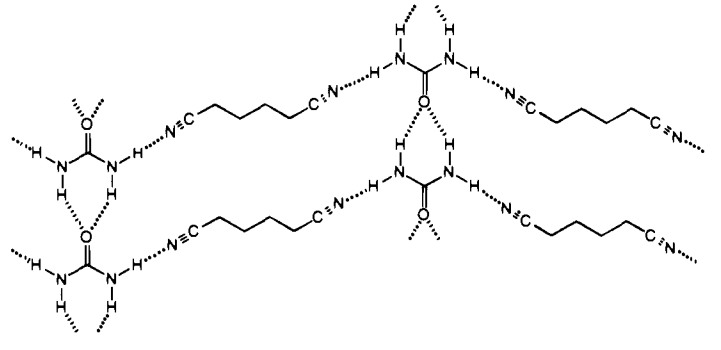
(The symbol ▭ represents a range of organic groups.)

l)



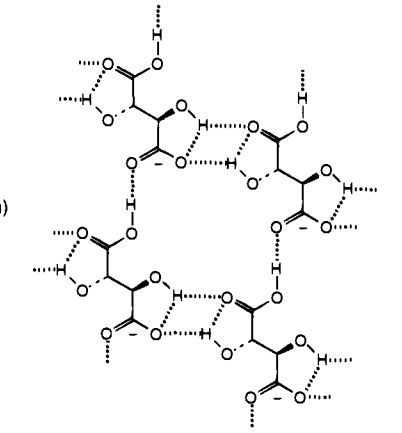
N,N'-bis(2-carboxymethyl)urea (layer)[130, 131]

m)



1,4-dicyanobutane•urea cocrystal (layer)[132, 133]

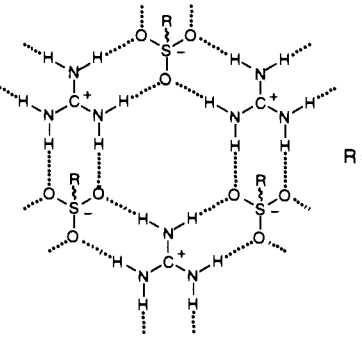
n)



(S)-1-phenylethylammonium hydrogen-L-tartrate salt (layer)[79, 134]

[(S)-1-phenylethylammonium cations are not shown]

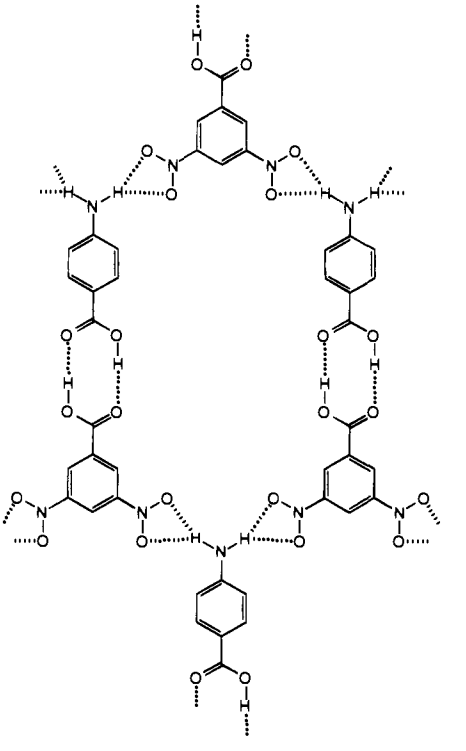
o)



R = alkyl or aryl

guanidinium alkane- and arenesulfonates (layer)[6, 84]

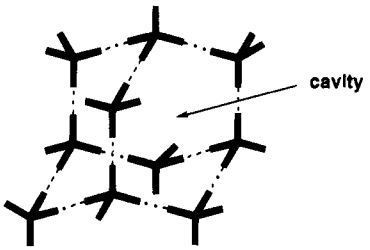
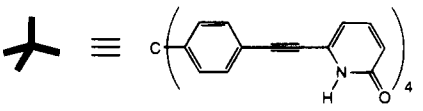
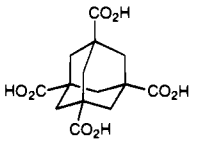
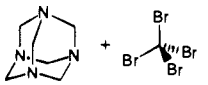
p)



4-aminobenzoic acid•3,5-dinitrobenzoic acid cocrystal (layer)[12, 135]

Table 1 (Continued)

Three-Dimensional Motifs

q)			N—H···O cavity filled by six interpenetrating lattices and by enclathrated carboxylic acid molecules.
			O—H···O cavity filled by four interpenetrating lattices
			C—Br···N cavity filled by one interpenetrating lattice
	three-dimensional "diamondoid" lattice[136-136]		

"crystal engineering"—still present severe challenges.[40]

A. Impediments to Crystal Engineering

Three problems make crystal engineering so difficult: the multiplicity of possible orientations of molecules in crystals, the inaccuracies in estimating energies, and the entanglement of thermodynamic and kinetic contributions to crystal growth. Sorting through all possible arrangements in space that show translational symmetry for an organic molecule of even modest structural complexity is a task that exceeds current analytical capabilities. A number of approaches to simplifying this problem have been considered. One approach is to incorporate into the molecule a small number of functional groups that can interact *inter*molecularly and to use these interactions to limit the possible arrangements of the molecules in space with respect to one another. Several examples of structures with one-, two-, and three-dimensional motifs designed using this approach are illustrated in Table 1. A second approach is to take advantage of "host–guest" inclusion compounds such as clathrates that trap guest molecules within a host lattice of some other chemical species.[64-72] The host lattices of clathrates such as Dianin's compound form well-defined cavities that control the orientation of individual molecules or aggregates of molecules.[73] Another strategy for controlling molecular orientation in crystals is to dope the molecules of interest as an impurity into a host crystal of known structure. These types of host–guest complexes differ from inclusion complexes in that the guest molecule, which mimics the shape of the host molecule, is incorporated into the host lattice by "mistake" and in the absence of predefined cavities.[74-77] Molecular orientation in crystals can also be controlled by attaching a group of interest—for example, another molecule such as a fatty acid— that strongly influences crystal structure. Interactions between the hydrophobic portions of linear peptides with two to five residues are known to be critically important in determining the crystal packing patterns and crystal morphology of this class of compounds.[78]

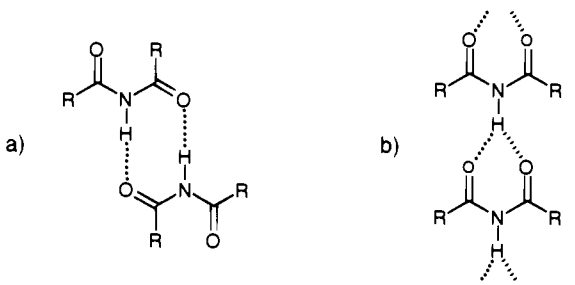


Figure 1. Two patterns of hydrogen bonds based on different conformations of acyclic imides: (a) dimer of *cis,trans*-acyclic imides; (b) chain of *trans,trans*-acyclic imides.

The most attractive types of functional groups for general use in controlling intermolecular orientations in crystals now seem to be those that can participate in hydrogen bonding.[79,80] Hydrogen bonds are moderately strong (1–5 kcal/mol) and directional,[81-83] and are thus more likely to enforce an *orientation* than charge–charge or van der Waals interactions.[59-79] Etter,[10-12,78,80,84-100] Leiserowitz,[101-106] Jeffrey,[81] Taylor and Kennard,[107,108] and others[109-113] have systematically characterized the structures of hydrogen-bonding interactions and identified patterns of hydrogen bonds occurring commonly between specific functional groups. Etter, in particular, has proposed rules that describe the selectivity of different functional groups in forming hydrogen bonds.[80,92] For example, acyclic imides form two different hydrogen-bonding motifs, a chain and a dimer (Figure 1); the motif adopted depends in part on the steric bulk of substituent groups (R).[86,89,90] The chain motif is an attractive one from the standpoint of crystal design, because it allows for controlled assembly of molecules in one dimension. In the case of diacetimide, however, (and doubtless for other molecules as well) the dimer and chain motifs are close enough in energy that both are observed.[114,115] This polymorphism complicates efforts to use the chain motif in crystal engineering.

Polymorphism—the occurrence of more than one crystalline form of a molecule—is a general and serious problem in crystal engineering.[40,79] *Conformational polymorphism*—that is, the formation of

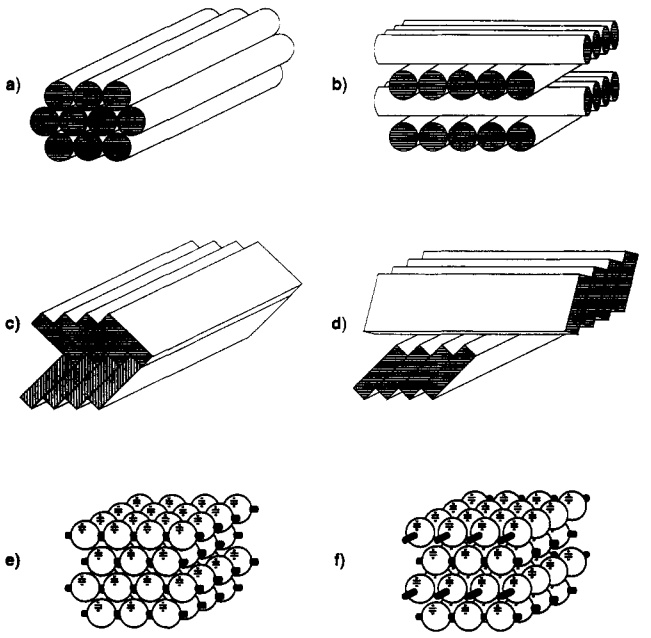


Figure 2. Schematic drawings of hypothetical packing arrangements of linear aggregates: (a,b) cylinders, helices, or tubes; (c,d) tapes; (e,f) spheres ("beads-on-a-string"). Cylinders and tapes pack efficiently with their long axes parallel both *within* and *between* layers. Chains of spheres also pack efficiently with their long axes parallel within a layer, but the layers of spheres pack equally well when the chain axes in adjacent layers are aligned either parallel or perpendicular.

crystals in which a molecule adopts different conformations[116]—can be limited by using rigid molecules. *Orientational polymorphism*—the formation of different crystals from the *same* conformation of the molecule—always remains a possibility. Various aspects of polymorphism in organic crystals have been addressed in several books[116-121] and in a number of reviews.[122,123]

This review describes a variety of crystalline structures. An important caution in interpreting these structures is that very few of them have been examined for polymorphism. Thus, in no case is it clear whether the observed structure reflects a thermodynamic minimum or a kinetic preference.

B. Tapes as a Motif for Crystal Engineering

In practice, simply introducing one or a few functional groups capable of forming hydrogen bonds into a molecule does not restrict the range of possible crystal structures open to it sufficiently to permit prediction of crystalline structure from molecular structure. We and others have considered strategies to restrict the range of possible crystal structures yet further, by trying to design molecules that will form intermolecular motifs with well-defined structures—spheres, sheets,[6,12,84,130-134,139-141,147] tapes,[109,125-127,142-146] helices,[91,95,109,148,149] cylinders or tubes[150,151] (Figure 2). These efforts build on the progress of molecular recognition in solution and attempt to reduce the dimensionality of the packing problem in the solid state. A particularly attractive motif to use in imposing predictable structural order on a molecular crystal is the tape. We expect rigid tapes to pack with their long axes parallel (like straws or matches).[152] The number of arrangements of molecules in space to be considered in this type of structure is dramatically reduced relative to the general case in which any possible orientation of molecules in space is possible.

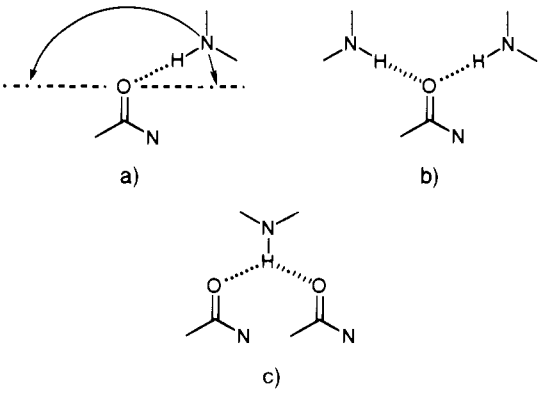


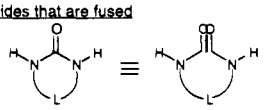
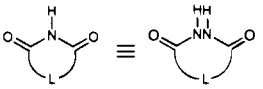
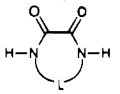
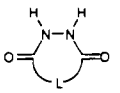
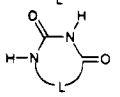
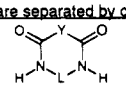
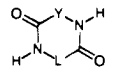
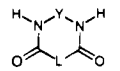
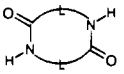
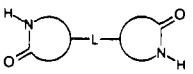
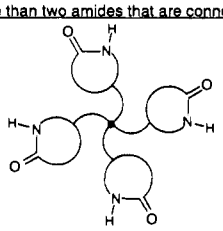
Figure 3. Different arrangements of NH donors with carbonyl acceptors: (a) single-point interaction with the *cis* or *trans* lone pair of electrons; (b) bifurcated carbonyl with two NH donors; (c) three-center O···NH···O interaction.

The amide group is an attractive functionality to use in designing tape structures in the solid state: it forms hydrogen bonds with well-understood geometrical constraints; it is itself planar; it is easily synthesized. This review summarizes the available literature on solid-state structures based on types of amides that seem plausible candidates for making tapes. It also reviews relevant sheet structures, albeit in less detail. Our analysis, in formulating this review, is based on four principles: (1) amides are minimal planar self-aggregating structures; (2) two amide groups (diamides) allow for extended hydrogen-bonded aggregates to form; (3) use of secondary amides equalizes the number of hydrogen-bonding donors (NH) and acceptors (C=O); and (4) use of *cyclic* amides restricts the amide group to the *cis* conformation, thus promoting two-point dimeric interactions rather than single-point interactions.

C. Constraint on the Geometry of Hydrogen Bonds

Although the use of cyclic secondary *cis* diamides simplifies the packing problem significantly, there is still a substantial range in structures possible for molecules connected by hydrogen bonds. This multiplicity in structures can be traced to the fact that hydrogen bonding involving donor and acceptor sites in amides imposes only limited geometrical constraints on possible crystal structures. Both the carbonyl oxygen and amide hydrogen can, in principle, form hydrogen bonds with more than one of the complementary groups, and the carbonyl group, in particular, can form hydrogen bonds with a wide range of geometries (Figure 3). Hydrogen-bond donors show a statistical preference to approach the carbonyl oxygen in the plane of the carbonyl group in the solid state, but show substantial variation in the directions of approach within this plane.[107,153-155] By contrast, gas-phase microwave studies by Legon and Millen show there is a preference for donors to approach along the direction of carbonyl lone

Table 2. Types of Structures Surveyed

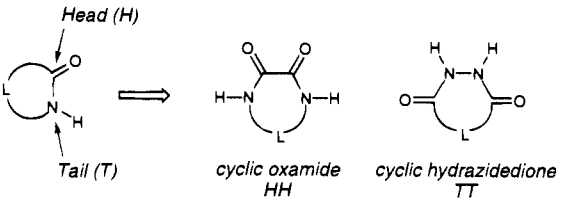
Structure[a]	Type of Compound	Connection	Section
Amides that are fused			
	Cyclic Ureas	"HH"	IIA
	Cyclic Imides	"TT"	IIB
Amides that are directly joined			
	Cyclic Oxamides	HH	IIIA
	Cyclic Diacylhydrazides	TT	IIIB
	Cyclic Acylureas	HT	IIIC
Amides that are separated by one atom (Y)[b]			
	Cyclic HH Diamides	HH	IVA
	Diketopiperazines	HT	IVB
	Cyclic TT Diamides	TT	IVC
Amides that are separated by more than one atom			
	Large Cyclic Diamides		VA
	Linked Lactams		VB
More than two amides that are connected by a high-symmetry core			
			VI

[a] L represents that portion of the molecule linking the amide groups. [b] Y represents a single atom separating to the amide groups.

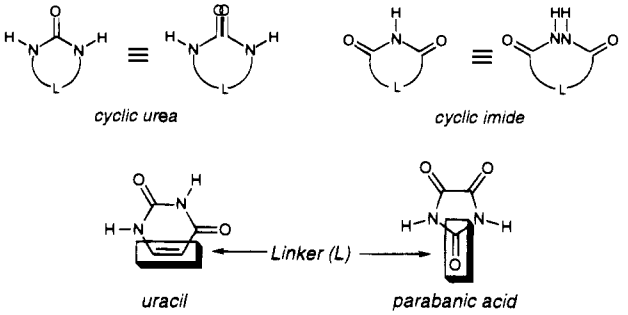
pairs.[156,157] Most likely, there is an energetic preference for donors to approach along the direction of lone pairs, but this preference is less important than other effects of crystal packing in determining the geometries of hydrogen-bonding interactions in the solid state.[107]

D. Nomenclature, Methods, and Scope of the Review

Table 2 summarizes the types of structures included in this review. It is organized with the principle that we are considering primarily cyclic molecules incorporating two *cis* amide groups. For convenience in describing these systems we label the carbonyl end of the molecule as the head (H), and the amine-derived end as the tail (T). The two amide groups in an oxamide are thus considered to be connected head-to-head (HH), while the amide groups in a cyclic diacyl hydrazide are connected tail-to-tail (TT). Cyclic ureas and imides are special cases in



which we consider two C=O groups (for the former) or NH groups (for the latter) to be "fused". We refer to that portion of the molecule connecting the amide groups as the linker (L). For example, the amide groups in uracil (a HT diamide) have an ethylene linker (L = −CH=CH−) while those in parabanic acid (a HH diamide) are linked by a carbonyl group (L =)C=O).



Throughout this review, we distinguish between patterns of hydrogen bonds involving amides that form *tapes* and patterns that form *ribbons*. Although these two motifs are similar structurally (they both give flat linear arrays of molecules), ribbons are less attractive as a structural motif for crystal engineering because several different variations on this motif can be generated from different combinations of NH···O interactions. We distinguish tapes and ribbons in the following manner: a tape motif is generated when each molecule is hydrogen bonded to *two* neighboring molecules, and when the hydrogen bonds between *any two molecules* form a cyclic eight-membered ring; a ribbon motif is generated when each molecule is hydrogen bonded to *three or more* molecules, regardless of the connectivity of hydrogen bonds between the molecules. Examples of tape and ribbon motifs are given in Figure 4.

In order to evaluate the hydrogen-bonding motifs of cyclic diamides, we performed a connectivity search on the appropriate diamide fragment from each structural category in Table 2 using the cambridge Structural Database (CSD; 1993 version 5.06).[158] Structures containing alkali, earth alkali, or transition metals were excluded, because cations of these elements compete with NH donors in forming intermolecular interactions with C=O groups. Patterns of hydrogen bonds summarized in this review are given as reported by the original authors. In cases where structural information about hydrogen bonding was not reported, we retrieved the crystallographic coordinates and examined molecular packing and hydrogen-bonding interactions using the Quanta crystallographic software package.[159] Since our objective was to assess the preferred modes of hydrogen bonding of *cis* amides in the absence of

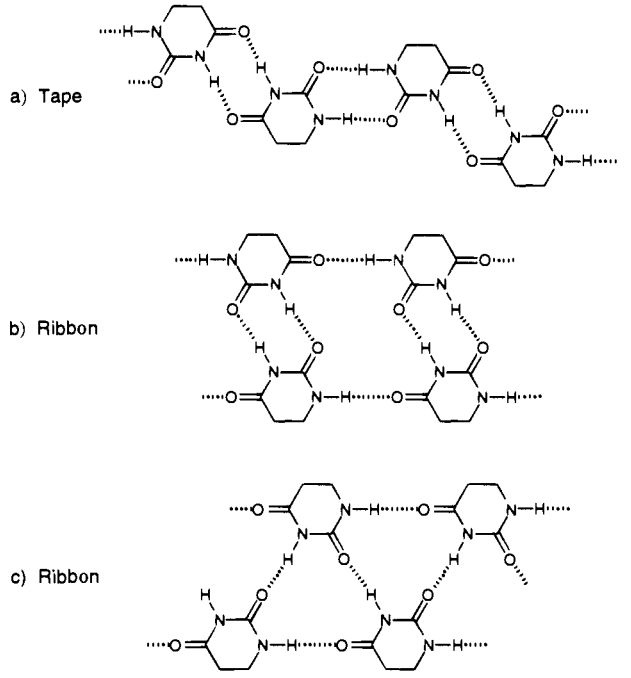


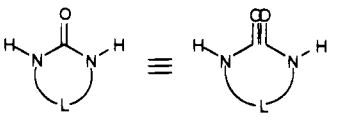
Figure 4. Hypothetical examples of tape (a) and ribbon (b and c) motifs.

competing interactions, a number of diamide structures were not considered for this review; these include diamides that form salts, hydrates, or cocrystals or those that have substituents with hydrogen-bonding functional groups that can disrupt the self-association of amides. These compounds are listed in tables for several classes of diamides that form a large number of such structures. All structures are referred by the six- to eight-letter CSD reference code (refcode). Refcodes for all structures are listed in Chart 1 of the Appendix with the corresponding compound names and literature references.

II. Amides That Are Fused

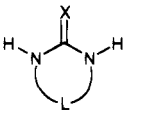
The category of fused amides includes two classes of cyclic molecules containing two overlapping amide groups: the cyclic ureas and the cyclic imides. The patterns of hydrogen bonds found in crystal structures of molecules containing ureas or imides as a subset of their hydrogen-bonding functionality (e.g. barbituric acids) are described in later sections.

A. Cyclic Ureas



The urea functional group can be viewed as two amides sharing the same carbonyl group. Both NH protons in cyclic ureas are constrained in the *cis* conformation with respect to the urea carbonyl. Even though the urea functional group contains only one acceptor, the oxygen atom of the carbonyl can form NH···O interactions with two neighboring urea molecules. This arrangement of donors and acceptors should be ideal for making tapes based on series of dimers.

Table 3. Structural Data for Cyclic Ureas



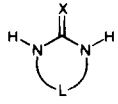
Motif[a]	X[b]	L[c]	Refcode
Tape	O	·$CH_2CH_2CH_2$·	APYFEB
	S	·$CH_2CH_2CH_2$·	TMETHU
	O	Form I	ZEFXIR[d]
	O	Form II	ZEFXIR01[d]
	S		MCBZIM
	O		BIOIND
	O		BIOTME10
	O		DINTAV10
	O		FUSRAM
Layer I	O	[e]	DMGLUR
Layer II	S	·CH_2CH_2·	ETTHUR01
3D I	O		JEZZOD
3D II	S		KIVDOI
Dimer	S		VUXZIX

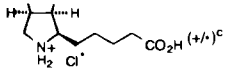
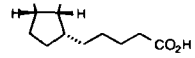
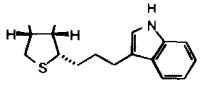
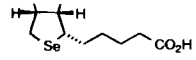
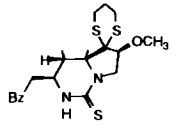
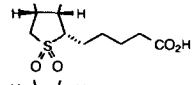
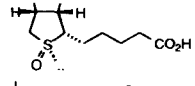
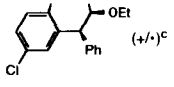
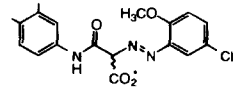
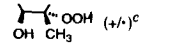
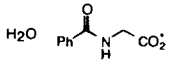
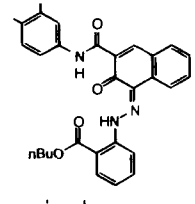
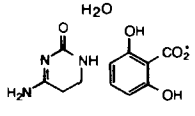
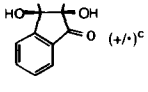
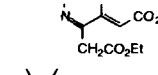
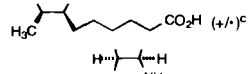
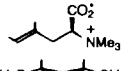
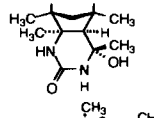
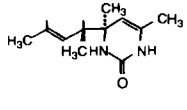
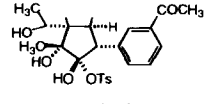
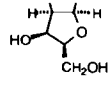
[a] The patterns of hydrogen bonds are shown schematically in Figure 5. [b] Heteroatom acting as a hydrogen-bond acceptor. [c] Substituent group linking the nitrogen atoms of the urea. [d] Two different crystalline forms (I and II) give the same tape motif. [e] See Figure 5.

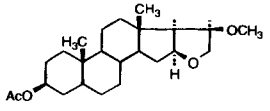
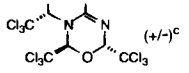
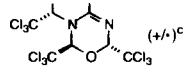
The hydrogen-bonding motifs and molecular structures of 12 cyclic ureas are summarized in Figure 5 and Table 3. Although almost 60 structures of cyclic ureas are known, most of these compounds form hydrates or salts or have substituents with hydrogen-bonding functional grops, and thus we have not examined their patterns of hydrogen bonds. These cyclic ureas are listed in Table 4.

Eight of the cyclic ureas shown in Figure 5 form tapes. One compound 2,3-dihydrobenzimidazol-2-one, crystallizes in two polymorphic forms (form I [ZEFXIR] and form II [ZEFXIR01]). The molecules in both polymorphs aggregate as flat tapes that have similar packing patterns in the respective crystals. Differences in the two structures arise primarily because two crystallographically independent molecules define the asymmetric unit in form II, while only one molecule defines the asymmetric unit in form I.

Table 4. Cyclic Ureas Forming Hydrates, Hydrogen-Bonded Solvates, Cocrystals, or Having Substituents with Competing Hydrogen-Bonding Functionality



X[a]	L[b]	Guest Molecules	Refcodes	X[a]	L[b]	Guest Molecules	Refcodes
O		H_2O	AZBIOT10	O		·	BIOTNA
O		0.5 H_2O	BIOIND	O		·	BIOTNC
O		0.5 H_2O	CARVOG	O		·	BIOTND
				O		·	BIOTNE
O		0.5 H_2O 0.25 dioxane	CEPBZA	O		·	BIRZIL
S	·CH=CH·	0.5 H_2O	CEZXEK	O		·	BOBHUV
O			CYTBGL	O		·	CIPGMR10
O		H_2O 	CYTRES10				
O		H_2O	GAXTII	S		·	CUJZUC
O	·CH_2CH_2·	0.5 H_2O	KALZIG	O		·	DETBIO10
S		2 H_2O	LETHIO	O		·	DIUREA (dimorph C)
O		2 H_2O	TZTCHD10	O		·	DIUREA01 (dimorph P)
O		2 EtOH	MPYMOD10	O		·	DPACTS
				O		·	DURXYF

S		MeOH	VOHGAA
O		2 dioxane	BOFJAH
O		2 dioxane	BOFJAH
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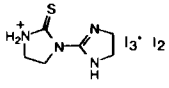
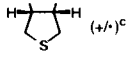
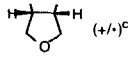
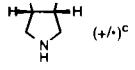
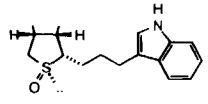
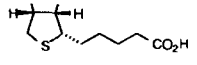
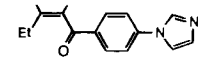
S	·CH_2CH_2·	1.5 I_2	CEWMOG
S	·CH_2CH_2-		CEWNAT
O		·	AZOCTA
O		·	AZOCTB
O		·	AZOCTC
O		·	BINDOX
O		·	BIOTIN01
O		·	FOBZIF
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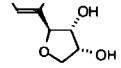
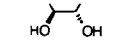
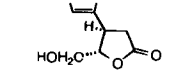
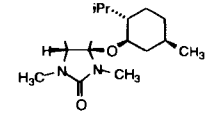
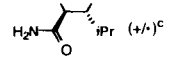
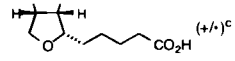
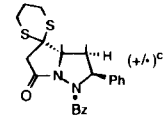
S		·	FURIMT
O		·	GADPEG
O		·	HXIMOZ
O		·	JEHMOY
O		·	KOFZUA
O		·	OXBIOT10
O		·	SPUNON
S	·$CH_2CH_2CH_2CH_2$-	·	TMTHUR

[a] Heteroatom acting as a hydrogen-bond acceptor. [b] Substituent group separating the nitrogen atoms of the urea group. [c] The crystal is racemic but only one enantiomer is shown.

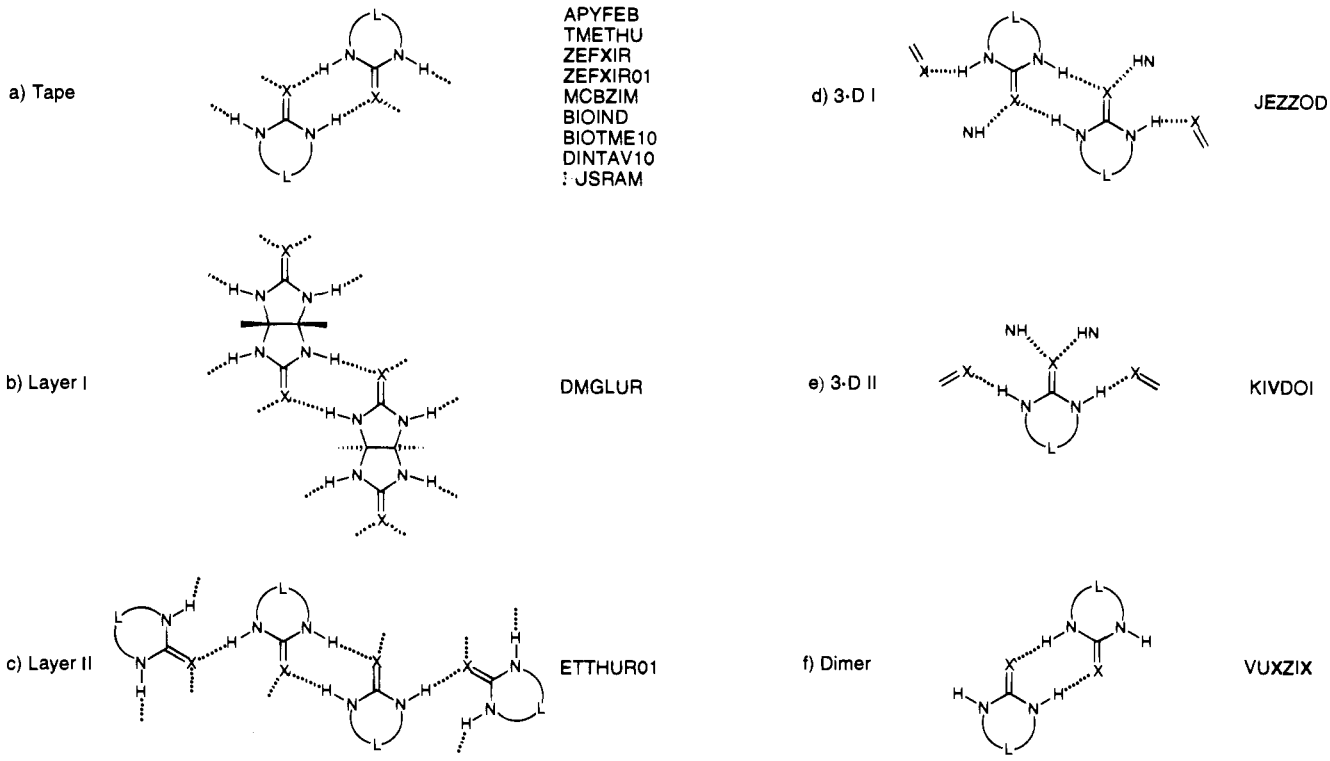


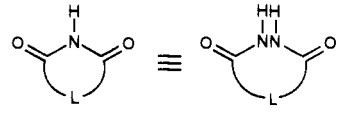
Figure 5. Patterns of hydrogen bonds found in crystals of cyclic ureas. X denotes a heteroatom acting as a hydrogen-bond acceptor, and L represents a substituent group linking the two nitrogen atoms of urea (Table 3).

The remaining five compounds crystallize in a variety of different hydrogen-bonding motifs. The dimethyl analog of diurea, 3a,6a-dihydro-3a,6a-dimethylimidazo(4,5-*d*)imidazole-2,5-(1*H*,6*H*)-dione [DMGLUR], contains two cyclic ureas that are fused. Both halves of the molecule independently form tapes that, in combination, give layer I (Figure 5b). Molecules of ethylenethiourea [ETTHUR01] crystallize by forming layer II (Figure 5c). This layer differs slightly from layer I in that only one half of the urea forms a dimer. The other half of the molecule interacts with neighboring molecules by forming chains of hydrogen bonds.

Molecules of cubanourea [JEZZOD] and 4,5,6,7-tetrahydro-1,3-benzimidazole-2-thione [KIVDOI] form hydrogen bonds in three dimensions. On the basis of the molecular structures, it is not obvious why either compound fails to form a tape.

6-Methyl-4-phenyl-8-(phenylmethylene)-3,4,5,6,7,8-hexahydro-2(1*H*)-quinazolinethione [VUXZIX] is the only cyclic urea we have examined that does not crystallize by forming an infinite network of hydrogen bonds. Molecules of this compound aggregate as simple dimers in which one NH donor is not used in hydrogen bonding.

B. Cyclic Imides



Unlike cyclic ureas, cyclic imides have only one NH donor; consequently, only one imide carbonyl group is used in hydrogen bonding. Studies of hydrogen-bonding preferences of cyclic imides indicate that this group usually forms cyclic dimers or chains (Figure 6) in the solid state.[160] Preferential formation of chains rather than dimers may reflect repulsive secondary interactions between the hydrogen-bonded carbonyl groups of the dimer and the nonbonded carbonyl oxygen atoms.[161] Solution NMR studies on the dimerization of cyclic imides and lactams also suggest these secondary interactions reduce the hydrogen-bonding affinity of imides relative to lactams.[162] Cyclic monoimides appear not to be useful for the design of tapes because the one NH donor cannot give rise to the two NH···O interactions required to form a chain. Molecules containing *two* or more cyclic imides can, however, form tapes based on infinite sets of dimeric interactions. The hydrogen-bonding motifs and molecular structures for known examples of such compounds, all of which are diimides, are summarized in Figure 7 and Table 5, respectively. Seven of the 10 diimides form tape motifs (*i*–*v*) involving dimeric interactions between both imide groups. The 1,2-L-bis(4-piperazine-2,6-dione) derivatives (tape *i*) have imide groups joined by an alkyl linker, L, that offers the potential for variations in the structure connecting the cyclic imide groups; the generality of this structural type remains to be established. The molecules in tapes *ii*–*v* all have two imide groups joined by a rigid framework.

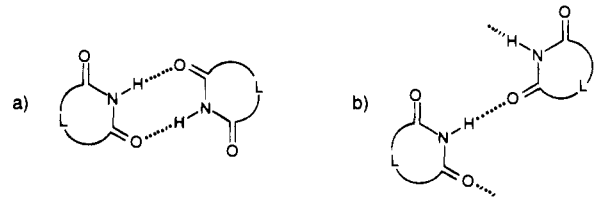


Figure 6. Two patterns of hydrogen bonds formed commonly by cyclic imides: (a) cyclic dimer and (b) chain.

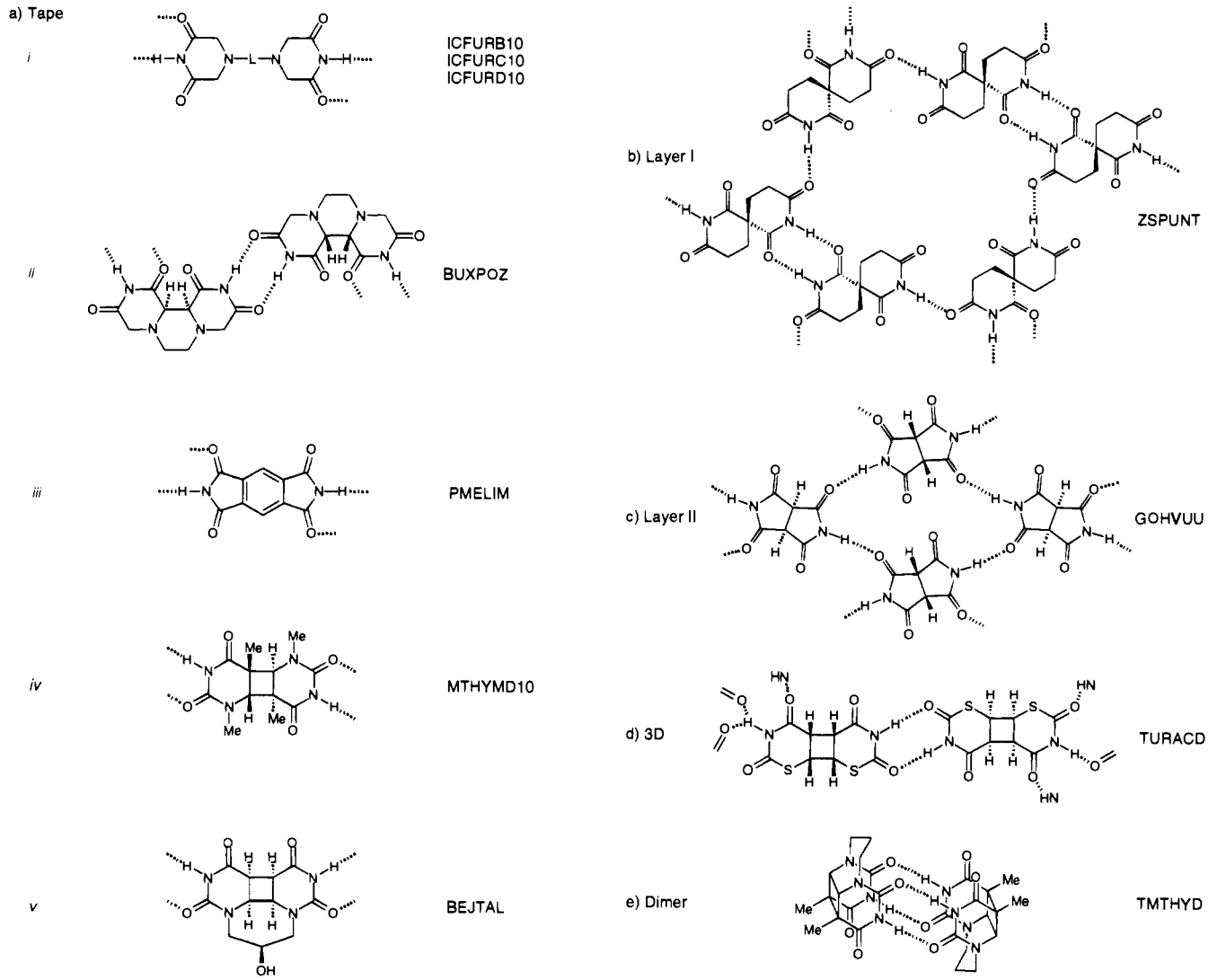
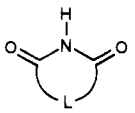


Figure 7. Patterns of hydrogen bonds found in crystals of cyclic diimides. L represents a substituent group linking the two imide rings in molecules forming tape *i* (Table 5).

Table 5. Structural Data for Cyclic Imides



Motif[a]	L[b]	Refcode	Motif[a]	L[b]	Refcode
Tape			Tape		
i	·CH(CH$_3$)CH$_2$·	ICRFRB10	*iii*	c	PMELIM
			iv	c	MTHYMD10
		ICRFRC10	*v*	c	BEJTAL
			Layer I	c	ZSPUNT
		ICRFRD10	Layer II	c	GOHVUU
			3D	c	TURACD
ii	c	BUXPOZ	Dimer	c	TMTHYD

[a] The patterns of hydrogen bonds are shown schematically in Figure 7. [b] Substituent group linking the carbonyl groups of the cyclic imides. [c] See Figure 7.

2,7-Diazaspiro[5.5]undecane-1,3,6,8-tetraone [ZSPUNT] forms a layer motif (I) made up of dimers and chains (Figure 7b). These chains differ slightly from those found in structures of monoimides, in that the NH donor and carbonyl acceptor reside on different imide groups. The fact that this structure forms a layer, rather than a three-dimensional motif, is surprising since the spiro carbon orients the imide

groups orthogonally with respect to one another.

Molecules of urazourazole [GOHVUU] form a second layer motif (II). The connectivity of the hydrogen bonds in this two-dimensional network (Figure 7c) differs from that in layer I because it contains chains only.

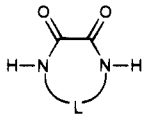
The *cis–syn* photodimer of 1-thiauracil [TURACD] forms extended NH···O interactions in three dimensions (Figure 7d). Two molecules of the asymmetric unit are joined together as dimers that, in turn, are linked by chains of NH···O interactions in three dimensions.

The 1,1′-trimethylene-linked *cis–syn* thymine photodimer [TMTHYD] illustrated in Figure 7e is the only diimide forming a finite aggregate. The molecules in this structure adopt a boat conformation that orients the imide groups to one side of the molecule. These U-shaped molecules form imide–imide dimers in which the molecules are related through a center of symmetry. A tape motif forms also in the crystal structure of the *trans–anti* photodimer of 1-methylthymine [MTHYMD10], where the imide groups point in opposite directions.

III. Amides That Are Directly Joined

Several tape motifs are possible based on molecules containing two adjacent amide units. Amide groups can be joined structurally in three different configurations depending on the amide orientation.

A. Joined HH Diamides



Cyclic molecules featuring amide groups that are directly joined HH lack a molecular center of symmetry. These noncentrosymmetric molecules are polar—that is, they have a permanent molecular dipole—and hydrogen-bonded aggregates preserving this polarity are potentially useful as the framework for crystalline materials with properties requiring a permanent bulk dipole[32,163] (e.g. second-harmonic generation,[9] piezoelectricity,[164] pyroelectricity,[165] and triboluminscence[166–168]).

Only a few crystal structures of HH diamides have been determined (Figure 8 and Table 6). HH diamides form hydrogen bonds that give layer motifs I–III. Layer I is found in the structures of parabanic acid [PARBAC] and 4,5,6,7-tetrahydro-1,2,5-oxodiazolo[3,4-*b*]pyrazine [TAFKAM]. These compounds form two-dimensional polar networks of hydrogen bonds in which all of the molecules are oriented in one direction (Figure 8a). The tertiary structure of the crystal is constructed by stacking the hydrogen-bonded layers at van der Waals separation. The polarity of the individual layers is lost in the bulk crystal because the stacked layers are related through inversion symmetry.

Molecules of 1,4-dihydro-2,3-quinoxalinedione [HQOXDO] aggregate and give a second type of two-dimensional network: layer II. In this structure,

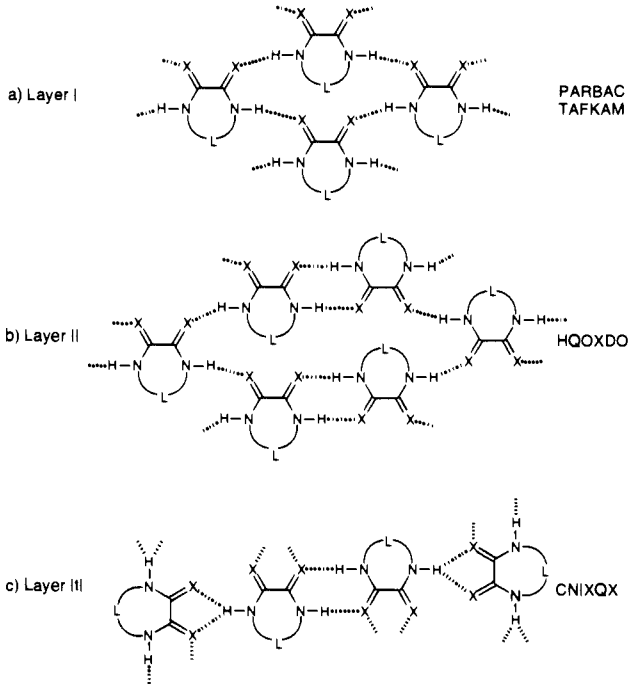
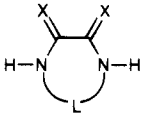
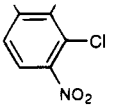


Figure 8. Patterns of hydrogen bonds found in crystals of joined HH diamides. X denotes a heteroatom acting as a hydrogen-bond acceptor, and L represents a substituent group linking the nitrogen atoms (Table 6).

Table 6. Structural Data for HH Diamides



Motif[a]	X[b]	L[c]	Refcode
Layer I	O	>C=O	PARBAC
	N·O·N	·CH_2CH_2·	TAFKAM
Layer II	O		HQOXDO
Layer III	O		CNIXQX

[a] The patterns of hydrogen bonds are shown schematically in Figure 8. [b] Heteroatom acting as a hydrogen-bond acceptor. [c] Substituent group linking the nitrogen atoms of the amides.

pairs of molecules joined as cyclic dimers are further connected into a sheet by chains of hydrogen bonds (Figure 8b). This layer pattern is similar topologically to layer III (Figure 8c) in the structure of 5-chloro-7-nitro-2,3-dihydroxyquinoxaline [CNIXQX]. Layer III differs slightly from layer II only in that the NH donor of the chain forms a bifurcated hydrogen bond involving both carbonyl acceptors.

Despite the small number of HH diamides in this survey, the absence of tapes in any of the structures is surprising. The presence of cyclic dimers in layers II and III indicates that a tape based on dimers is at least plausible (Figure 9). A structural feature shared by the two compounds forming layer I is a small linker group L (Table 6). This feature appears

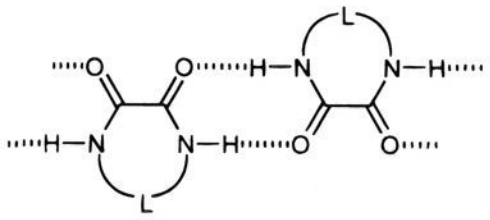


Figure 9. A hypothetical tape motif involving HH diamides.

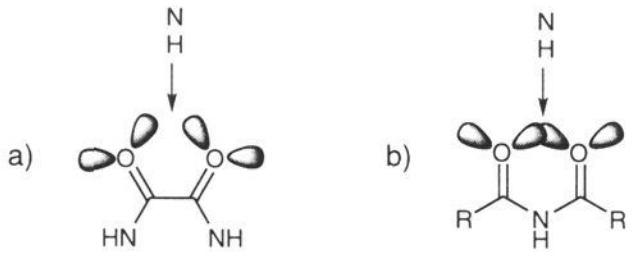
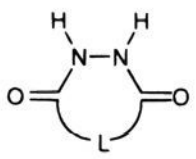


Figure 10. Schematic representation of the lone pairs of electrons in (a) joined HH diamides and (b) acyclic imides. Regions of electron density between adjacent oxygen atoms of the carbonyl groups promote formation of chains based on three-center O···NH···O interactions.

to be critical for molecules to pack in a near-planar arrangement while maintaining the pattern of layer I. It should be possible, therefore, to prevent layer I from forming and to promote dimer formation by increasing the size of L; layers II and III demonstrate this effect, although the result is not a tape.

Other factors such as the close proximity of carbonyl groups in HH diamides may, in some cases, promote molecular aggregation in layers rather than tapes. The HH configuration creates a cleft occupied by the *syn* lone pairs of electrons of both carbonyl oxygen atoms (Figure 10). Studies of hydrogen bonding in crystal structures of acyclic imides reveal that the region of electron density between the carbonyl groups of *trans–trans* acyclic imides promotes formation of chains (Figure 1).[86] If such bifurcated hydrogen bonds are more stable than dimeric pairs of hydrogen bonds, layered structures of the type shown in Figure 8c (layer III) will be preferred over tapes.

B. Joined TT Diamides



Directly joined TT diamides is another class of cyclic molecules showing promise as potential building blocks for making tapes. Unlike HH diamides, the amide carbonyl groups of TT diamides are directed away from each other on opposite ends of the molecule. This configuration provides a geometry optimal for forming dimers, while eliminating the possibility of forming chains involving bifurcated O···NH···O interactions.

Figure 11 and Table 7 illustrate the hydrogen-bonding motifs and molecular structures of the three uncomplicated TT diamide structures found in the crystallographic literature. One compound, hexahydro-3,6-pyridazinedione [HPYDZO10], forms a tape motif (Figure 11a). The molecules adopt a pseudo-chair conformation that twists the carbonyl groups of the amides with respect to one another along the

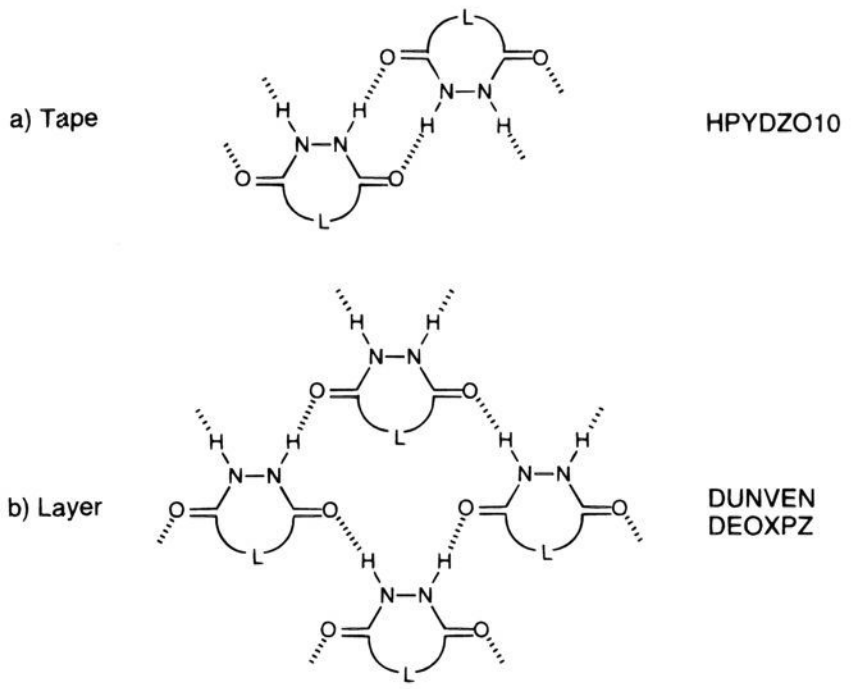
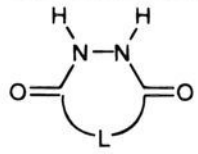


Figure 11. Patterns of hydrogen bonds observed in the crystal structures of TT diamides. L represents a substituent group linking the carbonyl groups (Table 7).

Table 7. Structural information for TT diamides

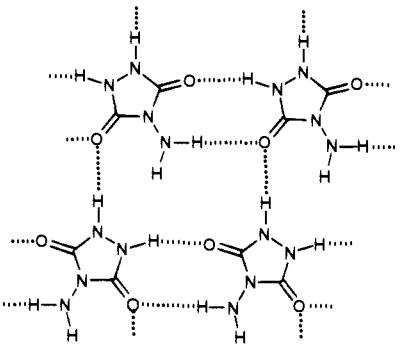


Motif[a]	L[b]	Refcode
Tape	$-CH_2CH_2-$	HPYDZO10
Layer	$>CEt_2$	DUNVEN
	$>CH_2$	DEOXPZ

[a] The patterns of hydrogen bonds are shown schematically in Figure 11. [b] Substituent group linking the carbonyl groups.

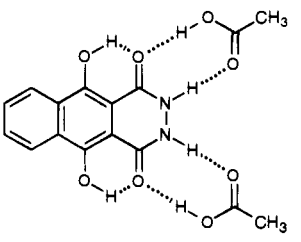
N–N bond (C–N–N–C = 25°); this tape is severely buckled along the long tape axis. The remaining two compounds, 3,5-pyrazolidinedione [DUNVEN] and 4,4-diethyl-3,5-pyrazolidinedione [DEOXPZ] both crystallize in approximately planar polar layers. This layer is similar topologically to layer I observed in joined HH diamides. Two other structures of TT diamides worth mentioning have additional functional groups that form hydrogen bonds. The first, urazine [SAZGOP], forms polar layers in which the L group, $\rangle NNH_2$, participates in hydrogen bonding (Figure 12). Even if NH···O interactions involving the $\rangle NNH_2$ linker are disregarded, all amide NH donors and carbonyl acceptors are still used in hydrogen bonding and the layer pattern is maintained.

The second structure is a cocrystal between 1,2,3,4-tetrahydro-1,4-dioxo-5,10-dihydroxybenzo[*g*]phthalazine and acetic acid [DHBPHT]. Each amide group forms a mixed dimer with a molecule of acetic acid giving a finite 1:2 aggregate (Figure 13). Etter's rules for hydrogen bonding predict that a cocrystal will form in cases such as this one, where the best donor (acid OH) and best acceptor (amide carbonyl) are located on different molecules.[80,96] In the absence of competing hydrogen-bonding groups, such as the carboxylic acid group of acetic acid, self-aggregation of the amide groups should give an extended tape or layer motif during crystallization.



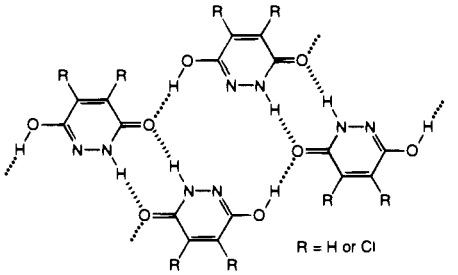
SAZGOP

Figure 12. Polar layer formed by molecules of urazine [SAZGOP].



DHBPHT

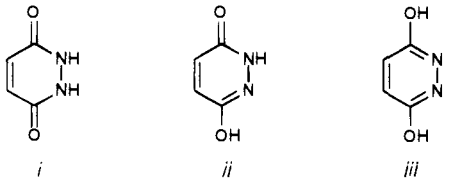
Figure 13. 1:2 Aggregate formed between 1,2,3,4-tetrahydro-1,4-dioxo-5,10-dihydroxybenzo(*g*)phthalazine and acetic acid [DHBPHT].



MALEHY01
MALEHY10
DCPYZO01

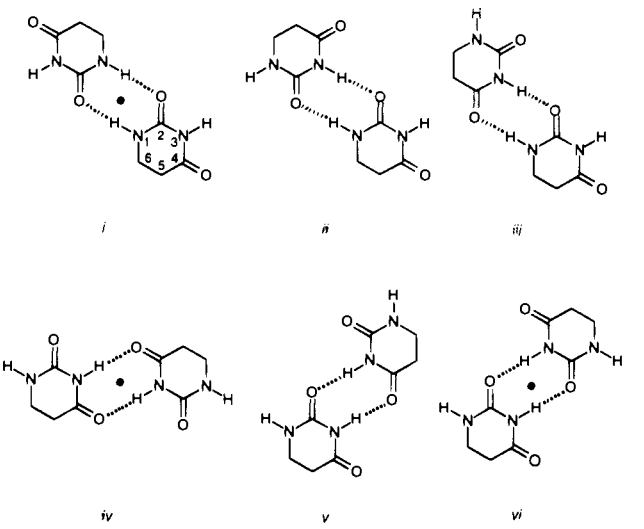
Figure 14. Ribbon of hydrogen bonds formed in two polymorphs of maleic hydrazide ([MALEHY01] and [MALEHY10]) and by 4,5-dichloromaleic hydrazide [DCPYZO01].

Maleic hydrazides represent a special class of TT diamides that have three possible tautomeric forms (*i*–*iii*). The parent compound, maleic hydrazide (MH),



i *ii* *iii*

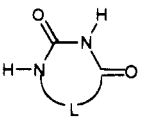
can form heterobase pairs both with purines (uracil or thymine) and with pyrimidines (adenine).[169] Crystallographic studies of two polymorphs of MH ([MALEHY10][170] and [MALEHY01][171]) and the related 4,5-dichloro derivative, 2ClMH [DCPYZO01],[172] have shown that these molecules are present in the monolactim form (*ii*) in the solid state. The molecules in all three structures share the same ribbon motif (Figure 14), in which dimers are joined by two antiparallel chains of hydrogen bonds.



i *ii* *iii* *iv* *v* *vi*

Figure 15. Possible configurations of dimers formed between joined HT diamides. Dimers with centrosymmetric configurations (*i*, *iv*, and *vi*) are indicated by a dot (•) at the center of symmetry.

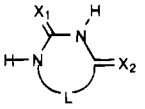
C. Joined HT Diamides

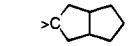
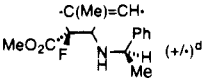
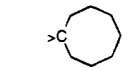
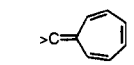
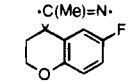
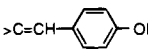
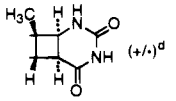
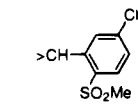
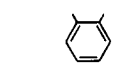
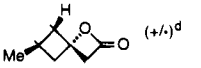
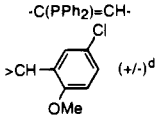


The head-to-tail arrangement of NH donors and C=O acceptors in joined HT diamides gives rise to a wide variety of extended aggregates with hydrogen-bonding motifs that are not accessible to HH and TT diamides. Previous discussions of joined HH and TT diamide structures have shown that patterns of hydrogen bonds based on dimers are common elements of tapes. In fact, a molecule *must* form separate dimeric interactions with two neighboring molecules in order for a tape to grow. A large number of amide–amide dimers are possible for HT diamides. Before examining the crystal structures of HT diamides, it is instructive to consider all possible configurations of dimers between HT diamides. Jeffrey and Saenger have shown that six configurations of dimers (*i*–*vi*) are possible (Figure 15).[81] These configurations apply to the general class of HT diamides (Figure 16). Dimers *i*, *iv*, and *vi* form centrosymmetric (nonpolar) aggregates[173] while *ii*, *iii*, and *v* form noncentrosymmetric (polar) aggregates. Since tape polarity is determined by the presence or absence of an internal center of symmetry, one can, in principle, design polar tapes by using HT diamides that form the appropriate dimers. For example, polar tapes can be constructed using molecules that form dimers with configuration *ii* (Figure 16c).

The patterns of hydrogen bonds and the molecular structures of 39 HT diamides are summarized in Figure 16 and Table 8. HT diamides self-assemble in at least 13 different hydrogen-bonding motifs in the solid state. More than half of these compounds form tapes I–III (Figure 16a–c). The HT diamides in tapes I and II are joined by pairs of dimers having configurations *i*/*iv* and *i*/*vi*; these tapes are nonpolar. The dimers in tape III are joined using only configuration *ii*; this tape is polar.

Table 8. Structural Information for Joined HT Diamides



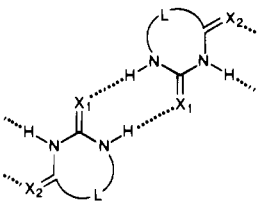
Motif[a]	X_1[b]	X_2[b]	L[c]	Refcode	Motif[a]	X_1[b]	X_2[b]	L[c]	Refcode
Tape I	O	O	·CH_2CH_2·	DHURAC10	Tape III	O	O	·CH(Me)CH_2· (+/-)[d]	DHTHYM
	O	O	·C(Et)=C(Me)·	EMURAC		O	O	·CH_2O·	XDHURC
	O	O	>NH	KOXRIY		O	O	·C(Me)=CH·	THYMIN
	O	O		BCOCHY		O	O	 (+/-)[d]	BIZMAY
	O	O		OCSHYD	Ribbon I	O	O	·C(Me)=N·	AZTHYM10
	O	O		KESWOU		O	O		DAFFIZ
	O	O	>C=CH-  OMe	FINVON		O	O	 (+/-)[d]	THYMDM10
	O	O		VARBAR	Ribbon II	O	O	·C(NO_2)=C(Me)·	NIMURC10
	O	S		DAFPEF		O	O	 (+/-)[d]	BEVLIX
	S	O	·CH=CH·	TURCIL01	Layer I	O	O	·C(PPh_2)=CH·	FORHAV
	S	S	·CH=CH·	DTURAC		O	O	 (+/-)[d]	VAPZUH
	Se	Se	·CH=CH·	DSEURC					
	S	O	>CMe_2	FILXIH		S	O	·CH=CMe·	ZZZGEO01
	S	S	>CMe_2	FILXED	Layer II	O	O	·CH=CH·	URACIL
	S	Se	>CMe_2	FILXON		S	O	>CH_2	THHYDT
Tape II	O	O	>CMe_2	BEPNIT	Layer III	O	O	·NH·CH(OMe)· (+/-)[d]	FEMCEF
	O	O	·C(Cl)=CH·	CLURAC10		S	O	·CH_2CH_2·	DHTURC
	O	O	·C(Br)=CH·	BRURAC10	Layer IV	O	O	·C(F)=CH·	FURACL
	O	O	·C(Et)(Ph)CH_2· (+/-)[d]	TAJXAD	Layer V	O	O	·C(I)=CH·	IURACL10
					3-D	O	O	·CH=N·	AZURAC01
					Dimer	S	O	·CH=C(CH_2Ph)·	FICBEY

[a] The patterns of hydrogen bonds are shown schematically in Figure 16. [b] Heteroatom acting as a hydrogen-bond acceptor. [c] Substituent group linking the carbonyl group and the amido nitrogen atom of the HT diamide. [d] The crystal is racemic but only one enantiomer is shown.

Uracil [URACIL], 2-thiouracil [TURCIL01], 2,4-dithiouracil [DTURAC], and 2,4-diselenouracil [DSEURC] form an isostructural series in which the heteroatoms of the carbonyl groups (X_1/X_2) are O/O, S/O, S/S, and Se/Se, respectively (Table 8). Of these, the parent compound, uracil, forms layer II and the remaining three uracil derivatives form tape I. 5,5-Dimethylhydantoin [BEPNIT], 5,5-dimethyl-2-selenohydantoin [FILXIH], 5,5-dimethyl-2,4-dithiohydantoin [FILXED], and 5,5-dimethyl-2-seleno-4-thiohydantoin [FILXON] form a similar isostructural series in which the combinations of acceptors (X_1/X_2) are O/O, Se/O, S/S, and S/Se, respectively. The O/O compound forms tape II, and the other derivatives all form tape I. In both series, switching from the O/O compound to analogs where X_1 is a less electronegative S or Se atom causes the hydrogen bonds to rearrange and form tape I. This result suggests that electronic "tuning" of hydrogen-bonding functional groups might provide a useful tool for designing tapes, if the underlying relations between molecular and crystal structure were understood.

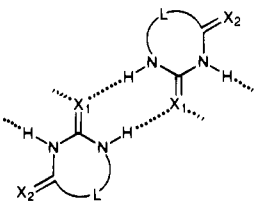
The patterns of hydrogen bonds found in the crystal structures of 5-Y-uracils, (where Y = H [URACIL], F [FURACL], Cl [CLURAC10], Br [BRURAC], CH_3 [THYMIN], and I [IURACL10]) reveal that even small changes in the size of substituents greatly affects molecular aggregation during crystallization. Polymorphism has not been investigated in this series, and it is not presently clear whether packing patterns in these structures are determined by kinetics or thermodynamics. Nonetheless, in this series, the progression in substituent size from H to I results in five different patterns of hydrogen bonds that include three layer motifs (II, V, and VI) and two tape motifs (II and III). Of these structures, only 5-chlorouracil and 5-bromouracil form the same hydrogen-bond motif (tape II). Despite the fact that methyl groups are isosteric with chlorine and bromine atoms, molecules of 5-methyluracil form polar tape III. The origin of this wide range of crystal structures is not obvious, since the molecules are structurally very similar. Until polymorphism has been investigated in this series, it is not possible to draw firm conclu-

a) Tape I



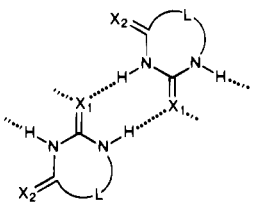
DHURAC10 DAFPEF
EMURAC TURCIL01
KOXRIY DTURAC
BCOCHY DSEURC
OCSHYD FILXIH
KESWOU FILXED
FINVON FILXON
VARBAR

b) Tape II



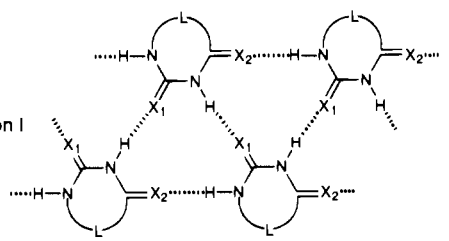
BEPNIT
CLURAC10
BRURAC10
TAJXAD

c) Tape III



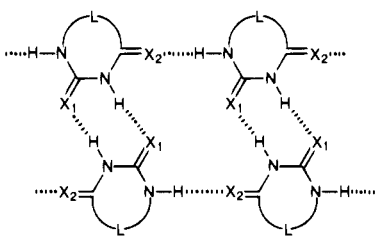
DHTHYM
XDHURC
THYMIN
BIZMAY

d) Ribbon I



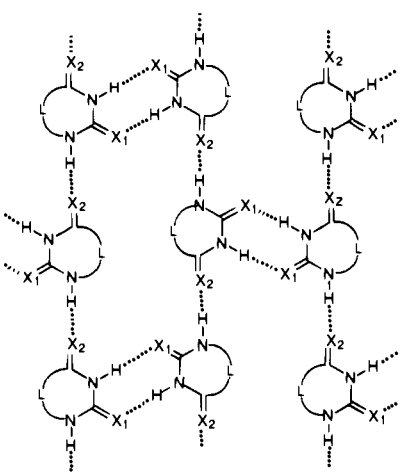
AZTHYM10
DAFFIZ
THYMDM10

e) Ribbon II



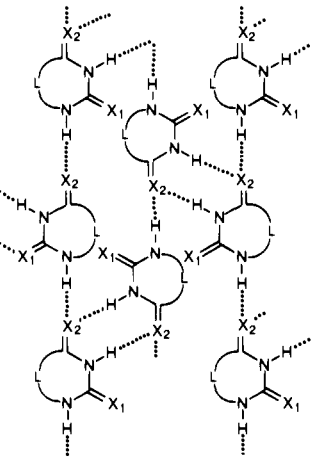
NIMURC10
BEVLIX

f) Layer I



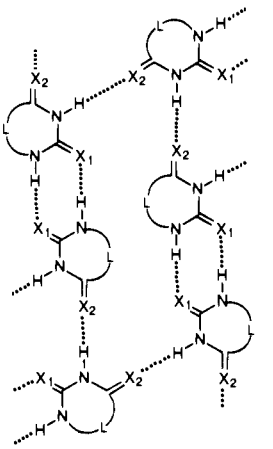
FORHAV
VAPZUH
ZZZGEO01

g) Layer II



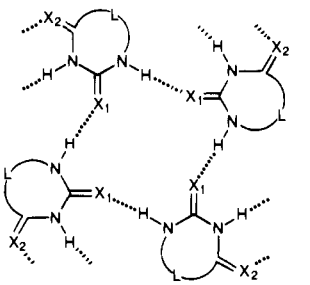
URACIL
THHYDT

h) Layer III



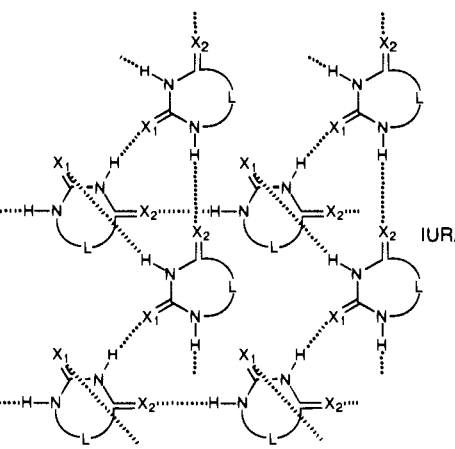
FEMCEF
DHTURC

i) Layer IV



FURACL

j) Layer V



IURACL10

Figure 16. Patterns of hydrogen bonds found in crystals of joined HT diamides. X_1 and X_2 denote heteroatoms acting as a hydrogen-bond acceptors, and L represents a substituent group linking the carbonyl group and amide nitrogen atom (Table 8).

sions about relative stabilities of these structures.[174]

Layer motifs I–V involve different combinations of dimers and chains (Figure 16). Layers I–III incorporate dimers with centrosymmetric configurations *vi*, *iv*, and *i*, respectively. The dimers in layer IV also have configuration *iv*, but the molecules in this structure form tetrameric rings rather than chains. While ring patterns of this type are common among certain functional group classes such as phenols,[175] tetrameric rings are unusual for amides. The absence of any dimers in the pattern of layer V makes this motif unique. Layer V is defined by two independent sets of amide chains.

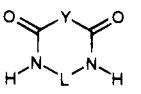
HT diamides give two additional patterns of hydrogen bonds. The first compound, 6-azauracil [AZURAC10], forms chains of amides in three dimensions (Figure 16k); these define the entire crystal structure. The second compound, 4-benzyl-2-thiouracil [FICBEY], forms dimers with configuration *iv* (Figure 16l). In this configuration, the C=O group makes a hydrogen bond with the imido NH donor (N(3)H) while the C=S group and the amido NH donor (N(1)H) do not participate in hydrogen bonding. Donahue[176] and others[80,96] have proposed sets of empirical rules for hydrogen bonding in organic molecules based on the concept that a sterically accessible donor always forms a hydrogen bond if acceptor atoms are available. The failure of the amido NH donor to form a hydrogen bond in the presence of unbonded oxygen and sulfur acceptors is unusual.

IV. Amides Separated by One Atom

We refer to cyclic molecules containing two amide groups that are separated by one atom as *separated* diamides. The atom between the two amides (Y) can be a single element such as O, S, or Se, or part of a larger functional group. Separating the amide groups introduces at least two factors that can affect patterns of hydrogen bonding and crystal packing. First, the atom spacer isolates the amide groups electronically, and thus reduces changes in the hydrogen-bonding affinity of amide groups caused by the effects of cooperativity in hydrogen bonding.[81] Second, a spacer allows for variability in the conformation of the ring, and thus may promote conformational polymorphism.[116]

Separated diamides are divided, according to the configuration of the amide groups, into three general classes. These amide–amide configurations are described using the HH (NH–CO–Y–CO–NH), HT-(NH–CO–Y–NH–CO), and TT (CO–NH–Y–NH–CO) designations introduced previously.

A. Separated HH Diamides



Surprisingly, only two crystal structures of separated HH diamides have been determined. 6,6-Diethylperhydro-1,4-diazepine-5,7-dione [JAMKOX] forms the tape motif shown in Figure 17a. The

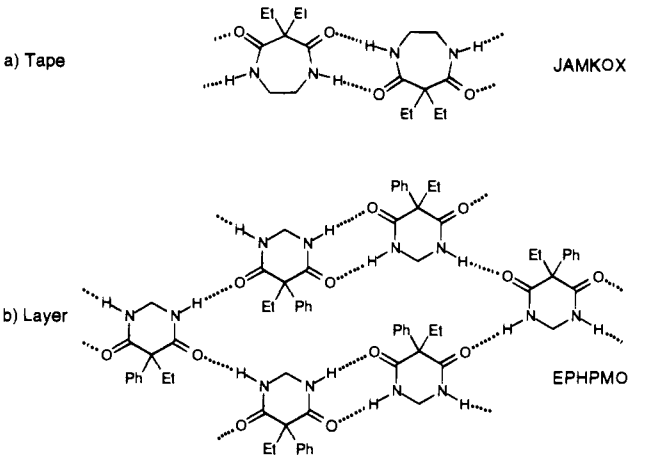
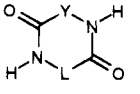


Figure 17. Patterns of hydrogen bonds formed by separated HH diamides: (a) tape motif of 6,6-diethylperhydro-1,4-diazepine-5,7-dione [JAMKOX] and (b) layer motif of primidone [EPHPMO].

conformation of the seven-membered ring is controlled by the planarity of the amide groups and can be described as a flattened twist-chair.[177] As a result of this twisted conformation, the tapes are severely buckled along the long tape axis. Primidone [EPHPMO] forms a layer motif based on centrosymmetric amide–amide dimers joined by chains of NH···O interactions.

B. Separated HT Diamides



Separated HT diamides include one of the most widely studied classes of cyclic diamides: the 2,5-diketopiperazines. The crystal and molecular structures of diketopiperazines have been examined extensively because these molecules are the simplest class of cyclic peptides. The crystal structure of diketopiperazine (DKP), which was first determined by Corey in 1938,[178] has special significance since this compound was the first containing a peptide bond to be studied by X-ray diffraction.[179] Corey found that the DKP molecule was planar and formed flat hydrogen-bonded tapes (Figure 18a) that pack in paral-

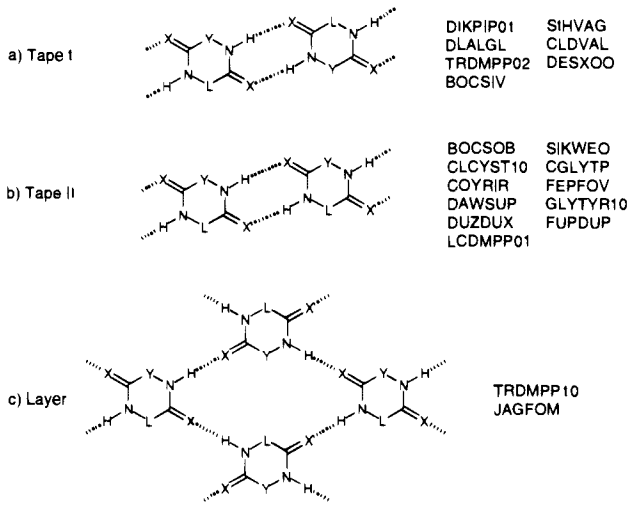


Figure 18. Patterns of hydrogen bonds found in crystals of diketopiperazines. X denotes a heteroatom acting as a hydrogen-bond acceptor. Y and L represent an atom or substituent group linking the carbonyl groups to amide nitrogen atoms (Table 9).

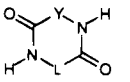
lel offset stacks. Benedetti later established the structure of cyclo(D-alanyl-L-alanyl) [TRDMPP10] and found that molecules in this structure formed hydrogen-bonded layers (Figure 18c).[180] He proposed that two patterns, tapes and layers, are the most likely modes of association for diketopiperazines having an internal center of symmetry.

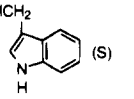
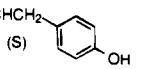
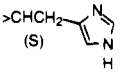
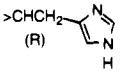
The crystal structures of 41 different diketopiperazines are currently available.[181] The patterns of hydrogen bonds and the molecular structures of the 19 compounds that do not crystallize with other molecules and that do not contain competing hydrogen-bonding functional groups are summarized in Figure 18 and Table 9. The patterns of hydrogen bonds were not analyzed for the remaining 22 structures that form hydrates, hydrogen-bonded solvates, or cocrystals or that have substituents with additional functional groups that disrupt amide-amide hydrogen bonding. Table 10 lists the molecular structures for this latter group of compounds.

The geometry of the DKP rings varies roughly as a function of the number and placement of substituents on the ring. The central ring in symmetric tetrasubstituted DKPs (e.g. DIKPIP01, BOCSIV, SIHVAG) generally adopts a planar conformation, while those in symmetric *trans*-disubstituted DKPs (e.g. TRDMPP02, CLDVAL) vary from planar to flattened-chair conformations. Several studies in solution and in the solid state have shown that the DKP ring in *cis*-disubstituted and trisubstituted compounds usually adopt flattened-boat or twist-boat conformations, particularly when the substituents are arylmethyl groups.[182-186] The structures of DKPs we examined agree with these findings. Since planar molecules tend to self-associate as planar aggregates and to pack efficiently, symmetric tetrasubstituted DKPs should be good candidates for designing tapes.

Diketopiperazines crystallize in two tape motifs (Figure 18a,b) that differ in terms of the symmetry relationships between adjacent molecules within the tape. Molecules in tape I form centrosymmetric dimers that give nonpolar tapes. Of seven structures forming tape I, six have molecules with internal

Table 9. Structural Information for Diketopiperazines



Motif[a]	Y[b]	L[c]	Refcode
Tape I	>CH_2	>CH_2	DIKPIP01
	>CH_2	>CHMe	DLALGL
	>CHMe (R)	>CHMe (S)	TRDMPP02
	>CMe_2	>CMe_2	BOCSIV
			SIHVAG
	>$CHCMe_2$ (R)	>$CHCMe_2$(S)	CLDVAL
	>C=CH(Ph)	>C=CH(Ph)	DESXOO
Tape II	>CMe_2	>$CHCH(Me)CH_2CH_3$ (S)	BOCSOB
	(R) >$CHCH_2SSCH_2CH$< (R)		CLCYST10
	>CMe_2	>$CHCH_2Ph$ (S)	COYRIR
	>C=CH_2	>C=CH_2	DAWSUP
	>$CHCH_2Ph$ (S)	>$CHCH_2Ph$ (S)	DUZDUX
	>CHMe (S)	>CHMe (S)	LCDMPP01
	>$CHCH_2CH_2SCH_3$ (S)	>$CHCH_2CH_2SCH_3$ (S)	SIKWEO
	>CH_2		CGLYTP
	>CH(OH) (S)		FEPFOV
	>CH_2		GLYTYR10
	>CHMe (S)	>$CHCH_2CO_2H$ (S)	FUPDUP
Layer	>CHMe (S)	>CHMe (R)	TRDMPP10
			JAGFOM

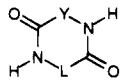
[a] The patterns of hydrogen bonds are shown schematically in Figure 18. [b] Substituent group separating the carbonyl groups and the amido nitrogen atoms of the amides. [c] Substituent group linking the carbonyl groups and the amido nitrogen atoms of the amides.

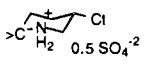
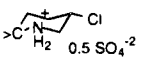
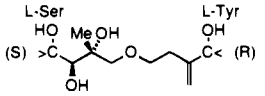
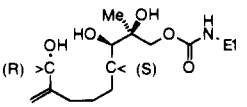
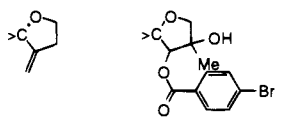
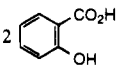
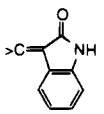
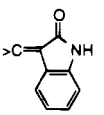
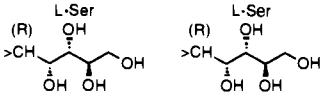
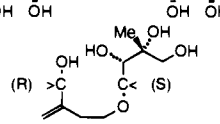
centers of symmetry. Although molecules of cyclo(DL-alanylglycyl) [DLALGL] have no internal symmetry, hydrogen bonds between racemates give centrosymmetric dimers in this structure.

The motif of tape II is based on dimers with a noncentrosymmetric configuration in which molecules are related by simple translation. Except for one structure, all diketopiperazines forming tape II have constituent molecules that are chiral. In most cases these diketopiperazines are derived from L-amino acids. Since the motif of tape II is polar, chiral diketopiperazines have excellent potential as building blocks for designing polar crystals.

Two diketopiperazines—cyclo(L-histidyl-D-histidyl) [JAGFOM] and cyclo(D-alanyl-L-alanyl) [TRDMPP-10]—form a layer motif (Figure 18c). The connectivity of hydrogen bonds in this pattern is similar to that observed in the polar layer motifs of directly joined HH and TT diamides. In this instance, the layer is nonpolar because the constituent molecules have a center of symmetry. The imidazole groups of cyclo(L-histidyl-D-histidyl) contain additional donors and

Table 10. Diketopiperazines Forming Hydrates, Hydrogen-Bonded Solvates, Cocrystals, or Having Substituents with Competing Hydrogen-Bonding Functionality



Y[a,b]	L[a,c]	Guest Molecules	Refcode
		5 H_2O	ANTSUL
L-His	L-Met	H_2O	BIMGEJ
L-Met	Gly	H_2O	BIVMUO
L-Leu	L-His	H_2O	CLEUHS
L-His	L-Asp	3 H_2O	CLHISP10
L-Thr	L-His	2 H_2O	CLTRHS
L-Leu	L-Tyr	H_2O	COPHOE
L-Ser	L-His	H_2O	CSEHSM
L-His	L-His	2.5 H_2O	DIKSIZ
L-Ser	L-Tyr	H_2O	SERTYR10
		H_2O	KOCJUH
		EtOH	SADCOP
		$CHCl_3$	HMOZST
L-Cys-L-Cys		CH_3CO_2H	CYLCYS
Gly	Gly	2 	DKPSAL
Gly	Gly	2 HCO_2H	KPIPFA
		2 $HCONMe_2$	VECTAY
L-Leu	L-Trp	·	BAGYOX
L-Asp	L-Asp	·	CANKEH
L-Ser	L-Ser	·	CYSESE
		·	SEGZAF
		·	BCYMYC

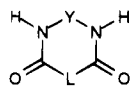
[a] Entries with a three-letter amino acid code refer to the corresponding side chain of the amino acid. [b] Substituent group separating the carbonyl group and the amido nitrogen atom of the amides. [c] Substituent group linking the carbonyl group and the amido nitrogen atom of the amides.

acceptors that participate in hydrogen bonding; these form chains of hydrogen bonds between imidazole rings in adjacent layers. This example nicely illustrates how the introduction of functional groups that do not compete with amide–amide hydrogen bonding might provide the basis for methods to control packing of extended aggregates such as tapes and layers.

Under different conditions of crystallization, cyclo(D-alanyl-L-alanyl) forms a second polymorphic modification (form II) [TRDMPP02], in which the molecules aggregate in the tape I motif.[187] A comparison of the crystal structures of forms I and II shows small differences in the conformations of the molecules in the two structures; accordingly, forms I and II are conformational polymorphs.

As with many amino acids and peptides, diketopiperazines are soluble in water and alcohols, and thus diketopiperazines are usually crystallized from these solvents. It is not surprising, therefore, to find that diketopiperazines frequently crystallize as hydrates or solvates. Inclusion of water or other hydrogen-bonding solvents is undesirable from the standpoint of crystal engineering, since these molecules often disrupt patterns of hydrogen bonds between amide groups. The entries in Table 10 suggest that diketopiperazines forming hydrates generally contain substituent groups that are capable of hydrogen bonding (e.g. diketopiperazines derived from His, Asp, Ser, etc.). Molecules with good donors or acceptors (e.g. carboxylic acids) can also disrupt the self-association of amides by forming cocrystalline complexes with diketopiperazines; Table 10 gives examples.

C. Separated TT Diamides



Separated tail-to-tail (TT) diamides are structurally similar to the separated HH diamides; in fact, structures with six-membered rings qualify both as TT and as HH diamides. All of the structures considered in this section belong to one class of separated TT diamides: the barbituric acids. The relationship between molecular structure and pharmaceutical activity of barbituric acids has been widely studied since Fischer and Von Mering discovered the hypnotic action of 5,5′-diethylbarbituric acid in 1903. Doran has reviewed the structures, physical and chemical properties, and pharmacological activities of several hundred different barbiturates.[188] The molecular details of the interaction of barbiturates with their receptors has not been established. Specific patterns of hydrogen bonds between barbituric acids and derivatives of adenine have been demonstrated.[189–193]

The arrangement of amide groups in barbituric acids give these molecules considerable flexibility in the patterns of hydrogen bonds that they form. The urea-like carbonyl group allows all of the modes of hydrogen bonding observed in the structures of joined HT diamides. The presence of a third carbonyl acceptor introduces the potential for even greater variability in the patterns of hydrogen bonds based on dimers. Figure 19 shows schematic drawings of the possible configurations of dimers. Of these configurations, *i*, *v*, *viii*, and *x* are centrosymmetric, and thus any pairwise combination of dimers with these configurations gives nonpolar aggregates.

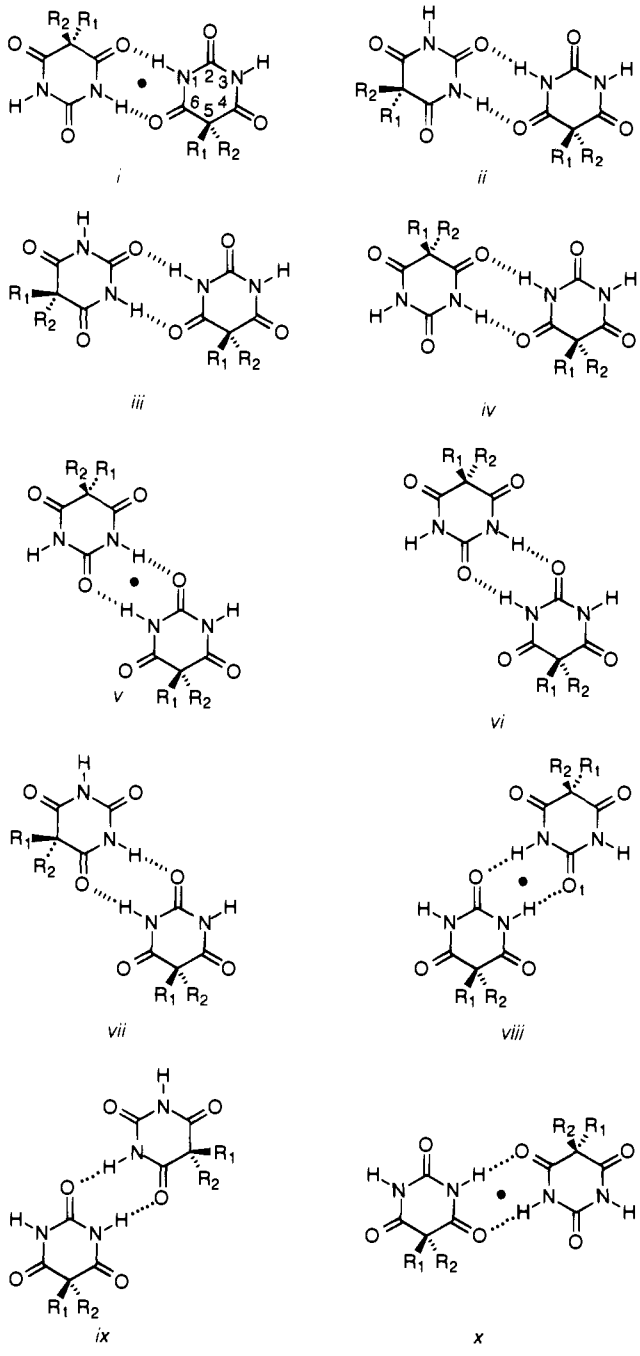
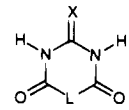


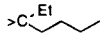
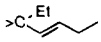
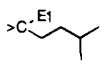
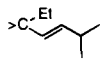
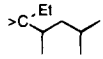
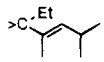
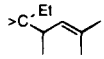
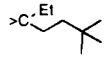
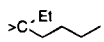
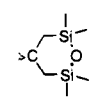
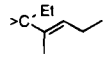
Figure 19. Possible configurations of dimers formed between barbituric acids. Dimers with centrosymmetric configurations (*i*, *v*, *viii*, and *x*) are indicated by a dot (•) at the center of symmetry.

The hydrogen-bonding motifs and molecular structures from 23 barbituric acid crystal structures are summarized in Figure 20 and in Table 11. We have not analyzed the patterns of hydrogen bonds of 65 barbituric acids that form hydrates, hydrogen-bonded solvates, cocrystals, or salts; Table 12 lists these barbituric acids.

Barbituric acids form two tape motifs (I and II), two ribbon motifs (I and II), and three layer motifs (I–III). Of these, tapes are the most common aggregate structure and occur in 18 structures. The molecules in tapes I and II are joined by pairs of dimers having centrosymmetric configurations *i*/*x* and *i*/*v*. In either pattern, two NH donors and two carbonyl acceptors are used in hydrogen bonding, leaving one carbonyl group unbonded. The oxygen

Table 11. Structural Information for Barbituric Acids



Motif[a]	X[b]	L[c]	Refcode
Tape I	O	>CEt$_2$	DETBAA02
	O		CBUSPY
	O		OXCBAR
	O		PHBARB
Tape II	O	>CEt$_2$	DETBAA01
	O		ETBBAR
	O		BEBWUA
	O		AMYTAL10
			AMYTAL11
	O		BECLIE
	O		MAOBAR
	O		BEBWOU
	O		JIFRIZ
	O		EMBBAR20
	O		AIPBAR
	O		DALLBA
	O		ETCYBA
	S		BEVYAC
Ribbon I	O		ENPBAR
Ribbon II	O	>CH$_2$	BARBAC
	O		ETBARB
	O		MPBRBL
	O		BEPHAF
Layer I	O	>CEt$_2$	DETBAA03
	O		VINBAR
Layer II	S	>CH$_2$	THBARB
Layer III	O		CHEBAR

[a] The patterns of hydrogen bonds are shown schematically in Figure 20. [b] Heteroatom acting as a hydrogen-bond acceptor. [c] Substituent group linking the carbonyl groups of the amides.

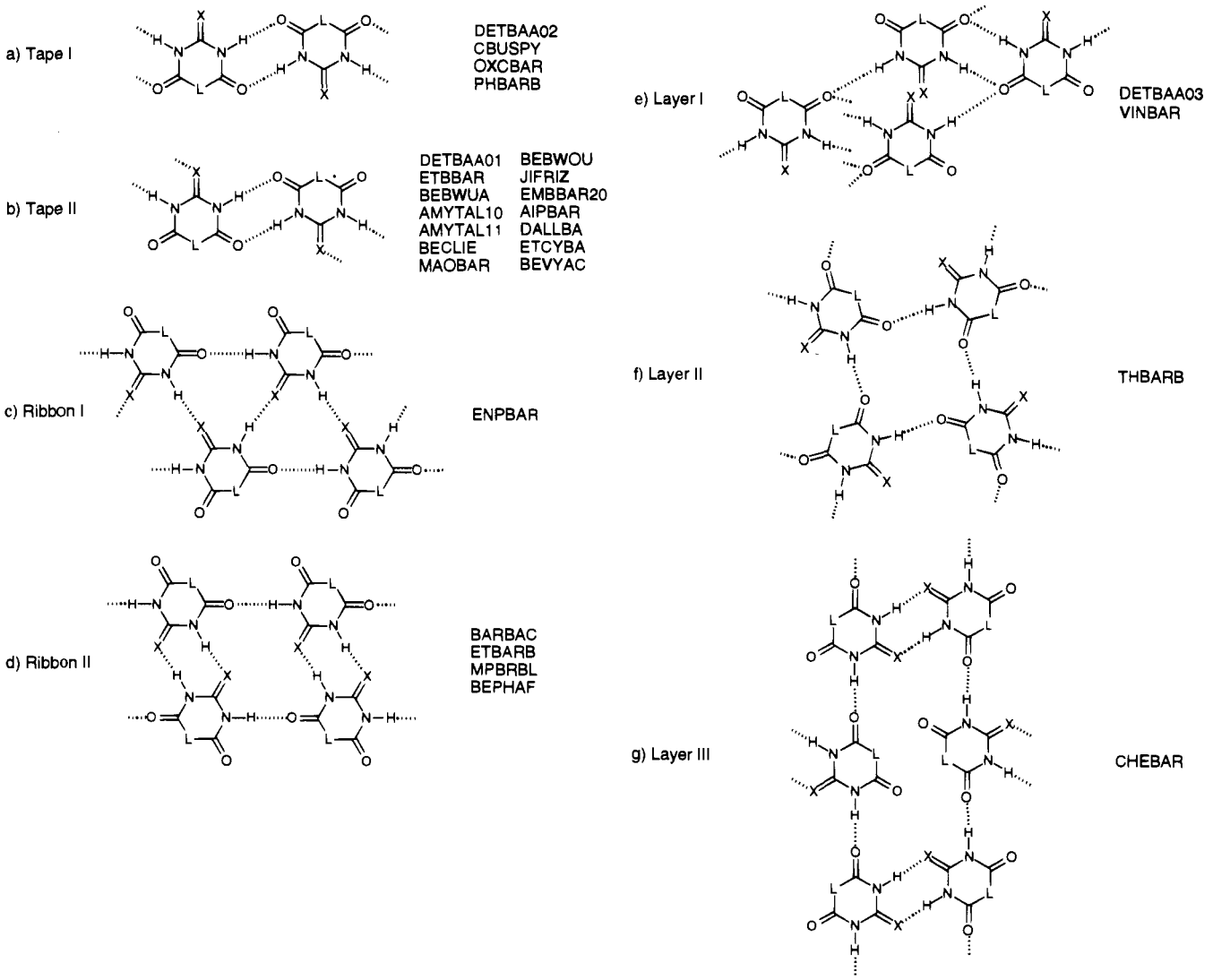


Figure 20. Patterns of hydrogen bonds found in crystals of barbituric acids. X denotes a heteroatom acting as a hydrogen-bond acceptor, and L represents a substituent group linking the carbonyl groups of the amides (Table 11).

atom of the urea-like carbonyl is a stronger acceptor than that of the amide-like carbonyl and should, according to Etter's rules, be used preferentially in hydrogen bonding.[80,96] This preference is indeed reflected in the fact that the relative frequency of occurrence of tape patterns I and II is one to four with barbituric acids.

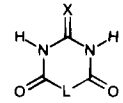
The molecules in ribbon I assemble with pairs of hydrogen-bonded chains that are aligned parallel (not antiparallel). These chains are then cross-linked by NH···O interactions, forming a polar ribbon. In ribbon II, centrosymmetric dimers (configuration *v*) hold adjacent chains in an antiparallel arrangement.

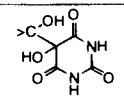
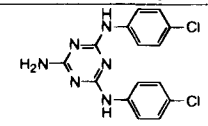
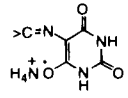
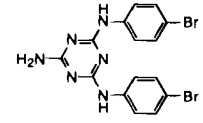
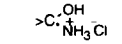
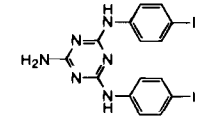
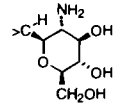
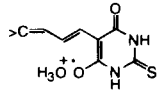
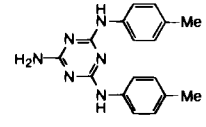
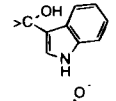
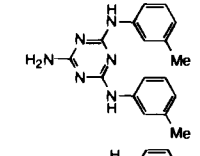
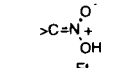
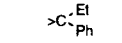
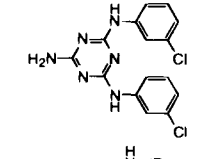
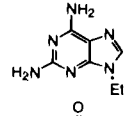
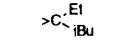
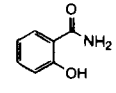
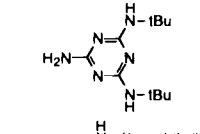
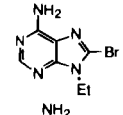
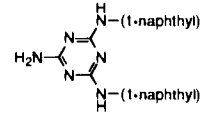
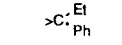
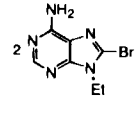
Layer I forms an unusual two-dimensional network of hydrogen bonds in which only one carbonyl group of the barbituric acid is used as an acceptor. Molecules of 2-thiobarbituric acid [THBARB] form a two-dimensional network of intersecting NH···O chains; this network is represented by layer II. The sulfur atom of the thiocarbonyl group is a much weaker acceptor than is the oxygen of a carbonyl group, and is not used in hydrogen bonding. Molecules of 5-(1′-cycloheptenyl)-5-ethylbarbituric acid [CHEBAR] form a third type of two-dimensional network (layer III) in which molecules form dimers that are further cross-linked by chains of NH···O interactions. Two of the three carbonyl groups are used in hydrogen bonding in this motif.

Substituted barbituric acids commonly crystallize in several different polymorphic forms, and this polymorphism has been studied extensively.[194-199] In one study, Cleverley and Williams characterized 20 barbituric and thiobarbituric acids using X-ray powder diffraction (XPD) and solid-state IR and found that nine compounds exhibited polymorphism.[200] In the case of 5-ethyl-5-phenylbarbituric acid, six polymorphs were detected by XPD. No correlation between molecular structure and the occurrence of polymorphism was established for these compounds.

Single crystals of three polymorphs of 5,5′-diethylbarbituric acid (barbital I, II, and IV) crystallize from the same ethanolic solution.[201] The crystal structures of barbital I [DETBAA02], II [DETBAA01], and IV [DETBAA03] show barbital molecules forming tape I, tape II, and layer I, respectively. Barbital I, which has the highest melting point of the three forms (range 190−176 °C), is the most stable structure: it shows the most efficient molecular packing and the best van der Waals overlap between the ethyl substituents of the three. The fact that all three polymorphs form under the same conditions of crystallization suggests that the

Table 12. Barbituric Acids Forming Hydrates, Hydrogen-Bonded Solvates, Cocrystals, or Having Substituents with Competing Hydrogen-Bonding Functionality



X[a]	L[b]	Guest Molecules	Refcode	X[a]	L[b]	Guest Molecules	Refcode
O		2 H_2O	ALANTD	O	$>CEt_2$		JICTOE
O		H_2O	AMPURM	O	$>CEt_2$		JICTUK
O	$>CH_2$	2 H_2O	BARBAD				
O		H_2O	CAGLEB	O	$>CEt_2$		JICVAS
O		3 H_2O	DINVIF				
S		H_2O	GEMCAC	O	$>CEt_2$		JICVEW
O	$>C(OH)_2$	3 H_2O	HBARBT				
O		2 H_2O	HINBAR	O	$>CEt_2$		JICVIA
O		3 H_2O	NBARBT				
O		H_2O	PHBARM	O	$>CEt_2$		JICVOG
O	$>CEt_2$		AEPDEB				
O			AMBSAM10	O	$>CEt_2$		JICVUM
O	>NH	H_2O 	BADCUR	O	$>C(CH_2-C_6H_4-Br)_2$		JICWAT
O		2 	BARAAD				

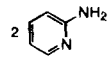
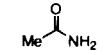
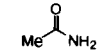
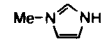
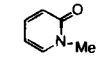
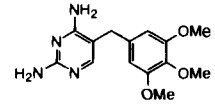
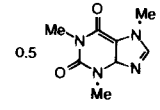
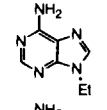
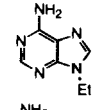
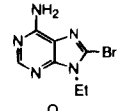
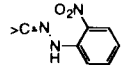
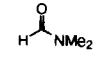
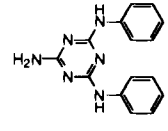
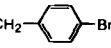
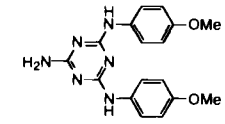
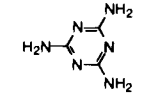
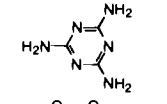
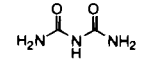
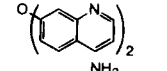
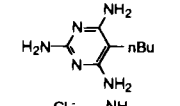
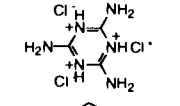
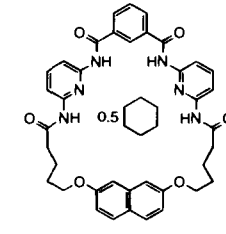
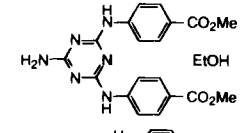
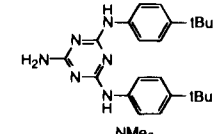
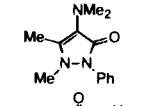
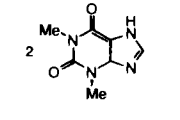
O	>CEt$_2$		BARAPY10
O	>CEt$_2$		BARBAM
O	>CEt$_2$		BARBUR10
O	>CEt$_2$	0.5 O=P(NMe$_2$)$_3$	BARHMP
O	>CEt$_2$		BARIMZ10
O	>CEt$_2$		BARMIM
O	>CEt$_2$		BARMPN
O	>CEt$_2$		BIGCUP
O	>CEt$_2$		CAFBAR20
O		13.5 H$_2$O	CIVBUE
		β-cyclodextrin	
O	>CEt$_2$	15.5 H$_2$O	DEVVAB
		β-cyclodextrin	
O	>CEt$_2$	12.5 H$_2$O	DEVVEF
		β-cyclodextrin	
O			EADBAC
O	>CEt$_2$		EADBAR10
O			EBAABB
O			FEGKAD
O	>CEt$_2$		JICTIY
O	>C(CH$_2$—  —Br)$_2$		JICWEX
O	>CBr$_2$		JICWIB
O	>CH$_2$		JICWOH
O	>NH		JOLSAE
O	>CEt$_2$		JUBRAZ
O	>CEt$_2$		KEGPUH
O	>NH		KEMWUU
O	>CEt$_2$		KOHJEW
O	>CEt$_2$		KUFPAC
O	>CEt$_2$		KUFPIK
O	>CEt$_2$		QQQEYV01
O			THOPBA

Table 12 (Continued)

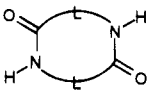
X^a	L^b	Guest Molecules	Refcode
O	>C=O	·	ALOXAN
O	>C(OH)$_2$	·	ALXANM01
O	>C(Et)(OH)	·	BARCOX
O	>C(Br)–N(Me)–C(=O)–	·	BMBARA10
O	>C(Me)–CH$_2$–CH$_2$–C(=O)–C$_6$H$_3$F–	·	DORFUL
O	>C(Et)–CH$_2$–CH$_2$–C(=O)–C$_6$H$_3$F–	·	DORGAS
O	>C(OMe)–NH–	·	FASFAG
O	>C(CONH$_2$)–CH$_2$–	·	HEBARB
O	>C(Et)(OH)–	·	KUKCAU
O	>C(CONH$_2$)–CH$_2$–C$_6$H$_4$–	·	ZZZAUP10
O	>C(OH)(CH$_3$)–CH$_2$–CH$_2$–	·	ZZZAUP10

[a] Heteroatom acting as a hydrogen-bond acceptor. [b] Substituent group linking the carbonyl groups of the amides.

aggregates in these structures are very similar in energy (within 1–2 kcal mol^{-1}).[116] This example clearly demonstrates the unpredictable variability in patterns of hydrogen bonds of barbituric acids and suggests that this class of compounds is sufficiently complex in its crystallization that it is presently a poor candidate for crystal engineering.

V. Amides Separated by More than One Atom

A. Large Cyclic Diamides



Large cyclic molecules containing two *cis* amide groups separated by two or more atoms represent a small but potentially useful class of diamides for making tapes. By definition, these molecules must have a minimum of eight atoms in the central diamide ring. Cyclo(di-β-alanyl) [DCBALA] is the simplest such compound and, surprisingly, it is the only large cyclic *cis* diamide whose crystal structure has been reported.[202] In this structure, molecules of cyclo(di-β-alanyl) adopt a boat conformation that places both amide groups pointing toward one side of the molecule. These U-shaped molecules self-assemble into tapes that buckle severely (Figure 21).

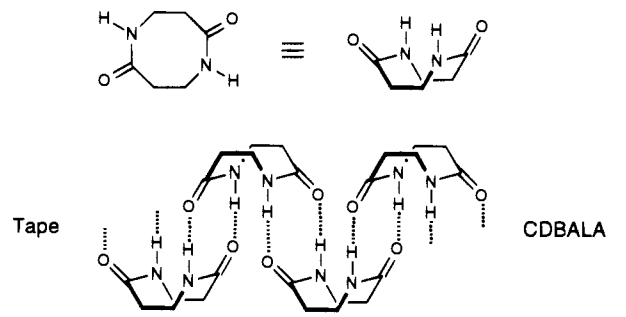
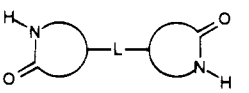


Figure 21. Tape motif formed by cyclo(di-b-alanyl) [CDBALA].

Our search for large cyclic diamides gave a number of compounds with ten-membered and larger sized rings. The amide groups in these structures are joined by flexible (alkyl or ether) linkers that allow for rotation about the C–N bond of the amide. Unlike HH, HT, and TT diamides (sections II–IV) where the amide groups are fixed in the *cis* conformation, all amide groups in these larger rings exist in the *trans* conformation, and this conformation prevents tapes from forming. These structures indicate that large flexible diamides are poor candidates for making tapes.

B. Linked Lactams



This class encompasses all molecules that have two lactam rings joined by a rigid or flexible linker (L). Wuest has demonstrated that bis-2-pyridones self-assemble in predictable motifs based on the complementarity (symmetry) of the NH donors and C=O

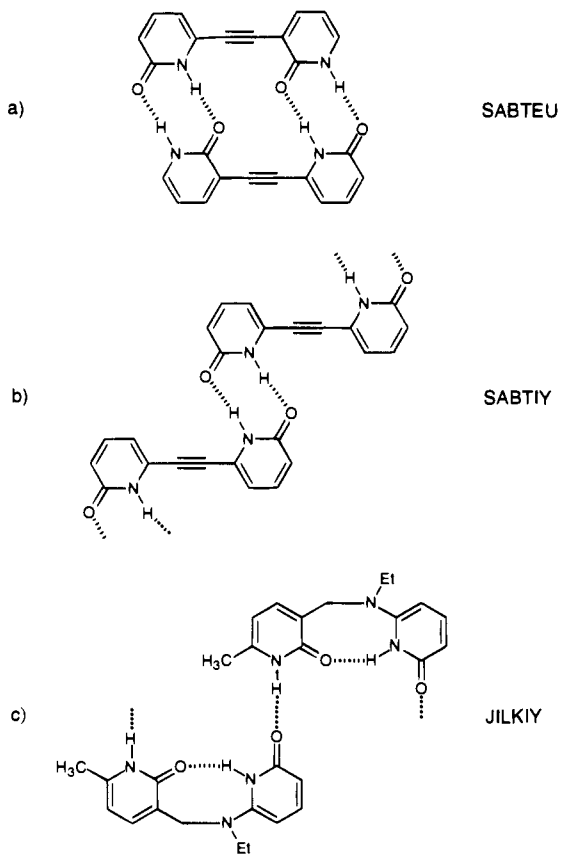


Figure 22. Patterns of hydrogen bonds of asymmetric and symmetric dipyridones. (a) Asymmetric dipyridone [SABTEU] with an acetylenic linker forms a dimer. (b) Symmetric dipyridone [SABTIY] with an acetylenic linker forms a tape. (c) Asymmetric dipyridone [JILKIY] with a flexible linker forms an intramolecular hydrogen bond and a chain.

acceptors. For example, asymmetric dipyridones joined by an acetylenic linker form a dimer while symmetric dipyridones form tapes (Figure 22a,b).[203] On switching to a more flexible linker, intramolecular hydrogen bonding becomes a competing factor (Figure 22c).[204]

In the acetylene-linked dipyridone systems, it is difficult to control the orientation of the pyridone rings along the tape axis, and hence, the symmetry of the resulting aggregate, because of free rotation of about the acetylenic linker. Lactams linked with rigid groups do not have this type of conformational flexibility. The structures of four compounds containing rigid linkers are shown in Figure 23. Of these, three form tapes (*i*–*iii*) and one forms a layer pattern. It is interesting that 2,7-diazaspiro[4.4]-nonane-1,6-dione [DSZNDO10] and 1,6-diazaspiro-[4.4]nonane-2,7-dione [ASPNOD], which differ only in the positions of the amide groups in the ring, crystallize in different motifs. The occurrence of different motifs may be attributed, in part, to the fact that the enantiomers of 1,6-diazaspiro[4.4]nonane-2,7-dione (layers) were resolved during crystallization,[205] while molecules of 2,7-diazaspiro[4.4]nonane-1,6-dione (tapes) formed racemic crystals.[206] Spontaneous resolution of enantiomers of 1,6-diazaspiro[4.4]nonane-2,7-dione into separate crystals—a process known as conglomeration—suggests that, in this case, layers containing a single enantiomer pack more efficiently than tapes or layers containing

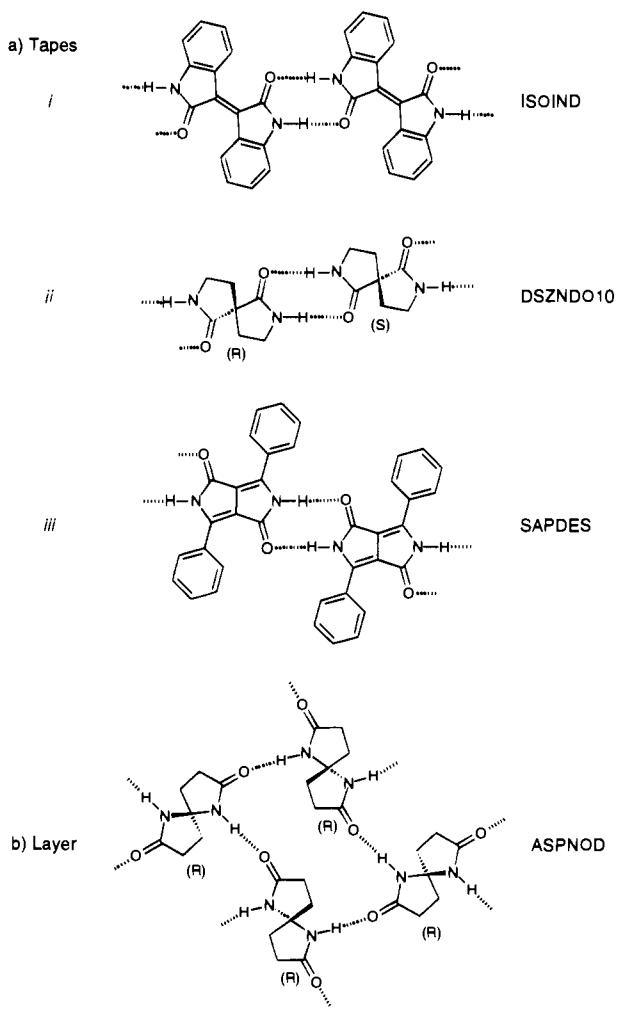


Figure 23. Patterns of hydrogen bonds formed by lactams with rigid linkers. (a) Tape *ii* contains alternating *R* and *S* enantiomers of 2,7-diazaspiro[4.4]nonane-1,6-dione [DSZNDO10]. (b) The layer (and entire crystal) contains only one enantiomer of 1,6-diazaspiro[4.4]nonane-2,7-dione [ASPNOD].

racemates. The fact that conglomerates form at all is surprising since, according to Kitaigorodsky's close-packing principle, molecules related by inversion (racemates) pack more efficiently than those related by translation or rotation (single enantiomers).[207] Brock and Dunitz have also suggested that crystals containing racemic pairs of molecules may be favored over their chiral counterparts simply because there are more possibilities for favorable packing arrangements in racemic space groups.[208]

VI. More than Two Amides Connected by a High Symmetry Core

This review has focused on molecules with two amide groups as candidate structures for efforts in crystal engineering. Intermolecular interactions involving two different amides often generate linear aggregates. Incorporating additional amide functionality should, in principle, promote formation of two- or three-dimensional networks of hydrogen bonds. This section lists several interesting examples of such structures, but does not provide a comprehensive review of them.

Cyanuric acid [CYURAC01] is the simplest molecule in this class of amides. This compound crystal-

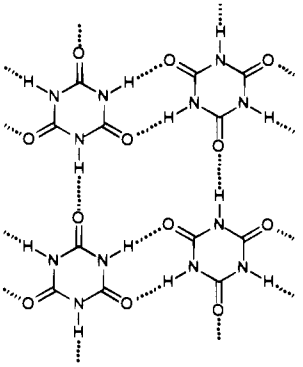


Figure 24. Layer motif found in the crystal structure of cyanuric acid [CYURAC01].

lizes in a layer motif (Figure 24). Interestingly, the internal 3-fold symmetry of this compound is not reflected in the patterns of hydrogen bonds. Two of the −NHCO− groups on opposite sides of the molecule form tapes similar to those formed by HH diamides (section IV.A). These tapes are linked in the second dimension by chains of hydrogen bonds between the remaining NH and C=O groups. This structure is compatible with the idea that N-monosubstituted cyanuric acids should exhibit patterns of hydrogen bonding similar to barbituric acids (section IV.C).

Wuest recently demonstrated a wonderful example of crystal engineering in which hydrogen bonds were used to create specific structural features. He demonstrated that self-assembly of a rigid tetrapyridone [VOJFAB] produces a diamondoid network with large internal chambers (Figure 25) and that this network selectively enclathrates guest molecules present during crystallization.[136] This strategy to control molecular aggregation with tetrahedrally disposed pyridones is particularly elegant since Wuest *predicted* the three-dimensional structure based on knowledge of the hydrogen-bonding motifs preferred by dipyridones.

VII. Concluding Remarks

The constrained diamides covered in this review present a wide range of structures potentially useful for crystal engineering. We have focused primarily on molecules that form tapes, because these rigid, linear aggregates simplify the packing problem by imposing predictable structural order in crystals. All but one class of diamides we surveyed (Table 2) form tapes. This fact is remarkable considering the range of possible packing patterns. Not surprisingly, many cyclic diamides also form structures other than tapes, including dimers, ribbons, layers, and three-dimensional motifs. While these structures are interesting in their own right as motifs for crystal engineering, the frequency with which tapes occur, and the large number of tapes that form relative to other motifs make tapes the motif of choice for designing crystals based on diamides.

One of our primary goals has been to identify molecules that form *functionalized* tapes. In other words, we want molecules that are easily modifiable, that are easy to synthesize, that form tapes that are robust when substituted with a range of functional groups, and that have interesting chemical or optical properties. On the basis of the structures of the

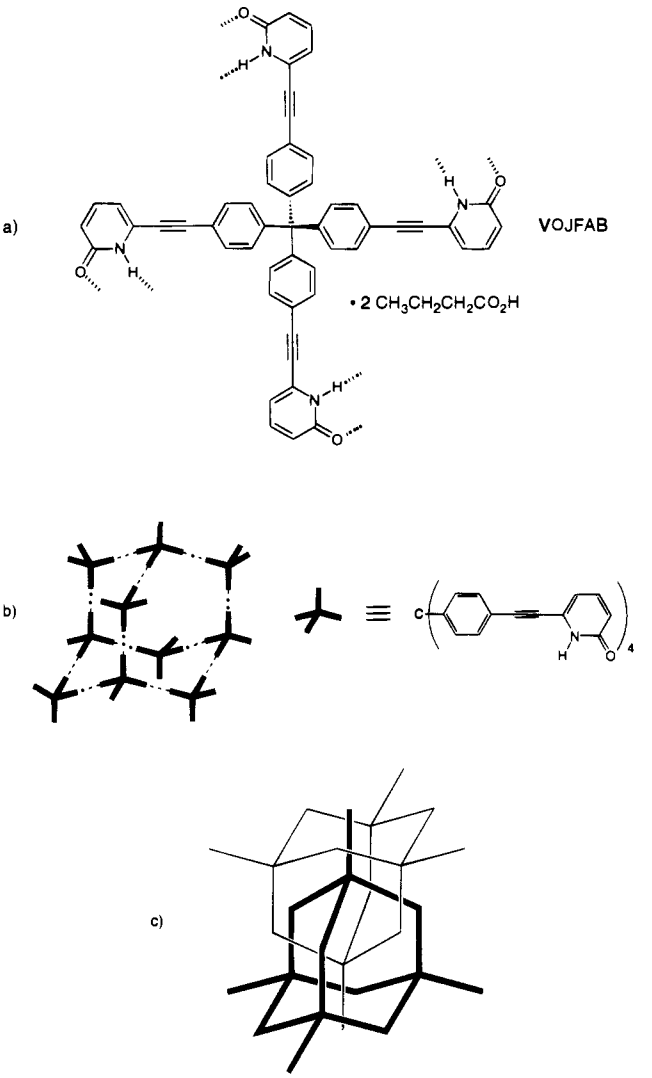


Figure 25. (a) Tetrakis(4-((6-oxopyrid-2-yl)ethynyl)phenyl)methane bis(butyric acid) clathrate [VOJFAB], (b) a schematic drawing of the three-dimensional diamondoid network of hydrogen bonds formed by the rigid tetrapyridone host, and (c) large chambers generated by the "host" lattice partially filled by six independent interpenetrating "guest" lattices and by molecules of carboxylic acids (butyric, isobutyric, valeric, or isovaleric) that are trapped during crystallization. A host lattice (thick lines) and one interpenetrating guest lattice (thin lines) are represented schematically.

diamides in this review, we infer that patterns of hydrogen bonds and crystal packing are determined, in part, by specific structural features of the molecules. The most important features of diamides to consider for making tapes are summarized below:

(1) *Equal Number of Donor and Acceptor Sites.* For tapes to form, a molecule should ideally have an equal number of NH donors and C=O acceptors. For example, cyclic imides have two C=O acceptors but only one NH donor, and thus they form only chains or dimers (Figure 6) in which one C=O group remains unbonded. In the case of cyclic ureas, which have one C=O acceptor and two NH donors, the C=O group is able to accommodate both NH donors by forming a hydrogen bond at each of the lone pairs of the oxygen atom. An imbalance in donors or acceptors increases the number of possible hydrogen-bonding motifs that can form, as examplified by barbituric acids.

(2) *Rigidity of the Diamide Ring.* Flexible alkyl linkers allow the central ring of diamides to deviate from planarity. Twisting of the NH and C=O groups out of the plane of the ring causes tapes to buckle (e.g. HPYDZO10, Figure 11; and CDBALA, Figure 21) or, perhaps, not form at all.

(3) *Size of the Diamide Ring.* Small cyclic rings (≤8 atoms) constrain secondary amide groups to the *cis* conformation and, thus, promote dimeric hydrogen-bonding interactions between amides. In large rings (>8 atoms) amide groups adopt the *trans* conformation; this conformation precludes the formation of tapes.

(4) *Steric Bulk of Substituents.* The size of substituents affects the type of motif adopted by diamides. For example, the small number of diketopiperazines forming layers relative to those forming tapes suggests that tapes are preferred because of unfavorable steric interactions between neighboring substituent groups in layers.

(5) *Proximity and Configuration of Donors and Acceptors.* The proximity and the configuration of NH donors and C=O acceptors determine, in part, the patterns of hydrogen bonds that form. For example, the close proximity of adjacent C=O groups in 5-chloro-7-nitro-2,3-dihydroxyquinoxaline [CNIXQX] (Figure 8) enables bifurcated O···NH···O interactions to form; this type of hydrogen bond prevents tapes from forming. In the structures of joined HT diamides (section III.C), the head-to-tail arrangement of adjacent amide groups allows these compounds to form dimeric interactions (configuration *vi*, Figure 15) that give unique ribbon (Figure 16e) and layer (Figure 16f) motifs.

(6) *Competing Hydrogen-Bonding Groups.* Substituents or solvent molecules with functional groups that compete with amide−amide hydrogen bonding can prevent tapes from forming (e.g. SAZGOP, Figure 12; and DHBPHT, Figure 13).

Among the more promising classes of cyclic diamides for designing tapes are (1) cyclic ureas (section II.A), (2) cyclic diacylhydrazides (section III.B), and (3) diketopiperazines (section IV.B). These three classes of diamides are attractive because the majority of these compounds crystallize as tapes and can be easily synthesized. Moreover, a variety of functional groups can be incorporated into these types of molecules without disrupting the tape motif. Introducing aromatic rings in cyclic ureas and cyclic diacylhydrazides as part of the linker should increase the rigidity of tapes and increase their packing efficiency by reducing conformational flexibility of the ring. Moreover, an aromatic ring also allows for a number of different substituent groups to be introduced on the periphery of the tape. Examples of potentially useful diamides from each of these classes are shown in Figure 26.

Many of the diamides we have examined exhibit polymorphism. In some cases, these polymorphs have different patterns of hydrogen bonds. For example, molecules of cyclo(D-alanyl-L-alanyl) crystallize in both tapes and layers (TRDMPP02 and TRDMPP10, respectively, Figure 18). For compounds such as barbituric acids, polymorphism appears to be the norm rather than the exception. Indeed, McCrone[121] has suggested that all compounds

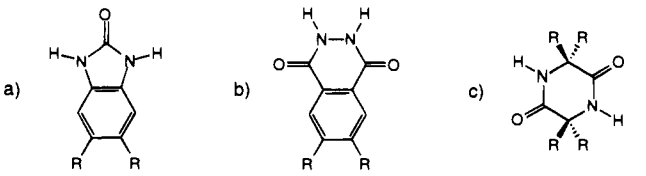


Figure 26. Hypothetical examples of cyclic diamides for designing functional tapes: (a) cyclic ureas, (b) cyclic diacylhydrazides, and (c) diketopiperazines. Rigid linkers in a and b reduce flexibility in the diamide ring.

have polymorphs and that the number of polymorphic modifications known for a compound is a function of the effort spent on that compound. Even when polymorphs are not found, we cannot be sure whether packing patterns in a given crystal are thermodynamically or kinetically determined until systematic studies of crystallization are performed. Studies directed toward the origin of polymorphism are still uncommon.

Surprisingly, there is little evidence for structures that form three-dimensional patterns of hydrogen bonds. The most likely explanation for the scarcity of these patterns is that the molecules studied generally have planar or nearly planar structures. Since NH donors prefer to approach in the plane of the C=O group, the resulting aggregate is usually planar and two dimensional. Another factor that may contribute to the infrequency with which three-dimensional motifs occur is the equal balance between donors and acceptors in most of the diamides we have examined. When a tape or layer forms between cyclic diamides, all donors and acceptors are used in hydrogen bonding. A three-dimensional pattern is more likely to form if unbonded donors or acceptors are still available after these patterns form.

The wide range in patterns of hydrogen bonds found in several classes of cyclic diamides that have similar structures is both intriguing and puzzling. For example, tape I and tape II for barbituric acids differ only in terms of which carbonyl acceptor is used in hydrogen bonding. In the case of 5,5-diethylbarbituric acid, these tapes are found in different polymorphs, suggesting that the difference in energy between the two structures is on the order of kT (*ca.* 2.5 kJ/mol at room temperature) or less.[40] It is difficult to determine, however, whether differences in energy between polymorphs of barbituric acids are caused by packing effects or differences in the strengths of the hydrogen bonds. Moreover, it is almost impossible to predict *a priori* which structure will form. When designing tapes, this problem is best avoided by choosing molecules with an equal number of donors and acceptors.

VIII. Acknowledgments

This work was supported by The National Science Foundation through Grant CHE-91-22331 to G.M.W. and by the Merck Corporation through a fellowship award to J.C.M.

IX. Appendix

Refcodes, compounds names, and references for all structures reported in this review are listed in Chart 1. All were found in the Cambridge Structural Database.

Chart 1

[AEPDEB] 2,6-Diamino-9-ethylpurine-5,5-diethylbarbituric acid ($C_7H_{10}N_6$,$C_8H_{12}N_2O_3$). G. J. Bunick, D. Voet (1976) A. C. A. (Winter), 30.

[AIPBAR] 5-Allyl-5-isopropylbarbituric acid (Aprobarbital i,form i) ($C_{10}H_{14}N_2O_3$). A. D. Rae (1975) Cryst. Struct. Commun., 4, 457.

[ALANTD] Alloxantin dihydrate ($C_8H_6N_4O_8$,$2H_2O$). C. Singh (1965) Acta Crystallogr., 19, 767.

[ALOXAN] Alloxan ($C_4H_2N_2O_4$). N. Bolton (1964) Acta Crystallogr., 17, 147.

[ALXANM01] 5,5-Dihydroxybarbituric acid (Alloxan monohydrate) ($C_4H_4N_2O_5$). J. M. Harrowfield, B. W. Skelton, A. A. Soudi, A. H. White (1989) Aust. J. Chem., 42, 1795.

[AMBSAM10] 5-Ethyl-5-isoamylbarbituric acid-salicylamide complex ($C_{11}H_{18}N_2O_3$,$C_7H_7N_1O_2$). I. -N. Hsu, B. M. Craven (1974) Acta Crystallogr., B30, 843.

[AMPURM] Ammonium purpurate monohydrate (Murexide) ($C_8H_4N_5O_6{}^1{}^-$,$H_4N_1{}^1{}^+$,H_2O). R. L. Martin, A. H. White, A. C. Willis (1977) J. Chem. Soc., Dalton Trans., 1336.

[AMYTAL10] 5-Ethyl-5-isoamylbarbituric acid (Amobarbital,form i) ($C_{11}H_{18}N_2O_3$). B. M. Craven, E. A. Vizzini (1969) Acta Crystallogr., B25, 1993.

[AMYTAL11] 5-Ethyl-5-isoamylbarbituric acid (Amobarbital,form ii) ($C_{11}H_{18}N_2O_3$). B. M. Craven, E. A. Vizzini (1969) Acta Crystallogr., B25, 1993.

[ANTSUL] Antibiotic 593A sulfate pentahydrate (absolute configuration) ($C_{14}H_{24}Cl_2N_4O_2{}^2{}^+$,$O_4S_1{}^2{}^-$,$5H_2O$). G. R. Pettit, R. B. Von Dreele, D. L. Herald, M. T. Edgar, H. B. Wood Junior (1976) J. Am. Chem. Soc., 98, 6742.

[APYFEB] Perhydropyrimidin-2-one ($C_4H_8N_2O_1$). S. Calogero, U. Russo, A. Del Pra (1980) J. Chem. Soc., Dalton Trans., 646.

[AZBIOT10] (+-)-Azabiotin hydrochloride monohydrate ($C_{10}H_{18}N_3O_3{}^1{}^+$,$Cl_1{}^1{}^-$,$H_2O$). M. D. Glick, H. C. Wormser, H. N. Abramson (1977) Acta Crystallogr., B33, 1095.

[AZOCTA] 3,6,8-Thiadiazabicyclo(3.3.0)octan-7-one ($C_5H_8N_2O_1S_1$). G. T. DeTitta, R. H. Blessing, W. Stallings (1979) Am. Cryst. Assoc., Ser. 2, 7, 52.

[AZOCTB] 3,6,8-Oxadiazabicyclo(3.3.0)octan-7-one ($C_5H_8N_2O_2$). G. T. DeTitta, R. H. Blessing, W. Stallings (1979) Am. Cryst. Assoc., Ser. 2, 7, 52.

[AZOCTC] 2,4,7-Triazabicyclo(3.3.0)octan-3-one ($C_5H_9N_3O_1$). G. T. DeTitta, R. H. Blessing, W. Stallings (1979) Am. Cryst. Assoc., Ser. 2, 7, 52.

[AZTHYM10] 6-Azathymine ($C_4H_5N_3O_2$). P. Singh, D. J. Hodgson (1975) Acta Crystallogr., B31, 2519.

[AZURAC01] 6-Azauracil ($C_3H_3N_3O_2$). J. N. Brown, L. M. Trefonas, A. F. Fucaloro, B. G. Anex (1974) J. Am. Chem. Soc., 96, 1597.

[BADCUR] 8-Bromo-9-ethyladenine-cyanuric acid monohydrate ($C_7H_8Br_1N_5$,$C_3H_3N_3O_3$,H_2O). H. -S. Shieh, D. Voet (1976) Acta Crystallogr., B32, 2354.

[BAGYOX] Cyclo(L-leucyl-L-tryptophyl) ($C_{16}H_{19}N_3O_2$). T. Shiba, H. Uratani, I. Kubota, Y. Sumi (1981) Biopolymers, 20, 1985.

[BARAAD] 5-Ethyl-5-phenylbarbituric acid-8-bromo-9-ethyladenine complex ($C_{12}H_{12}N_2O_3$,$2C_7H_8Br_1N_5$). S. H. Kim, A. Rich (1968) Proc. Nat. Acad. Sci. U. S. A., 60, 402.

[BARAPY10] 5,5-Diethylbarbituric acid-bis(2-aminopyridine) complex ($C_8H_{12}N_2O_3$,$2C_5H_6N_2$). I. -N. Hsu, B. M. Craven (1974) Acta Crystallogr., B30, 994.

[BARBAC] Barbituric acid ($C_4H_4N_2O_3$). W. Bolton (1963) Acta Crystallogr., 16, 166.

[BARBAD] Barbituric acid dihydrate ($C_4H_4N_2O_3$,$2H_2O$). G. A. Jeffrey, S. Ghose, J. O. Warwicker (1961) Acta Crystallogr., 14, 881.

[BARBAM] 5,5-Diethylbarbituric acid-acetamide complex ($C_8H_{12}N_2O_3$,$C_2H_5N_1O_1$). I. -N. Hsu, B. M. Craven (1974) Acta Crystallogr., B30, 974.

[BARBUR10] 5,5-Diethylbarbituric acid-urea complex ($C_8H_{12}N_2O_3$,$C_1H_4N_2O_1$). G. L. Gartland, B. M. Craven (1974) Acta Crystallogr., B30, 980.

[BARCOX] 5-(3-Oxocyclohexenyl)-5-ethyl-barbituric acid (3-Oxocyclobarbital) ($C_{12}H_{14}N_2O_4$). F. Chentli-Benchikha, J. P. Declercq, G. Germain, M. van Meerssche, R. Bouche, M. Draguet-Brughmans (1977) Acta Crystallogr., B33, 2739.

[BARHMP] bis(Barbital)-hexamethylphosphoramide complex ($2C_8H_{12}N_2O_3$,$C_6H_{18}N_3O_1P_1$). I. -N. Hsu, B. M. Craven (1974) Acta Crystallogr., B30, 1299.

[BARIMZ10] 5,5-Diethylbarbituric acid-imidazole complex ($C_8H_{12}N_2O_3$,$C_3H_4N_2$). I. -N. Hsu, B. M. Craven (1974) Acta Crystallogr., B30, 988.

[BARMIM] Barbital 1-methylimidazole ($C_8H_{12}N_2O_3$,$C_4H_6N_2$). A. Wang, B. M. Craven (1979) J. Pharm. Sci., 68, 361.

[BARMPN] 5,5-Diethylbarbituric acid-N-methyl-2-pyridone complex ($C_8H_{12}N_2O_3$,$C_6H_7N_1O_1$). I. -N. Hsu, B. M. Craven (1974) Acta Crystallogr., B30, 998.

Chart 1 (Continued)

[BCOCHY] cis-Bicyclo(3.3.0)octane-3-spiro-5'-hydantoin ($C_{10}H_{14}N_2O_2$). P. Smith-Verdier, F. Florencio, S. Garcia-Blanco (1979) Acta Crystallogr., B35, 216.

[BCYMYC] Bicyclomycin ($C_{12}H_{18}N_2O_7$). Y. Tokuma, S. Koda, T. Miyoshi, Y. Morimoto (1974) Bull. Chem. Soc. Jpn., 47, 18.

[BEBWOU] trans-5-Ethyl-5-(1',3'-dimethylbut-1'-enyl)-barbituric acid ($C_{12}H_{18}N_2O_3$). P. R. Andrews, G. P. Jones (1981) J. Cryst. Mol. Struct., 11, 135.

[BEBWUA] trans-5-Ethyl-5-but-2'-enyl-barbituric acid ($C_{10}H_{14}N_2O_3$). G. P. Jones, P. R. Andrews (1981) J. Cryst. Mol. Struct., 11, 125.

[BECLIE] 5-Ethyl-5-(3'-methylbut-2'-enyl)-barbituric acid ($C_{11}H_{16}N_2O_3$). G. P. Jones, P. R. Andrews (1981) J. Cryst. Mol. Struct., 11, 145.

[BEJTAL] 5,6-Dimethyl-12-hydroxy-1,3,8,10-tetra-azatetracyclo(8.3.2.0$5,14I.0$6,15I)pentadecane-2,4,7,9-tetraone(mul2$-2-Hydroxytrimethylene)-di-thymine-thymine cis-syn photodimer ($C_{13}H_{16}N_4O_5$). A. E. Koziol, A. Rajchel (1982) Acta Crystallogr., B38, 999.

[BEPHAF] 8,10-Diaza-2,4-disila-3-oxa-7,9,11-trioxo-2,2,4,4-tetramethyl-spiro(5.5)undecane ($C_{10}H_{18}N_2O_4Si_2$). I. L. Dubchak, V. E. Shklover, T. V. Timofeeva, Yu. T. Struchkov, A. A. Zhdanov, E. A. Kashutina, O. I. Shchegolikhina (1981) Zh. Strukt. Khim., 22, 147-5.

[BEPNIT] 5,5-Dimethyl-imidazolidine-2,4-dione (5,5-Dimethylhydantoin) ($C_5H_8N_2O_2$). R. E. Cassady, S. W. Hawkinson (1982) Acta Crystallogr., B38, 1646.

[BEVLIX] rel-(1R,6R,8R)-1-Methyl-3,5-dioxo-2,4-diazabicyclo(4.2.0)octane-8-spiro-2'-(oxetan)-4'-one ($C_9H_{10}N_2O_4$). T. Chiba, H. Takahashi, T. Kato, A. Yoshida, R. Moroi (1982) Chem. Pharm. Bull., 30, 544.

[BEVYAC] 5-Isopropyl-thiobarbituric acid ($C_7H_{10}N_2O_2S_1$). A. A. Dvorkin, S. G. Soboleva, Yu. A. Simonov, S. A. Andronati, T. I. Malinovskii (1982) Dokl. Akad. Nauk SSSR, 262, 99.

[BIGCUP] 2,4-Diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine 5,5-diethylbarbituric acid ($C_{14}H_{18}N_4O_3$,$C_8H_{12}N_2O_3$). N. Shimizu, S. Nishigaki, Y. Nakai, K. Osaki (1982) Acta Crystallogr., B38, 2309.

[BIMGEJ] Cyclo-(L-methionyl-L-histidine) monohydrate ($C_{11}H_{16}N_4O_2S_1$,H_2O). G. Valle (1982) Eur. Cryst. Meeting, 7, 190.

[BINDOX] (3aS-(3aalpha,4beta,6aalpha))-4-(3-(Indol-3-yl)-propyl)-hexahydro-2,5-alpha-dioxo-1H-thieno(3,4-d)-imidazole (Biotin(S,O)-C3-indole) ($C_{16}H_{19}N_3O_2S_1$). W. F. Paton, F. -T. Liu, I. C. Paul (1979) J. Am. Chem. Soc., 101, 1005.

[BIOIND] (3aS-(3aalpha,4beta,6aalpha))-4-(3-(Indol-3-yl) propyl)-hexahydro-2-oxo-1H-thieno(3,4-d)-imidazole hemihydrate (Biotin-C3-indole) ($C_{16}H_{19}N_3O_1S_1$,$0.5H_2O$). W. F. Paton, F. -T. Liu, I. C. Paul (1979) J. Am. Chem. Soc., 101, 1005.

[BIOTIN01] Biotin (Vitamin H) ($C_{10}H_{16}N_2O_3S_1$). G. T. DeTitta, J. W. Edmonds, W. Stallings, J. Donohue (1976) J. Am. Chem. Soc., 98, 1920.

[BIOTME10] Biotin methyl ester ($C_{11}H_{18}N_2O_3S_1$). G. T. DeTitta, R. Parthasarathy, R. H. Blessing, W. Stallings (1980) Proc. Nat. Acad. Sci. U. S. A., 77, 333.

[BIOTNA] Carbobiotin ($C_{11}H_{18}N_2O_3$). G. T. DeTitta, R. Parthasarathy, R. H. Blessing, W. Stallings (1980) Proc. Nat. Acad. Sci. U. S. A., 77, 333.

[BIOTNC] Selenobiotin ($C_{10}H_{16}N_2O_3Se_1$). G. T. DeTitta, R. Parthasarathy, R. H. Blessing, W. Stallings (1980) Proc. Nat. Acad. Sci. U. S. A., 77, 333.

[BIOTND] Biotin sulfone ($C_{10}H_{16}N_2O_5S_1$). G. T. DeTitta, R. Parthasarathy, R. H. Blessing, W. Stallings (1980) Proc. Nat. Acad. Sci. U. S. A., 77, 333.

[BIOTNE] Biotin-d-sulfoxide ($C_{10}H_{16}N_2O_4S_1$). G. T. DeTitta, R. Parthasarathy, R. H. Blessing, W. Stallings (1980) Proc. Nat. Acad. Sci. U. S. A., 77, 333.

[BIRZIL] 5-(2-(5-Chloro-2-methoxyphenyl-1-azo)-acetoacetamido)-benzimidazolone ($C_{18}H_{16}Cl_1N_5O_4$). K. Hunger, E. F. Paulus, D. Weber (1982) Farbe Lack, 88, 453.

[BIVMUO] Cyclo-L-methionyl-glycine trihydrate ($C_7H_{12}N_2O_2S_1$,$3H_2O$). M. Bressan, R. Ettore, F. Marchiori, G. Valle (1982) Int. J. Pept. Protein Res., 19, 402.

[BIZMAY] (+)-5-Fluoro-r-5-methoxycarbonyl-t-6-(alpha-methylbenzylamino)-5,6-dihydrouracil ($C_{14}H_{16}F_1N_3O_4$). O. Miyashita, T. Kasahara, Y. Wada (1982) Chem. Pharm. Bull., 30, 3005.

[BMBARA10] Bromo-meso-sarcosinuric acid ($C_8H_7Br_1N_4O_5$). C. Pascard-Billy (1970) Acta Crystallogr., B26, 1418.

[BOBHUV] r-4-Hydroperoxy-t-5-hydroxy-4-methylimidazolidin-2-one ($C_4H_8N_2O_4$). G. Rapi, M. Chelli, M. Ginanneschi, D. Donati, A. Selva (1982) J. Chem. Soc., Chem. Comm., 1339.

[BOCSIV] Cyclo-bis(alpha-aminoisobutyryl) ($C_8H_{14}N_2O_2$). K. Suguna, S. Ramakumar, N. Shamala, B. V. V. Prasad, P. Balaram (1982) Biopolymers, 21, 1847.

[BOCSOB] Cyclo(alpha-aminoisobutyryl-isoleucyl) ($C_{10}H_{18}N_2O_2$). K. Suguna, S. Ramakumar, N. Shamala, B. V. V. Prasad, P. Balaram (1982) Biopolymers, 21, 1847.

[BOFJAH] (2S,4S,6R)-2,6,7,9-Tetrahydro-2,4,6-tris(trichloromethyl)-8H-(1,3,5)triazino(1,2-c)(1,3,5)oxadiazin-8-one

Chart 1 (Continued)

dioxane solvate ($C_8H_5ClgN_4O_2$,$2C_4H_8O_2$). K. H. Pilgram, R. D. Skiles, E. J. Silveira, L. H. Gale, G. E. Pollard (1982) J. Org. Chem., 47, 3046.

[BRURAC10] 5-Bromouracil ($C_4H_3Br_1N_2O_2$). H. Sternglanz, C. E. Bugg (1975) Biochim. Biophys. Acta, 378, 1.

[BUXPOZ] cis-Tetrahydro-dipyrazino(1,2-a:2',1'-c)pyrazine-1,3,10,12(2H,4H,9H,11H)-tetrone ($C_{10}H_{12}N_4O_4$). A. Hempel, N. Camerman, A. Camerman (1983) J. Am. Chem. Soc., 105, 2350.

[CAFBAR20] bis(Barbital)-caffeine complex ($2C_8H_{12}N_2O_3$,$C_8H_{10}N_4O_2$). B. M. Craven, G. L. Gartland (1974) Acta Crystallogr., B30, 1191.

[CAGLEB] 5-Amino-5-hydroxy-1H,3H,5H-pyrimidine-2,4,6-trione hydrochloride monohydrate ($C_4H_6N_3O_4{}^1{}^+$,$Ch_1{}^1{}^-$,H_2O). M. Poje, B. Rocic, M. Sikirica, I. Vickovic, M. Bruvo (1983) J. Med. Chem., 26, 861.

[CANKEH] (3S,6S)-3,6-bis(Carbamoylmethyl)-piperazine-2,5-dione (Cyclo-(l-asparagyl-L-asparagyl)) ($C_8H_{12}N_4O_4$). C. Howes, N. W. Alcock, B. T. Golding, R. W. McCabe (1983) J. Chem. Soc., Perkin Trans. 1, 2287.

[CARVOG] 1,3-Dithiane-2-spiro-2'-(8-benzyloxymethyl-3-methoxy-11-oxo-O-thio-5,7,10,12-tetra-azatricyclo(7.3.0.0$1,5l)dodecane) hemihydrate ($C_{20}H_{26}N_4O_3S_3$,$0.5H_2O$). S. M. Hannick, Y. Kishi (1983) J. Org. Chem., 48, 3833.

[CBUSPY] Cyclobutane-1,5-spiro-2,4,6-triketo-hexahydropyrimidine ($C_7H_8N_2O_3$). G. Giacomello, P. Corradini, C. Pedone (1965) Gazz. Chim. Ital., 95, 1100.

[CDBALA] Cyclo(di-beta-alanyl) ($C_6H_{10}N_2O_2$). D. N. J. White, J. D. Dunitz (1972) Isr. J. Chem., 10, 249.

[CEPBZA] 7-Chloro-4-ethoxy-5-phenyl-1,3,5-tetrahydro-1,3-benzodiazepin-2-one dioxane monohydrate ($2C_{17}H_{17}Cl_1N_2O_2$,$0.5C_4H_8O_2$,H_2O). D. Mastropaolo, A. Camerman, N. Camerman, L. Chan (1979) Am. Cryst. Assoc., Ser. 2, 7, 22.

[CGLYTP] Cyclo(glycyl-tryptophyl) ($C_{13}H_{13}N_3O_2$). A. J. Morris, A. J. Geddes, B. Sheldrick (1974) Cryst. Struct. Commun., 3, 345.

[CHEBAR] 5-(1'-Cyclohepten-1'-yl)-5-ethylbarbituric acid ($C_{13}H_{18}N_2O_3$). J. -P. Bideau, F. Leroy, J. Housty (1969) C. R. Acad. Sci., Ser. C, 268, 1590.

[CIVBUE] beta-Cyclodextrin 5-ethyl-5-phenyl-barbituric acid clathrate hydrate (beta-Cyclodextrin phenobarbital clathrate hydrate) ($2C_{42}H_{70}O_{35}$,$2C_{12}H_{12}N_2O_3$,$27H_2O$). I. Nakanishi, T. Fujiwara, K. Tomita (1984) Acta Cryst., A40, C78.

[CLCYST10] Cyclo-L-cystine ($C_6H_8N_2O_2S_2$). K. I. Varughese, C. T. Lu, G. Kartha (1981) Int. J. Pept. Protein Res., 18, 88.

[CLDVAL] cyclo(L-Valyl-D-valyl) ($C_{10}H_{18}N_2O_2$). E. Benedetti (1976) Izv. Jug. Cent. Krist., Ser. A, 11, 151.

[CLEUHS] Cyclo(L-leucyl-L-histidyl) monohydrate ($C_{12}H_{18}N_4O_2$,H_2O). I. Tanaka, T. Iwata, N. Takahashi, T. Ashida, M. Tanihara (1977) Acta Crystallogr., B33, 3902.

[CLHISP10] Cyclo(L-histidyl-L-aspartyl) trihydrate ($C_{10}H_{12}N_4O_4$,$3H_2O$). R. Ramani, K. Venkatesan, R. E. Marsh (1978) J. Am. Chem. Soc., 100, 949.

[CLTRHS] Cyclo(L-threonyl-L-histidinyl) dihydrate ($C_{10}H_{14}N_4O_3$,$2H_2O$). M. Cotrait, M. Ptak, B. Busetta, A. Heitz (1976) J. Am. Chem. Soc., 98, 1073.

[CLURAC10] 5-Chlorouracil ($C_4H_3Cl_1N_2O_2$). H. Sternglanz, C. E. Bugg (1975) Biochim. Biophys. Acta, 378, 1.

[CNIXQX] 5-Chloro-7-nitro-2,3-dihydroxyquinoxaline ($C_8H_4Cl_1N_3O_4$). M. J. Grabowski, A. Stepien, M. Cygler, E. Wajsman (1977) Acta Crystallogr., B33, 2851.

[COPHOE] Cyclo-(L-leucyl-L-tyrosyl) monohydrate ($C_{15}H_{20}N_2O_3$,H_2O). K. Suguna, S. Ramakumar, K. D. Kopple (1984) Acta Cryst., C40, 2053.

[COYRIR] Cyclo(alpha-amino-isobutyryl-L-phenylalanyl) ($C_{13}H_{16}N_2O_2$). K. Suguna, S. Ramakumar, R. Nagaraj, P. Balaram (1985) Acta Cryst., C41, 284.

[CSEHSM] Cyclo(L-seryl-L-histidyl) monohydrate ($C_9H_{12}N_4O_3$,H_2O). M. Cotrait, M. Ptak (1978) Acta Crystallogr., B34, 528.

[CYLCYS] Cyclo-L-cystine acetic acid solvate ($C_6H_8N_2O_2S_2$,$C_2H_4O_2$). H. -C. Mez (1974) Cryst. Struct. Commun., 3, 657.

[CYSESE] Cyclo(L-seryl-L-seryl) ($C_6H_{10}N_2O_4$). G. G. Fava, M. F. Belicchi, R. Marchelli, A. Dossena (1981) Acta Crystallogr., B37, 625.

[CYTBGL] Cytosine-N-benzoylglycine complex monohydrate ($C_9H_8N_1O_3{}^1{}^-$,$C_4H_6N_3O_1{}^1{}^+$,H_2O). C. Tamura, T. Hata, S. Sato, N. Sakurai (1972) Bull. Chem. Soc. Jpn., 45, 3254.

[CYTRES10] bis(Cytosine) gamma-resorcylic acid complex monohydrate ($C_4H_6N_3O_1{}^1{}^+$,$C_4H_5N_3O_1$,$C_7H_5O_4{}^1{}^-$,H_2O). C. Tamura, S. Sato, T. Hata (1973) Bull. Chem. Soc. Jpn., 46, 2388.

[CYURAC01] Cyanuric acid ($C_3H_3N_3O_3$). P. Coppens, T. M. Sabine, A. Vos, R. G. Delaplane, J. A. Ibers (1968) A. C. A. (Summer), 67.

[DAFFIZ] (4S)-2,3-Dihydro-6-fluorospiro(4H-1-benzopyran-4,4'-imidazolidine)-2',5'-dione (Sorbinil) ($C_{11}H_9F_1N_2O_3$). C. R. Kissinger, E. T. Adman, J. I. Clark, R. E. Stenkamp (1985) Acta Cryst., C41, 988.

Chart 1 (Continued)

[DAFPEF] 2-Thioxo-quinazol-4-one ($C_8H_6N_2O_1S_1$). B. Tashkhodzhaev, S. Yangibaev, Kh. M. Shakhidayatov (1985) Zh. Strukt. Khim., 26, 155-1.

[DALLBA] 5,5-Diallyl-barbituric acid ($C_{10}H_{12}N_2O_3$). C. Escobar (1975) Acta Crystallogr., B31, 1059.

[DAWSUP] 3,6-Dimethylene-piperazine-2,5-dione (Cyclo-bis(dehydro-alanyl)) ($C_6H_6N_2O_2$). K. H. Ongania, G. Granozzi, V. Busetti, M. Casarin, D. Ajo (1985) Tetrahedron, 41, 2015.

[DCPYZO01] 4,5-Dichloro-3,6-pyridazinedione (Dichloromaleic hydrazide) ($C_4H_2Cl_2N_2O_2$). T. Ottersen (1973) Acta Chem. Scand., 27, 797.

[DEOXPZ] 4,4-Diethyl-3,5-dioxo-pyrazolidine ($C_7H_{12}N_2O_2$). O. Dideberg, L. Dupont, J. Toussaint (1974) Acta Crystallogr., B30, 2444.

[DESXOO] 3,6-bis(Phenylmethylene)-piperazine-2,5-dione (Cyclo-bis(dehydrophenylalanine)) ($C_{18}H_{14}N_2O_2$). D. Ajo, M. Casarin, R. Bertoncello, V. Busetti, H. C. J. Ottenheijm, R. Plate (1985) Tetrahedron, 41, 5543.

[DETBAA01] 5,5-Diethylbarbituric acid (Barbital,form i) ($C_8H_{12}N_2O_3$). B. M. Craven, E. A. Vizzini, M. M. Rodrigues (1969) Acta Crystallogr., B25, 1978.

[DETBAA02] 5,5-Diethylbarbituric acid (Barbital,form ii) ($C_8H_{12}N_2O_3$). B. M. Craven, E. A. Vizzini, M. M. Rodrigues (1969) Acta Crystallogr., B25, 1978.

[DETBAA03] 5,5-Diethylbarbituric acid (Barbital,form iv) ($C_8H_{12}N_2O_3$). B. M. Craven, E. A. Vizzini (1971) Acta Crystallogr., B27, 1917.

[DETBIO10] DL-Dethiobiotin ($C_{10}H_{18}N_2O_3$). C. -S. Chen, R. Parthasarathy, G. T. DeTitta (1976) J. Am. Chem. Soc., 98, 4983.

[DEVVAB] bis(beta-Cyclodextrin) bis(barbital) clathrate hentriacontahydrate (form I) ($2C_{42}H_{70}O_{35},2C_8H_{12}N_2O_3,31H_2O$). I. Nakanishi, M. Arai, T. Fujiwara, K. Tomita (1984) J. Inclusion Phenomena, 2, 689.

[DEVVEF] tetrakis(beta-Cyclodextrin) tetrakis(barbital) clathrate pentacontahydrate (form II) ($4C_{42}H_{70}O_{35},4C_8H_{12}N_2O_3,50H_2O$). I. Nakanishi, M. Arai, T. Fujiwara, K. Tomita (1984) J. Inclusion Phenomena, 2, 689.

[DHBPHT] 5,10-Dihydroxybenzo(g)phthalhydrazide acetic acid solvate ($C_{12}H_8N_2O_4,2C_2H_4O_2$). M. C. Apreda, C. Foces-Foces, F. H. Cano, S. Garcia-Blanco (1980) Eur. Cryst. Meeting, 6, 311.

[DHTHYM] Dihydrothymine ($C_5H_8N_2O_2$). S. Furberg, L. H. Jensen (1968) J. Am. Chem. Soc., 90, 470.

[DHTURC] 5,6-Dihydro-2-thiouracil ($C_4H_6N_2O_1S_1$). B. Kojic-Prodic, Z. Ruzic-Toros, E. Coffou (1976) Acta Crystallogr., B32, 1099.

[DHURAC10] Dihydrouracil ($C_4H_6N_2O_2$). D. C. Rohrer, M. Sundaralingam (1970) Acta Crystallogr., B26, 546.

[DIKPIP01] Diketopiperazine ($C_4H_6N_2O_2$). R. Degeilh, R. E. Marsh (1959) Acta Crystallogr., 12, 1007.

[DIKSIZ] Cyclo-(L-histidyl-L-histidyl) hydrate ($C_{12}H_{14}N_6O_2,2.5H_2O$). Y. Kojima, T. Yamashita, S. Nishide, K. Hirotsu, T. Higuchi (1985) Bull. Chem. Soc. Jpn., 58, 409.

[DINTAV10] 4,5-Dihydro-4,5-dimethoxy-1-methyluric acid ($C_8H_{12}N_4O_5$). M. Poje, I. Vickovic (1987) Acta Cryst., C43, 539.

[DINVIF] 5-(3-Amino-beta-D-glucopyranosyl)-barbituric acid trihydrate ($C_{10}H_{15}N_3O_7,3H_2O$). C. F. Conde, M. Millan, A. Conde, R. Marquez (1985) Eur. Cryst. Meeting, 9, 324.

[DIUREA] 1H,6H-3,3a,4,6a-Tetrahydroimidazo(4,5-d)imidazol-2,5-dione (Diurea,dimorph C) ($C_4H_6N_4O_2$). R. H. Blessing, G. T. DeTitta (1979) Am. Cryst. Assoc., Ser. 2, 7, 54.

[DIUREA01] 1H,6H-3,3a,4,6a-Tetrahydroimidazo(4,5-d)imidazol-2,5-dione (Diurea,dimorph P) ($C_4H_6N_4O_2$). R. H. Blessing, G. T. DeTitta (1979) Am. Cryst. Assoc., Ser. 2, 7, 54.

[DKPSAL] Diketopiperazine bis(salicylic acid) ($C_4H_6N_2O_2,2C_7H_6O_3$). G. Kartha, K. I. Varughese (1978) Acta Crystallogr., A34, S90.

[DLALGL] Cyclo(DL-alanyl-glycyl) ($C_5H_8N_2O_2$). T. Srikrishnan, P. K. S. Gupta, R. Parthasarathy (1977) Am. Cryst. Assoc., Ser. 2, 5, 34.

[DMGLUR] 3a,6a-Dihydro-3a,6a-dimethylimidazo(4,5-d)imidazole-2,5(1H,6H)-dione ($C_6H_{10}N_4O_2$). V. L. Himes, C. R. Hubbard, A. D. Mighell, A. J. Fatiadi (1978) Acta Crystallogr., B34, 3102.

[DORFUL] 5-Methyl-5-p-fluorobenzoylpropyl-barbituric acid ($C_{15}H_{15}F_1N_2O_4$). X. Xiaojie, J. Sheng, H. Yuzhen, T. Youqi, W. H. Xuebao (1985) Acta Phys. -Chim. Sin., 1, 207.

[DORGAS] 5-Ethyl-5-p-fluorobenzoylpropyl-barbituric acid ($C_{16}H_{17}F_1N_2O_4$). X. Xiaojie, J. Sheng, H. Yuzhen, T. Youqi, W. H. Xuebao(1985) Acta Phys. -Chim. Sin., 1, 207.

[DPACTS] Desalipactamycate tosylate (absolute configuration) ($C_{25}H_{31}N_3O_8S_1$). D. J. Duchamp (1972) A. C. A. (Winter), 23.

[DSEURC] 2,4-Diselenouracil ($C_4H_4N_2Se_2$). E. Shefter, M. N. G. James, H. G. Mautner (1966) J. Pharm. Sci., 55, 643.

[DTURAC] 2,4-Dithiouracil ($C_4H_4N_2S_2$). E. Shefter, H. G. Mautner (1967) J. Am. Chem. Soc., 89, 1249.

Chart 1 (Continued)

[DUNVEN] 3,5-Pyrazolidinedione ($C_3H_4N_2O_2$). G. Fritsch, G. Zinner, M. Beimel, D. Mootz, H. Wunderlich (1986) Arch. Pharm., 319, 70.

[DURXYF] (1S,2R,3R,4R)-1,2-Dideoxy-1,2-ureylene-D-xylofuranose (absolute configuration) ($C_6H_{10}N_2O_4$). G. A. Ellestad, D. B. Cosulich, R. W. Broschard, J. H. Martin, M. P. Kunstmann, G. O. Morton, J. E. Lancaster, W. Fulmor, F. M. Lovell (1978) J. Am. Chem. Soc., 100, 2515.

[DUZDUX] Cyclo(L-phenylalanyl-L-phenylalanyl) (3,6-Dibenzyl-2,5-piperazinedione) ($C_{18}H_{18}N_2O_2$). M. Gdaniec, B. Liberek (1986) Acta Cryst., C42, 1343.

[EADBAC] 9-Ethyladenine-5-isopropyl-5-bromoallylbarbituric acid complex ($C_7H_9N_5$,$C_{10}H_{13}Br_1N_2O_3$). D. Voet, A. Rich (1972) J. Am. Chem. Soc., 94, 5888.

[EADBAR10] 9-Ethyladenine-5,5-diethylbarbituric acid complex ($C_7H_9N_5$,$C_8H_{12}N_2O_3$). D. Voet (1972) J. Am. Chem. Soc., 94, 8213.

[EBAABB] 8-Bromo-9-ethyladenine-5-allyl-5-isobutylbarbituric acid ($C_7H_8Br_1N_5$,$C_{11}H_{16}N_2O_3$). R. H. Epstein, A. V. Zeiger, C. Crocker, D. Voet (1976) Acta Crystallogr., B32, 2180.

[EMBBAR20] 5-Ethyl-5-(3,3-dimethyl-n-butyl)-barbituric acid (gamma-Methylamobarbital) ($C_{12}H_{20}N_2O_3$). G. L. Gartland, B. M. Craven (1971) Acta Crystallogr., B27, 1909.

[EMURAC] 5-Ethyl-6-methyluracil ($C_7H_{10}N_2O_2$). G. N. Reeke Junior, R. E. Marsh (1966) Acta Crystallogr., 20, 703.

[ENPBAR] 5-Ethyl-5-(n-pentyl)-barbituric acid ($C_{11}H_{18}N_2O_3$). J. -P. Bideau, P. Marsau (1974) Cryst. Struct. Commun., 3, 511.

[EPHPMO] 5-Ethyl-5-phenyl-hexahydro-pyrimidine-4,6-dione (Primidone) ($C_{12}H_{14}N_2O_2$). D. G. R. Yeates, R. A. Palmer (1975) Acta Crystallogr., B31, 1077.

[ETBARB] 5-Ethylbarbituric acid (monoclinic form) ($C_6H_8N_2O_3$). B. M. Gatehouse, B. M. Craven (1971) Acta Crystallogr., B27, 1337.

[ETBBAR] 5-Ethyl-5-butyl-barbituric acid ($C_{10}H_{16}N_2O_3$). J. -P. Bideau (1971) C. R. Acad. Sci., Ser. C, 272, 757.

[ETCYBA] 5-(Cyclohexene-1'-yl)-5-ethyl-barbituric acid (Cyclobarbital) ($C_{12}H_{16}N_2O_3$). J. -P. Bideau, M. Artaud (1970) C. R. Acad. Sci., Ser. C, 271, 806.

[ETTHUR01] Imidazolidine-2-thione (Ethylenethiourea) ($C_3H_6N_2S_1$). T. C. W. Mak, K. S. Jasim, C. Chieh (1984) Can. J. Chem., 62, 808.

[FASFAG] 5-Methoxy-5-ureidobarbituric acid ($C_6H_8N_4O_5$). R. Faggiani, C. J. L. Lock (1986) Acta Cryst., C42, 1853.

[FEGKAD] Pyrimidine-2(1H),4(3H),5,6-tetraone 5-(2-nitrophenyl)hydrazone dimethylformamide solvate ($C_{10}H_7N_5O_5$,$C_3H_7N_1O_1$). H. G. Beaton, G. R. Willey, M. G. B. Drew (1987) J. Chem. Soc., Perkin Trans. 2, 469.

[FEMCEF] 5-Aza-6-methoxyuracil (1,2,3,4-Tetrahydro-6-methoxy-1,3,5-triazine-2,4-dione) ($C_4H_7N_3O_3$). R. Gilardi, C. George (1987) Acta Cryst., C43, 363.

[FEPFOV] (8S)-8-Hydroxymethyl-6,9-diazaspiro(4.5)decane-7,10-dione ($C_9H_{14}N_2O_3$). J. Symersky, K. Blaha, V. Langer (1987) Acta Cryst., C43, 303.

[FICBEY] 4-Benzyl-2-thiouracil ($C_{11}H_{10}N_2O_1S_1$). C. Delage, A. H'Naifi, M. Goursolle (1986) C. R. Acad. Sci., Ser. 2, 303, 1645.

[FILXED] 5,5-Dimethylimidazoline-2,4-dithione (5,5-Dimethyl-2,4-dithiohydantoin) ($C_5H_8N_2S_2$). F. A. Devillanova, F. Isaia, G. Verani, L. P. Battaglia, A. B. Corradi (1987) J. Chem. Res., 192, 1617.

[FILXIH] 5,5-Dimethyl-2-selenoxoimidazolidin-4-one (5,5-Dimethyl-2,4-selenohydantoin) ($C_5H_8N_2O_1Se_1$). F. A. Devillanova, F. Isaia, G. Verani, L. P. Battaglia, A. B. Corradi (1987) J. Chem. Res., 192, 1617.

[FILXON] 5,5-Dimethyl-4-selenoxoimidazolidine-2-thione (5,5-Dimethyl-2-seleno-4-thiohydantoin) ($C_5H_8N_2S_1Se_1$). F. A. Devillanova, F. Isaia, G. Verani, L. P. Battaglia, A. B. Corradi (1987) J. Chem. Res., 192, 1617.

[FINVON] (Z)-5-((4-Methoxyphenyl)methylene)imidazoline-2,4-dione ($C_{11}H_{10}N_2O_3$). M. G. B. Drew, K. F. Mok, K. P. Ang, S. F. Tan (1987) Acta Cryst., C43, 743.

[FOBZIF] 1,3-Dihydro-4-ethyl-5-(4-(1H-imidazol-1-yl)benzoyl)-2H-imidazol-2-one ($C_{15}H_{14}N_4O_2$). A. A. Hagedorn III, P. W. Erhardt, W. C. Lumma Junior, R. A. Wohl, E. Cantor, Yuo-Ling Chou, W. R. Ingebretsen, J. W. Lampe, D. Pang, C. A. Pease, J. Wiggins (1987) J. Med. Chem., 30, 1342.

[FORHAV] 5-(Diphenylphosphino)uracil ($C_{16}H_{13}N_2O_2P_1$). H. Zimmermann, M. Gomm, J. Ellermann, E. Kock (1987) Acta Cryst., C43, 1798.

[FUPDUP] cyclo-L-Aspartyl-L-alanyl ((3,6-Dioxo-5-methyl-2-piperazinyl)acetic acid) ($C_7H_{10}N_2O_4$). C. H. Gorbitz (1987) Acta Chem. Scand. Ser. B, 41, 83.

[FURACL] 5-Fluorouracil ($C_4H_3F_1N_2O_2$). L. Fallon III (1973) Acta Crystallogr., B29, 2549.

[GADPEG] trans-4,5-Dihydroxy-2-imidazolidinone ($C_3H_6N_2O_3$). E. Grillon, R. Gallo, M. Pierrot, J. Boileau, E. Wimmer (1988) Tetrahedron Lett., 29, 1015.

[GAXTII] 3a,8b-Dihydroxy-1,3,3a,8b-tetrahydroindeno(1,2-d)imidazole-2,4-dione monohydrate (Ninhydrylurea monohydrate) ($C_{10}H_8N_2O_4$,H_2O). R. Caputo, C. Ferreri, G. Palumbo, V. Adovasio, M. Nardelli (1987) Gazz. Chim. Ital., 117, 731.

Chart 1 (Continued)

[GEMCAC] Oxonium 5,5'-(propane-1,3-diylidene)-bis(2-thioxopyrimidine-4,6-dione) monohydrate ($C_{11}H_7N_4O_4S_2^-$,$H_3O_1^+$,H_2O). G. Read, R. Randal, M. B. Hursthouse, R. Short (1988) J. Chem. Soc., Perkin Trans. 2, 1103.

[GLYTYR10] Cyclo(glycyl-L-tyrosyl) ($C_{11}H_{12}N_2O_3$). C. -F. Lin, L. E. Webb (1973) J. Am. Chem. Soc., 95, 6803.

[GOHVUU] (1,2,4)Triazolo(1,2-a)(1,2,4)triazole-1,3,5,7(2H,6H)-tetrone (Urazourazole) ($C_4H_2N_4O_4$). E. Nachbaur, G. Faleschini, F. Belaj, R. Janoschek (1988) Angew. Chem., Int. Ed. Engl., 27, 701.

[HBARBT] 5,5-Dihydroxybarbituric acid trihydrate ($C_4H_4N_2O_5$,$3H_2O$). D. Mootz, G. A. Jeffrey (1965) Acta Crystallogr., 19, 717.

[HEBARB] 5-Hydroxy-5-ethylbarbituric acid ($C_6H_8N_2O_4$). B. M. Gatehouse, B. M. Craven (1971) Acta Crystallogr., B27, 1337.

[HINBAR] 5-Hydroxy-5-(3'-indole)-barbituric acid dihydrate ($C_{12}H_9N_3O_4$,$2H_2O$). Z. Taira, K. Osaki (1974) Cryst. Struct. Commun., 3, 369.

[HMOZST] 3-Hydroxy-3-methyl-12-methylene-4-(p-bromobenzoyloxy)-trans-1,9-dioxa-6,13-diazadispiro(4.2.4.2)tetradeca-7,14-dione chloroform solvate (absolute configuration) ($C_{19}H_{19}Br_1N_2O_7$,$C_1H_1Cl_3$). H. Magg, J. F. Blount, D. L. Coffen, T. V. Steppe, F. Wong (1978) J. Am. Chem. Soc., 100, 6786.

[HPYDZO10] Hexahydro-3,6-pyridazinedione ($C_4H_6N_2O_2$). T. Ottersen, J. Almlof (1978) Acta Chem. Scand. Ser. A, 32, 219.

[HQOXDO] 1,4-Dihydro-2,3-quinoxalinedione ($C_8H_6N_2O_2$). C. Svensson (1976) Acta Chem. Scand. Ser. B, 30, 581.

[HXIMOZ] 5alpha-(Hydroxymethyl)-4beta-(2-oxo-4-imidazolin-4-yl)-2-oxazolidinone ($C_7H_9N_3O_4$). G. A. Ellestad, D. B. Cosulich, R. W. Broschard, J. H. Martin, M. P. Kunstmann, G. O. Morton, J. E. Lancaster, W. Fulmor, F. M. Lovell (1978) J. Am. Chem. Soc., 100, 2515.

[ICRFRB10] (S)-(+)-4,4'-(1,2-Propanediyl)-bis(4-piperazine-2,6-dione) ($C_{11}H_{16}N_4O_4$). A. Hempel, N. Camerman, A. Camerman (1982) J. Am. Chem. Soc., 104, 3453.

[ICRFRC10] cis-Cyclopropyl-bis(dioxopiperazine) ($C_{11}H_{14}N_4O_4$). A. Hempel, N. Camerman, A. Camerman (1982) J. Am. Chem. Soc., 104, 3456.

[ICRFRD10] trans-Cyclopropyl-bis(dioxopiperazine) ($C_{11}H_{14}N_4O_4$). A. Hempel, N. Camerman, A. Camerman (1982) J. Am. Chem. Soc., 104, 3456.

[IURACL10] 5-Iodouracil ($C_4H_3I_1N_2O_2$). H. Sternglanz, G. R. Freeman, C. E. Bugg (1975) Acta Crystallogr., B31, 1393.

[JAGFOM] cyclo(L-Histidyl-D-histidyl) ($C_{12}H_{14}N_6O_2$). E. Benedetti, A. Bavoso, B. Di Blasio, V. Pavone, C. Pedone, L. Paolillo, M. D'Alagni (1988) Int. J. Pept. Protein Res., 31, 220.

[JAMKOX] 6,6-Diethylperhydro-1,4-diazepine-5,7-dione ($C_9H_{16}N_2O_2$). T. Borowiak, I. Wolska (1989) Acta Cryst., C45, 936.

[JEHMOY] (1R,5R)-1-p-Menth-3-yloxy-2,4-dimethyl-cis-2,4,6,8-tetra-azabicyclo(3.3.0)octane-3,7-dione ($C_{16}H_{28}N_4O_3$). N. Modric, M. Poje, I. Vickovic, M. Bruvo (1990) Acta Cryst., C46, 1336.

[JEZZOD] 3,5-Diazahexacyclo(5.4.0.0$2,6!.0$2,10!.0$6,9!.0$8,11!)undecan-4-one (Cubanourea) ($C_9H_8N_2O_1$). P. E. Eaton, K. Pramod, R. Gilardi (1990) J. Org. Chem., 55, 5746.

[JICTIY] 5,5-Diethylbarbituric acid N,N'-diphenylmelamine ($C_8H_{12}N_2O_3$,$C_{15}H_{14}N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICTOE] 5,5-Diethylbarbituric acid N,N'-bis(p-chlorophenyl)melamine ($C_8H_{12}N_2O_3$,$C_{15}H_{12}Cl_2N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICTUK] 5,5-Diethylbarbituric acid N,N'-bis(p-bromophenyl)melamine ($C_8H_{12}N_2O_3$,$C_{15}H_{12}Br_2N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICVAS] 5,5-Diethylbarbituric acid N,N'-bis(p-iodophenyl)melamine ($C_8H_{12}N_2O_3$,$C_{15}H_{12}I_2N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICVEW] 5,5-Diethylbarbituric acid N,N'-bis(p-tolyl)melamine ($C_8H_{12}N_2O_3$,$C_{17}H_{18}N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICVIA] 5,5-Diethylbarbituric acid N,N'-bis(m-tolyl)melamine ($C_8H_{12}N_2O_3$,$C_{17}H_{18}N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICVOG] 5,5-Diethylbarbituric acid N,N'-bis(m-chlorophenyl)melamine ($C_8H_{12}N_2O_3$,$C_{15}H_{12}Cl_2N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICVUM] 5,5-Diethylbarbituric acid N,N'-bis(t-butyl)melamine ($C_8H_{12}N_2O_3$,$C_{11}H_{22}N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICWAT] 5,5-bis(p-Bromobenzyl)barbituric acid N,N'-bis(1-naphthyl)melamine ($C_{18}H_{14}Br_2N_2O_3$,$C_{23}H_{18}N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

Chart 1 (Continued)

[JICWEX] 5,5-bis(p-Bromobenzyl)barbituric acid N,N'-bis(p-methoxyphenyl)melamine ($C_{18}H_{14}Br_2N_2O_3$,$C_{17}H_{18}N_6O_2$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICWIB] 5,5-Dibromobarbituric acid melamine ($C_4H_2Br_2N_2O_3$,$C_3H_6N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JICWOH] Barbituric acid melamine ($C_4H_4N_2O_3$,$C_3H_6N_6$). J. A. Zerkowski, C. T. Seto, D. A. Wierda, G. M. Whitesides (1990) J. Am. Chem. Soc., 112, 9025.

[JIFRIZ] 5-Ethyl-5-(1,3-dimethylbut-2-enyl)barbituric acid ($C_{12}H_{18}N_2O_3$). G. P. Jones, E. Horn (1986) J. Cryst. Spectrosc., 16, 629.

[JILKIY] N-Ethyl-1,2-dihydro-N-(1,6-dihydro-6-oxo-2-pyridinyl)-6-methyl-2-oxo-3-pyridinemethanamine ($C_{14}H_{17}N_3O_2$). M. Gallant, M. T. P. Viet, J. D. Wuest (1991) J. Org. Chem., 56, 2284.

[JOLSAE] tetrakis(Cyanuric acid) tetrabiuret ($4C_3H_3N_3O_3$,$4C_2H_5N_3O_2$). N. M. Stainton, K. D. M. Harris, R. A. Howie (1991) J. Chem. Soc., Chem. Comm., 1781.

[JUBRAZ] 6,6'-Diquinolyl ether 5,5-diethylbarbituric acid ($C_8H_{12}N_2O_3$,$C_{18}H_{12}N_2O_1$). L. Haixin, W. Xin, Z. Xinmin (1992) Acta Cryst., C48, 2096.

[KALZIG] 2-Imidazolidinone hemihydrate (Ethyleneurea hemihydrate) ($C_3H_6N_2O_1$,$0.5H_2O_1$). M. Kapon, G. M. Reisner (1989) Acta Cryst., C45, 780.

[KEGPUH] 5-t-Butyl-2,4,6-triaminopyrimidine diethylbarbituric acid ($C_8H_{15}N_5$,$C_8H_{12}N_2O_3$). J. -M. Lehn, M. Mascal, A. DeCian, J. Fischer (1990) J. Chem. Soc., Chem. Comm., 479.

[KEMWUU] Cyanuric acid melamine trihydrochloride ($C_3H_3N_3O_3$,$C_3H_9N_6^{3+}$,$3Cl^-$). Y. Wang, B. Wei, Q. Wang (1990) J. Cryst. Spectrosc., 20, 79.

[KESWOU] 5-Cycloheptatrienylidene-2,4-imidazolidinedione ($C_{10}H_8N_2O_2$). N. C. Mathur, H. Shechter (1990) J. Org. Chem., 55, 3001.

[KIVDOI] 4,5,6,7-Tetrahydro-1,3-benzimidazole-2-thione ($C_7H_{10}N_2S_1$). Y. Kitano, A. Ishitani, H. Sato, S. Imamura, T. Ashida (1991) Acta Cryst., C47, 1269.

[KOCJUH] (1R,2S,3S,9R)-1,2,3,9-Tetrahydroxy-3-methyl-8-methylene-5-oxa-10,12-diazabicyclo(7.2.2)tridecane-11,13-dione monohydrate ($C_{12}H_{18}N_2O_7$,H_2O). M. A. Vela, H. Kohn (1991) J. Org. Chem., 56, 5462.

[KOFZUA] trans-5-(1-Methylethyl)-2-oxo-4-imidazolidinecarboxamide ($C_7H_{13}N_3O_2$). R. Mohan, Yuo-Ling Chou, R. Bihovsky, W. C. Lumma Junior, P. W. Erhardt, K. J. Shaw (1991) J. Med. Chem., 34, 2402.

[KOHJEW] 1,3,5,11,13,15-Tetra-aza-21,27-dioxabenzo(gh)dipyrido(bc,lm)naphtho(vwxy)dotriacontane-6,10,16,32-tetraone barbital clathrate cyclohexane solvate ($C_{38}H_{36}N_6O_6$,$C_8H_{12}N_2O_3$,$0.5C_6H_{12}$). S. -K. Chang, D. Van Engen, E. Fan, A. D. Hamilton (1991) J. Am. Chem. Soc., 113, 7640.

[KOXRIY] 1,2,4-Triazolidine-3,5-dione (Urazole) ($C_2H_3N_3O_2$). F. Belaj (1992) Acta Cryst., C48, 1088.

[KPIPFA] 2,5-Diketopiperazine formic acid ($C_4H_6N_2O_2$,$2C_1H_2O_2$). K. I. Varughese, G. Kartha, C. T. Lu (1978) Am. Cryst. Assoc., Ser. 2, 6, 27.

[KUFPAC] N,N'-bis(4-Carboxymethylphenyl)melamine barbital ethanol solvate ($C_{19}H_{18}N_6O_4$,$C_8H_{12}N_2O_3$,$C_2H_6O_1$). J. A. Zerkowski, C. T. Seto, G. M. Whitesides (1992) J. Am. Chem. Soc., 114, 5473.

[KUFPIK] N,N'-bis(4-t-Butylphenyl)melamine barbital ($C_{23}H_{30}N_6$,$C_8H_{12}N_2O_3$). J. A. Zerkowski, C. T. Seto, G. M. Whitesides (1992) J. Am. Chem. Soc., 114, 5473.

[KUKCAU] 4'-Acetamidobenzalbarbituric acid ($C_{13}H_{11}N_3O_4$). K. Kondo, S. Ochiai, K. Takemoto, Y. Kai, N. Kasai, K. Yoshida (1992) Chem. Phys. Lett., 188, 282.

[LCDMPP01] cis-3,6-Dimethylpiperazine-2,5-dione (Cyclo-L-alanyl-L-alanyl) ($C_6H_{10}N_2O_2$). E. Sletten (1970) J. Am. Chem. Soc., 92, 172.

[MALEHY01] 1,2-Dihydropyridazine-3,6-dione (Maleic hydrazide,monoclinic polymorph) ($C_4H_4N_2O_2$). A. Katrusiak (1993) Acta Cryst., C49, 36.

[MALEHY10] Maleic hydrazide (6-Hydroxy-2H-pyridazin-2-one,triclinic polymorph) ($C_4H_4N_2O_2$). P. D. Cradwick (1976) J. Chem. Soc., Perkin Trans. 2, 1386.

[MAOBAR] 5-Ethyl-5-(1,3-dimethylbutyl)barbituric acid (alpha-Methylamobarbital) ($C_{12}H_{20}N_2O_3$). P. H. Smit, J. A. Kanters (1974) Acta Crystallogr., B30, 784.

[MCBZIM] 2-Mercaptobenzimidazole (thioketo form) ($C_7H_6N_2S_1$). G. R. Form, E. S. Raper, T. C. Downie (1976) Acta Crystallogr., B32, 345.

[MPBRBL] Methyl-phenyl-barbital ($C_{11}H_{10}N_2O_3$). G. Bravic, J. Housty, J. -P. Bideau (1968) C. R. Acad. Sci., Ser. C, 266, 969.

[MPYMOD10] 6,6'-bis(3,6-Dihydro-4,6-dimethylpyrimid-2-one) ethanol solvate ($C_{12}H_{18}N_4O_2$,$2C_2H_6O_1$). B. Czochralska, D. Shugar, S. K. Arora, R. B. Bates, R. S. Cutler (1977) J. Am. Chem. Soc., 99, 2583.

[MTHYMD10] 1-Methylthymine trans-anti dimer ($C_{12}H_{16}N_4O_4$). C. H. Wei, J. R. Einstein (1981) Acta Crystallogr., B37, 410.

Chart 1 (Continued)

[NBARBT] 5-Nitrobarbituric acid trihydrate (monoclinic form) ($C_4H_3N_3O_5$,$3H_2O$). B. M. Craven, S. Martinez-Carrera, G. A. Jeffrey (1964) Acta Crystallogr., 17, 891.

[NIMURC10] 5-Nitro-6-methyluracil ($C_5H_5N_3O_4$). R. Parthasarathy, T. Srikrishnan (1977) Acta Crystallogr., B33, 1749.

[OCSHYD] Cyclo-octane-spiro-5'-hydantoin ($C_{10}H_{16}N_2O_2$). R. W. Miller, A. T. McPhail (1979) J. Chem. Res., 330, 3831.

[OXBIOT10] (+-)-Oxybiotin ($C_{10}H_{16}N_2O_4$). G. T. DeTitta, R. Parthasarathy, R. H. Blessing, W. Stallings (1980) Proc. Nat. Acad. Sci. U. S. A., 77, 333.

[OXCBAR] 5-(6-Oxocyclohexenyl)-5-ethyl-barbituric acid (6-Oxocyclobarbital) ($C_{12}H_{14}N_2O_4$). F. Chentli-Benchikha, J. P. Declercq, G. Germain, M. van Meerssche, R. Bouche, M. Draguet-Brughmans (1977) Acta Crystallogr., B33, 2739.

[PARBAC] Parabanic acid ($C_3H_2N_2O_3$). D. R. Davies, J. J. Blum (1955) Acta Crystallogr., 8, 129.

[PHBARB] Phenobarbitone (5-Ethyl-5-phenylbarbituric acid,form II) ($C_{12}H_{12}N_2O_3$). P. P. Williams (1974) Acta Crystallogr., B30, 12.

[PHBARM] 5-Ethyl-5-phenylbarbituric acid monohydrate (Phenobarbitone monohydrate) ($C_{12}H_{12}N_2O_3$,H_2O). P. P. Williams (1973) Acta Crystallogr., B29, 1572.

[PMELIM] Pyromellitic di-imide ($C_{10}H_4N_2O_4$). I. V. Bulgarovskaya, L. A. Novakovskaya, Yu. G. Federov, Z. V. Zvonkova (1976) Kristallografiya, 21, 515.

[QQQEYV01] Aminopyrine-barbital complex ($C_8H_{12}N_2O_3$,$C_{13}H_{17}N_3O_1$). S. Kiryu (1971) J. Pharm. Sci., 60, 699.

[SABTEU] 1-(2-Pyridon-3-yl)-2-(2-pyridon-6-yl)ethyne ($C_{12}H_8N_2O_2$). Y. Ducharme, J. D. Wuest (1988) J. Org. Chem., 53, 5787.

[SABTIY] 1,2-bis(2-Pyridon-6-yl)ethyne ($C_{12}H_8N_2O_2$). Y. Ducharme, J. D. Wuest (1988) J. Org. Chem., 53, 5787.

[SADCOP] Bicyclomycin-3'-ethyl carbamate ethanol solvate ($C_{15}H_{23}N_3O_8$,$C_2H_6O_1$). H. Kohn, S. Abuzar, J. D. Korp, A. S. Zektzer, G. E. Martin (1988) J. Heterocycl. Chem., 25, 1511.

[SAZGOP] 4-Amino-1,2,4-triazolidine-3,5-dione (Urazine) ($C_2H_4N_4O_2$). F. Bigoli, M. Lanfranchi, M. A. Pellinghelli (1989) J. Cryst. Spectrosc., 19, 357.

[SEGZAF] (3R,6R)-bis((1R,2S,3R)-1,2,3,4-Tetrahydroxybutyl)-2,5-dioxopiperazine ($C_{12}H_{22}N_2O_{10}$). A. Perczel, M. Hollosi, J. Csaszar, V. Fulop, A. Kalman, G. D. Fasman (1989) Carbohydr. Res., 187, 187.

[SERTYR10] Cyclo(L-seryl-L-tyrosyl) monohydrate ($C_{12}H_{14}N_2O_4$,H_2O). C. -F. Lin, L. E. Webb (1973) J. Am. Chem. Soc., 95, 6803.

[SIHVAG] cyclo-bis(1-Aminocyclopropanecarboxylic acid) ($C_8H_{10}N_2O_2$). G. Valle, M. Crisma, C. Toniolo, E. M. Holt, M. Tamura, J. Bland, C. H. Stammer (1989) Int. J. Pept. Protein Res., 34, 56.

[SIKWEO] cyclo(L-Methionyl-L-methionyl) ($C_{10}H_{18}N_2O_2S_2$). G. Valle, V. Guantieri, A. M. Tamburro (1990) J. Mol. Struct., 220, 19.

[SPUNON] 1,3-Dithiacyclohexane-2-spiro-11-7-benzyl-6-phenyl-2,4,7,8-tetra-azatricyclo(6.3.0.0$1,5l)undeca-3,9-dione ($C_{23}H_{24}N_4O_2S_2$). P. A. Jacobi, A. Brownstein, M. Martinelli, K. Grozinger (1981) J. Am. Chem. Soc., 103, 239.

[SURTOX] Surugatoxin heptahydrate (absolute configuration) ($C_{25}H_{26}Br_1N_5O_{13}$,$7H_2O$). T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, H. Narita (1972) Tetrahedron Lett., 2545.

[TAFKAM] 4,5,6,7-Tetrahydro-1,2,5-oxadlazolo(3,4,-b)pyrazine ($C_4H_6N_4O_1$). C. K. Lowe-Ma, J. W. Fischer, R. L. Willer (1990) Acta Cryst., C46, 1853.

[TAJXAD] 5-Ethyl-5-phenyl-4,5-dihydro-2,6-(1H,3H)-pyrimidinedione 1,4-dioxane solvate (4-Deoxyphenobarbital 1,4-dioxane solvate) ($C_{12}H_{14}N_2O_2$,$0.5C_4H_8O_2$). D. Mastropaolo, A. Camerman, N. Camerman (1991) Acta Cryst., C47, 1050.

[THBARB] Thiobarbituric acid ($C_4H_4N_2O_2S_1$). M. -R. Calas, J. Martinez (1967) C. R. Acad. Sci., Ser. C, 265, 631.

[THHYDT] 2-Thiohydantoin (monoclinic form) ($C_3H_4N_2O_1S_1$). L. A. Walker, K. Folting, L. L. Merritt Junior (1969) Acta Crystallogr., B25, 88.

[THOPBA] bis(Theophylline) phenobarbital ($2C_7H_8N_4O_2$,$C_{12}H_{12}N_2O_3$). S. Nakao, S. Fujii, T. Sakaki, K. Tomita (1977) Acta Crystallogr., B33, 1373.

[THPSUR] 4-Thio-pseudouridine ($C_9H_{12}N_2O_5S_1$). C. L. Barnes, S. W. Hawkinson, P. W. Wigler (1980) Acta Crystallogr., B36, 2299.

[THYMDM10] trans-(5,6'.5',6)-Thymine dimer (Thymine dimer E) ($C_{10}H_{12}N_4O_4$). N. Camerman, S. C. Nyburg (1969) Acta Crystallogr., B25, 388.

[THYMIN] Thymine ($C_5H_6N_2O_2$). K. Ozeki, N. Sakabe, J. Tanaka (1969) Acta Crystallogr., B25, 1038.

[TMETHU] Trimethylenethiourea ($C_4H_8N_2S_1$). H. W. Dias, M. R. Truter (1964) Acta Crystallogr., 17, 937.

[TMTHYD] 1,1'-Trimethylene-(cis-syn)-thymine dimer ($C_{13}H_{16}N_4O_4$). N. J. Leonard, K. Golankiewicz, R. S. McCredie, S. M. Johnson, I. C. Paul (1969) J. Am. Chem. Soc., 91, 5855.

Chart 1 (Continued)

[TRDMPP02] Cyclo(D-alanyl-L-alanyl) (trans-3,6-Dimethylpiperazine-2,5-dione,form ii) ($C_6H_{10}N_2O_2$). J. Sletten (1980) Acta Chem. Scand. Ser. A, 34, 593.

[TRDMPP10] trans-3,6-Dimethylpiperazine-2,5-dione (Cyclo-D-alanyl-L-alanyl,form i) ($C_6H_{10}N_2O_2$). E. Benedetti, P. Corradini, C. Pedone (1969) J. Phys. Chem., 73, 2891.

[TURACD] cis-syn-1-Thiauracil photodimer ($C_8H_6N_2O_4S_2$). J. B. Bremner, R. N. Warrener, E. Adman, L. H. Jensen (1971) J. Am. Chem. Soc., 93, 4574.

[TURCIL01] 2-Thiouracil ($C_4H_4N_2O_1S_1$). E. R. T. Tiekink (1989) Z. Kristallogr., 187, 79.

[TZTCHD10] 6-Hydroxy-1,2,6,8-tetramethyl-3,5,9,11-tetra-azatricyclo(6.3.1.0$2,7l) decane-4,10-dione dihydrate ($C_{12}H_{20}N_4O_3$,$2H_2O$). B. Czochralska, D. Shugar, S. K. Arora, R. B. Bates, R. S. Cutler (1977) J. Am. Chem. Soc., 99, 2583.

[URACIL] Uracil ($C_4H_4N_2O_2$). R. F. Stewart, L. H. Jensen (1967) Acta Crystallogr., 23, 1102.

[VAPZUH] 5-(5'-Chloro-2'-methoxyphenyl)imidazolidine-2,4-dione ($C_{10}H_9Cl_1N_2O_3$). J. P. Rizzi, R. C. Schnur, N. J. Hutson, K. G. Kraus, P. R. Kelbaugh (1989) J. Med. Chem., 32, 1208.

[VARBAR] 5-(5'-Chloro-2'-(methylsulfonyl)phenyl)imidazolidine-2,4-dione ($C_{10}H_9Cl_1N_2O_4S_1$). J. P. Rizzi, R. C. Schnur, N. J. Hutson, K. G. Kraus, P. R. Kelbaugh (1989) J. Med. Chem., 32, 1208.

[VECTAY] 3,6-bis(2-Oxo-3-indolylidene)piperazine-2,5-dione dimethylformamide solvate ($C_{20}H_{12}N_4O_4$,$2C_3H_7N_1O_1$). A. R. Katritzky, Wei-Qiang Fan, A. E. Koziol, G. J. Palenik (1989) J. Heterocycl. Chem., 26, 821.

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(174) We have examined molecular packing in a series of structures with molecules differing in substitution at only one position. 1:1 Complexes between seven *N,N'*-bis(4-X-phenyl)melamines (X = H, F, Cl, Br, I, CH_3, and CF_3) and 5,5-diethylbarbituric acid all form linear tapes. The complex with X = Br exists in at least three polymorphic modifications (I–III). Form I is isomorphous to the X = Cl complex; form II is related to the X = I complex. The complex with X = CF3 grows in at least two crystalline forms (I and II), as shown by X-ray powder diffraction. Zerkowski, J. A., MacDonald, J. C.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 2382–2391.
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