C-4 and also in that due to C-3, indicating formation of 6β-hydroxytropine with the labeling pattern **9A** plus **9B**, identical with that found in the experiment with [1,2-$^{13}C_2$]acetate. Incorporation of an intact C_3 unit (**9G**), as observed in the case of *N*-methylpelletierine,[2] would have resulted in a doublet of doublets in the signal due to the CHOH group, C-3. Since the pattern of incorporation of ^{13}C from [1,2,3,4-$^{13}C_4$]acetoacetate was identical with that from [1,2-$^{13}C_2$]acetate, the acetoacetate had cleaved to acetate before incorporation of the label. Thus, the C_3 unit, C-2-4, was generated from two discrete acetate units, as demanded by the "cocaine mechanism"[1] (**2** → **3** → **4**, Scheme I), and not from an intact acetoacetate-derived C_3 unit, as demanded by the "pelletierine mechanism"[2] (**2** → → **5**, Scheme I).

Secondly, entry of the side chain into **2** may take place stereospecifically, eventually leading to a uniquely labeled tropine (**7**), but the hydroxylation whereby the 6β-OH group is introduced into the ornithine-derived moiety of the tropine unit of hyoscyamine (**8**), while diastereospecific, is not enantiospecific with respect to the tropine unit, forming a pair of diastereomers, (3*S*,6*S*)-6β-hydroxyhyoscyamine (**10**) and (3*R*,6*R*)-6β-hydroxyhyoscyamine (also known as 7β-hydroxyhyoscyamine), from which a pair of enantiomeric molecules, **9A** plus **9C** or **9B** plus **9D**, is generated on hydrolysis.

This explanation of the labeling pattern requires that the biosynthetic sample of 6β-hydroxytropine be a racemate, consisting of the (3*S*,6*S*) isomer (**9**) (see also **9A** and **9B**) and the (3*R*,6*R*) isomer (occasionally referred to erroneously as 3α,7β-dihydroxytropane,[15] i.e., 7β-hydroxytropine) (**9C** and **9D**). Esters of both enantiomers of 6β-hydroxytropine occur in plants of the genus Solanaceae, including several species of *Datura*, but no racemates have been reported, and the enzymic hydroxylation process whereby the 6β-hydroxy group is introduced into one of the alkaloids, (−)-hyoscyamine (**8**), is stereospecific[8] as well as substrate specific.[9] Furthermore, in the instances when diastereomeric alkaloids, namely, the *O*-3 (−)-(*S*)-tropic acid esters of (3*S*,6*S*)-dihydroxytropane ((−)-6β-hydroxyhyoscyamine) (**10**) and of (3*R*,6*R*)-dihydroxytropane ((−)-7β-hydroxyhyoscyamine), were isolated from the same plant, the latter compound was much less abundant than the former.[15,16] It is unlikely that hydrolysis of a mixture of ester alkaloids should fortuitously yield an equimolar mixture of the two enantiomeric dihydroxytropanes. This explanation of the incorporation pattern is thus unlikely.[17]

Thirdly, addition of the acetate-derived side chain to the *N*-methyl-Δ^1-pyrrolinium ion[5] (**2**) may take place by the "cocaine mechanism"[1] (analogous to route C in ref 2), yielding an equimolar mixture of (*R*)- and (*S*)-*N*-methylpyrrolidineacetoacetate (**4**), both of which are then further elaborated into tropine (**7**) either via (*R*)- and (*S*)-hygrine[7] (**5**) or directly. The mixture of (*R*)- and (*S*)-**4** can originate either by racemization[14] of a chiral species, namely (*R*)-**4** which is originally generated,[6] or less probably can be formed directly by nonstereospecific entry of the side chain into **2**.

A third experiment, with *N*-methyl-Δ^1-[2-^{2}H]pyrrolinium chloride (500 mg, 98% ^2H; prepared from DL-[2-^{2}H]proline by Eschweiler-Clarke methylation,[18] followed by heating with $POCl_3$[19]) as the substrate, provides evidence for the implication of racemic intermediates between **2** and **6**. This experiment gave a sample of 6β-hydroxytropine (ca. 3 mg, % enrichment 0.3%) whose ^2H NMR spectrum (76 MHz, 16 000 scans) indicated the presence of deuterium, equimolar within the limits of detection, at each of the two bridgehead sites (δ = 3.0, 3.6 ppm)[15] of the molecule, which thus consisted of an equimolar mixture of **9E** and **9F**. This result disposes of any scheme that does not accommodate the involvement of both enantiomers of *N*-methylpyrrolidineacetoacetate (**4**) (or of hygrine[7] (**5**)). Any mechanism that involves chiral intermediates (e.g., (*R*)-**4** and (*R*)-**5**) would have produced **9E** as the sole product rather than an equimolar mixture of **9E** and **9F**.

The evidence here presented leads to the inference that, contrary to conventional wisdom, the non-ornithine-derived moiety of the tropane ring system of 6β-hydroxytropine in *D. stramonium* does not originate from acetoacetate but by stepwise incorporation of acetate, whose nonregiospecific distribution within the C_3 unit implies the involvement of a racemic intermediate on the pathway.

Registry No. 9, 41164-06-1; acetate, 64-19-7.

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Solid-State Structures of "Rosette" and "Crinkled Tape" Motifs Derived from the Cyanuric Acid-Melamine Lattice[1]

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We are using the pattern of hydrogen bonds present in the 1:1 complex formed from cyanuric acid and melamine (CA·M) as the basis for the design of self-assembling structures.[2-5] We have described a solid-state structure based on a "linear" tape motif taken from this lattice (**3**, Figure 1),[3] and we have inferred the existence of cyclic aggregates containing three melamine and three isocyanurate moieties in solution.[4,5] Here we report solid-state structures of a new type of tape format (a "crinkled tape", **4**) and a cyclic structure (a "rosette", **5**), both obtained by combination of *N*,*N*′-bis(*p*-substituted phenyl)melamine (**1**) and 5,5-diethylbarbituric acid (**2**). We believe that the three solid-state structures **3**–**5** are the most plausible structural motifs that can be derived from the CA·M lattice: other, more collapsed tape or cyclic structures (e.g., **6** and **7**, and larger cyclic structures containing these units) are destabilized by nonbonded steric interactions (indicated by arrows in Figure 1). These two new structures, together with the structure of a linear tape (X = H) already described,[3] serve as paradigms for use in the design of self-assembling structures based on the CA·M lattice and provide structural parameters applicable to evaluation of the energetics of these structures using molecular mechanics.[6]

Figure 2 (middle) shows the structure of the 1:1 complex of **1a** (X = CO_2CH_3) and **2**.[7] This crinkled format occurs commonly: of 15 structures we have determined in the series of cocrystals incorporating substituted diphenylmelamines and **2**, three are crinkled tapes. The complex **1a**·**2** crystallizes from

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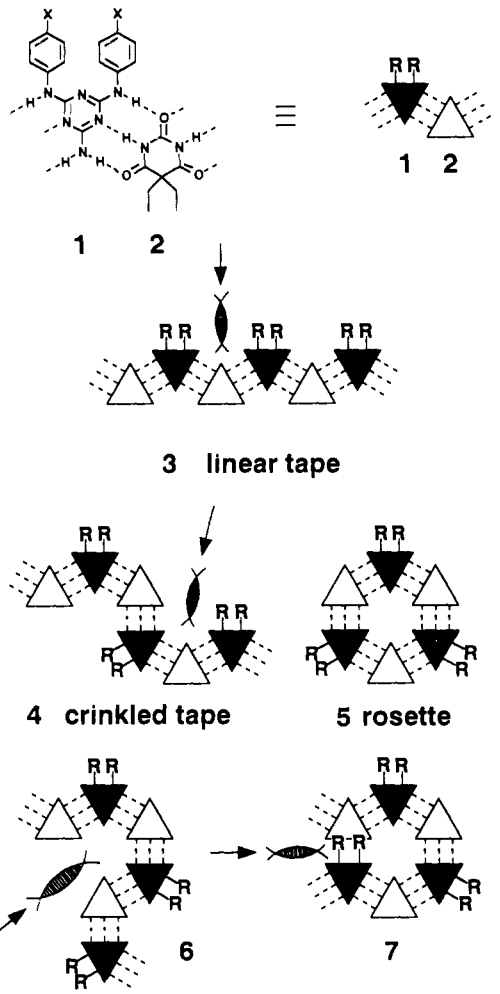

Figure 1. Schematic representation of structures based on repeating units of **1·2**. Melamines are represented by filled triangles, diethylbarbituric acid is represented by open triangles, and the triad of hydrogen bonds is represented by the three connecting dotted lines. Regions of unfavorable steric interactions are indicated by the arrows. The structure of **7** superimposes one pair of R groups on a unit of **2** to show the steric strain.

ethanol as a solvate.[8] Figure 2 (lower) shows the structure of **1b** (X = $C(CH_3)_3$) and **2**.[9] The mean planes of all the rosettes in the crystal are parallel: that is, they do not adopt a herringbone packing motif. No solvent of crystallization is included in the lattice.

We hypothesize that a competition between nonbonded steric interactions between the X groups and a tendency for a high packing coefficient[10] in the crystal is important in determining which structural motif is adopted by a 1:1 cocrystal of **1** and **2**. We assume that any structure must retain the triad pattern of hydrogen bonds. The linear tape **3** is observed for a number of groups X that are small (F, Cl, Br, I, CH_3). When X becomes larger than CF_3 or I,[11] unfavorable lateral nonbonding interactions between X groups on adjacent melamines (Figure 1) are relieved in going to the crinkled structure **4**, but are replaced by unfavorable interactions with the ethyl groups of **2** (Figure 2, bottom).[12] The crinkled structure is sufficiently loosely packed to accommodate one ethanol per dimer unit of **1a·2**.[8] Both types of steric interactions are relieved in the rosette **5**.

The structures reported here demonstrate that simple modifications in the molecular structures of a self-assembling system can lead to changes in crystalline architecture that can be rationalized (at least qualitatively) using steric arguments. By

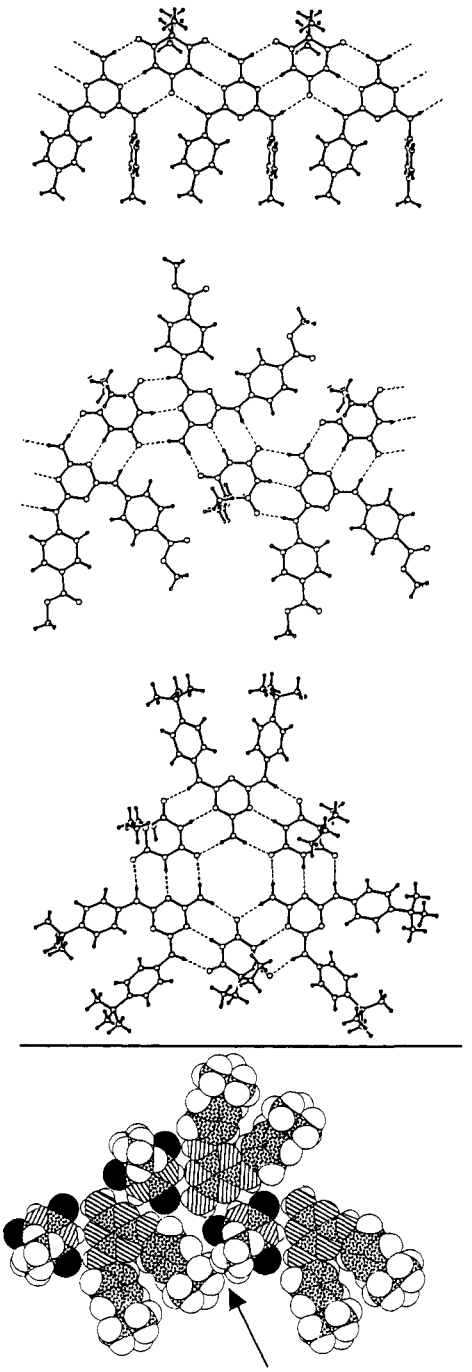

Figure 2. Top: crystal structures of linear tape (X = CH_3),[3] crinkled tape (X = CO_2CH_3), and rosette (X = $C(CH_3)_3$) motifs. The crinkled tape crystal contains disordered ethanol that has been deleted from this view for clarity; it is located above and below the planes of the phenyl rings. Bottom: hypothetical space-filling model generated by replacing the ester groups in the crinkled tape with *tert*-butyl groups, without changing any other nuclear positions. The arrow indicates regions of unfavorable steric interaction between the *tert*-butyl group and the ethyl groups of the diethylbarbituric acid.[12]

(8) All three of the crinkled diphenylmelamine structures we have observed are solvates.

(9) Crystal data for **1b·2** (X = $C(CH_3)_3$): $(C_{23}H_{30}N_6)_3(C_8H_{12}N_2O_3)_3$; space group $P\bar{1}$; a = 16.471 (3) Å, b = 19.930 (2) Å, c = 15.410 (4) Å, α = 95.10 (1)°, β = 99.79 (2)°, γ = 97.01 (1)°, V = 4917 (2) Å^3, D_{calcd} = 1.165 g/cm^3, Z = 2 rosettes (6 **1·2** pairs); R = 0.112 (four of the *tert*-butyl groups are disordered; we are continuing to refine the structure with alternative positions for the CH_3 groups).

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varying the steric demands of substituents around the periphery of our hydrogen-bonded components, we expect to be able to select from among alternative geometrical isomers of hydrogen-bonded assemblies in the solid state.

Supplementary Material Available: Brief synthetic outline, details of X-ray data collection, tables of crystal data and atomic positional parameters, and ORTEP drawings for both complexes (23 pages). Ordering information is given on any current masthead page.

β-Cyclodextrin/Pyridine Gel Systems. The Crystal Structure of a First β-Cyclodextrin–Pyridine–Water Compound

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General models for gel structure involve a dynamic interlocking three-dimensional network of solvent and "gelant" held together by ordered regions.[1-3] We report here the crystal structure of a compound in the β-cyclodextrin–pyridine–water gel system, which evidences such an interlocking network of β-cyclodextrin (β-CD) and solvent.

Isotropic physical gels are obtained from solutions of rigorously anhydrous β-CD in dry pyridine. For concentrations up to 2.5 × 10^{-1} M, melting points vary linearily with temperature; at higher concentrations the gels become sensitive to rapid temperature increases, with formation of a microcrystalline solid and free pyridine. Slow syneresis with formation of anhydrous needles[4] within the gel has been observed, although samples may be stable for several years. Ternary gels exist with toluene, chloroform, or tetrahydrofuran, with the cosolvent in the isotropic phase.

The ^{2}H NMR signals of pyridine-d_5 have line widths (10–15 Hz), in the melt and gel, typical for solution samples, implying the pyridine is in an isotropic fluid state. Solution technique ^{13}C NMR spectra of molten and gel samples show narrow line widths, requiring some β-CD molecules to be in an isotropic state. On going from liquid to gel, the intensity of the β-CD ^{13}C signals decreases considerably with respect to the signals of pyridine, due to a percentage of molecules becoming fixed in ordered junction zones as observed for agarose gels.[5] Addition of water by slow diffusion through the gel from $CuSO_4 \cdot 5H_2O$ yields a crystalline form, corresponding to the title compound.[6]

The structure is a novel packing of β-CD monomers that is less compact (2300 Å^3 per β-CD) than known monomeric (~1500–1750 Å^3) or dimeric (~1800 Å^3) structures. Monomers have been described either as the "herringbone" packing for hydrates[7] and inclusion[8] and cationic insertion[9] compounds or as arranged in sheets in the "brick" packing model.[10] Dimeric layers of inclusion compounds form C-centered layers in four classes of molecular packing.[11] In contrast to all of these compounds formed in aqueous solutions, in our pyridine medium, water was introduced under strict control.

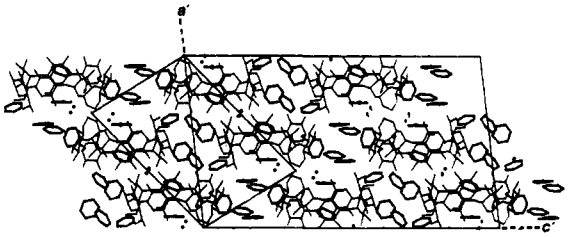

Figure 1. Projection of the structure along the *b* axis showing the packing of cyclodextrin layers in the triple unit cell: $a' = a + c = 23.641$, $b' = -b = 14.742$, $c' = 2a - c = 40.03$ Å, $\beta = 96.57°$ (similarly transformed anhydrous form: $a' = 22.135$, $b' = 15.224$, $c' = 39.94$ Å, $\beta = 95.83°$).

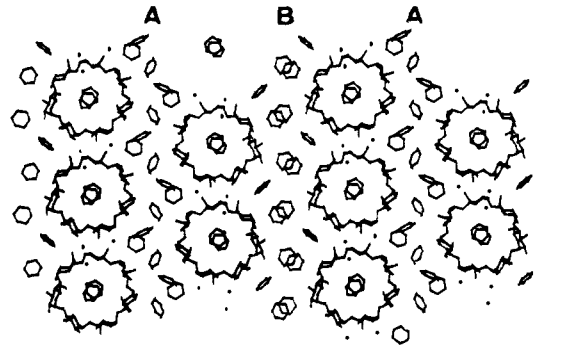

Figure 2. Section of the structure in the (1, 0, 2) plane, isolating a monomeric layer.

The crystal structure was solved using a new molecular replacement package.[12,13] Eight pyridine molecules per β-CD are located in inter- and intramolecular channels (Figure 1), and three water molecules are outside the cavity. One pyridine is included within the β-CD cavity, and a second is located at the primary hydroxyl level. Six others are present within two channels (A and B), both along the crystallographic 2-fold screw axis.

Sheets of β-CD molecules stacked nearly parallel to the *b* axis (inclination ≈ 10°) form an open arrangement of nonoverlapping β-CD monomers. The overall packing consists of layers, formed of pyridine and β-CD units, appearing with a 3-fold translational periodicity along $a' = a + c$; water molecules are located interlayer.

The interlayer distance (7.88 Å) is within the previously observed range; in the layers, β-CD molecules are packed more openly in a pseudo-C-centered arrangement (unit area 620 Å^2) than in dimer structures (unit area 460 Å^2). Each layer (Figure 2) contains two alternative symmetry-related rows of β-CD, each

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