Solid-State and Inclusion Properties of Hydrogen-Bonded 1,3-Cyclohexanedione Cyclamers

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Abstract. During crystallization 1,3-cyclohexanedione self assembles into either hydrogen-bonded chains or hexameric rings depending on the solvent conditions. The hexameric rings, called cyclamers, are the subject of this paper. These unusual structures occlude benzene as a guest molecule. The structural and crystal chemical properties of these host-guest compounds are explored here with the use of crystal growth studies, X-ray powder patterns, and thermal analysis. The crystal structure of the benzene cyclamer of 5-methyl-1,3-cyclohexanedione is reported (hexagonal, $a = b = 19.19(2)$Å, $c = 10.545(9)$Å, $R\bar{3}$, $Z = 18$, $V = 3362(6)$Å^3; 717 unique reflections, $R = 0.062$). An analysis of the stereochemical implications of cyclic directionality in these cyclamers is also discussed.

Key words. Cyclamer, hydrogen bonding, desolvation, solid-state, phase transformation, cyclostereoisomerism.

1. Background

Cyclamers are formed when small molecules associate into rings by strong, directed intermolecular interactions such as hydrogen bonds. These rings can selectively incorporate guest molecules, as found for cyclamers of 1,3-cyclohexanedione [1], intertwine like catenanes, as found for trimesic acid [2], or form rings with no cavities, as found for the rhombohedral form of acetamide [3] and for di-*n*-butyltin 3-thiopropionate [4]. Cyclamers constitute an important class of structures since they derive their chemical and structural integrity from molecular self assembly. They are found in crystal structures as subsets of the unit cell, but they can also exist in solution [4].

In the course of our studies on the role of hydrogen bonds in controlling packing patterns of organic molecules [5], we found that 1,3-cyclohexanedione (**I**) crystallizes in two different solid-state structures, **II** and **III**, both of which have a strong intermolecular hydrogen bond (O---O < 3.6Å) [1]. Hydrogen bonds in cyclic β-diketomethane compounds have a choice of four possible stereoelectronic patterns, based on orientation of the enolic proton in a *syn* or *anti* position and choice of the

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syn or *anti* nonbonding electron pairs of the carbonyl group as the proton acceptor. The two structures of **I** differ in the stereochemistry of these hydrogen bonds, with **II** having an *anti-anti* structure, and **III** having a *syn-anti* structure (specifying the proton orientation first). As a result of these differences, the aggregate form of **II** in the solid state is a straight chain polymer and that of **III** is a cyclamer that complexes with benzene (**III:B**) guest molecules, or with a mixture of benzene and thiophene (**III:B,T**). For 1,3-cyclohexanedione the *syn-syn* and *anti-syn* patterns of hydrogen bonding were not observed.

I

II (anti-anti)

III (syn-anti)   III:B   III:B,T
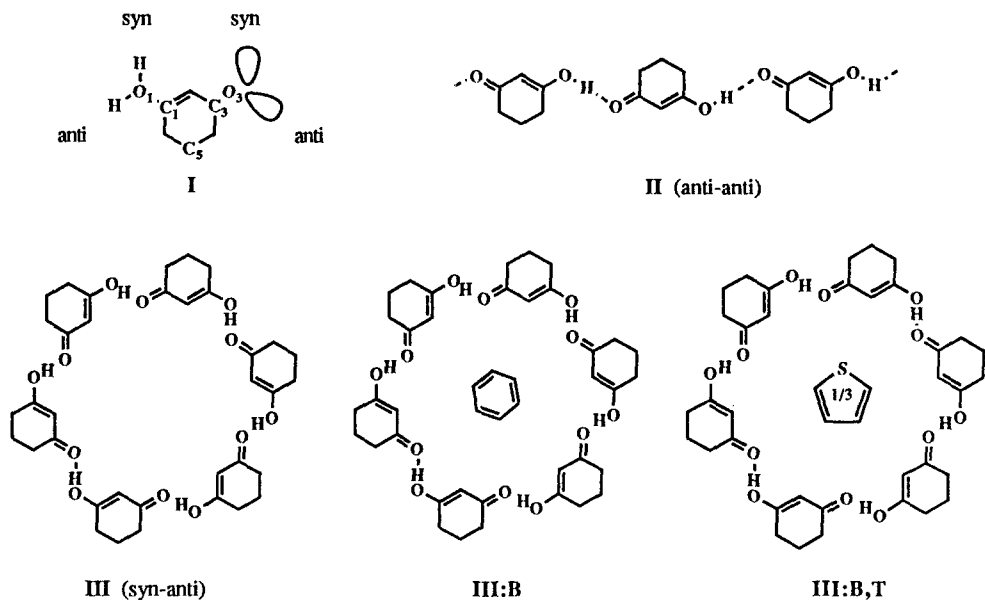
The *syn-syn* hydrogen-bond pattern has, however, been observed in the crystal structure of dimedone (**IV**, 5,5-dimethyl-1,3-cyclohexanedione). In this structure a short *syn-syn* intermolecular hydrogen bond is formed leading to a helical aggregate which does not include solvent [6]. We have attempted unsuccessfully to induce dimedone to form a cyclamer by crystallizing it from benzene. The main difference between dimedone and 1,3-cyclohexanedione molecules is that dimedone has a decidedly nonplanar structure with an axial methyl group in both of its low energy ring conformations. This structural feature may prevent dimedone cyclamers from packing in a favorable crystal structure. Compound **V** (5-methyl-1,3-cyclohexane-

IV   V
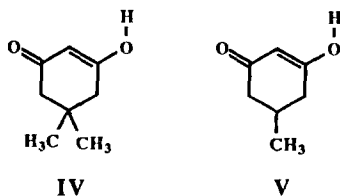
dione), on the other hand, can adopt a conformation with its methyl group in an equatorial position, and thus assume a conformation that is nearly as flat as **I**.

We report here the results of thermal stability and binding selectivity studies of 1,3-cyclohexanedione cyclamers, **III**, as well as the preparation of cyclamers (**VI**) made from molecules of **V**, their crystal structure, and a discussion of the symmetry implications of cyclic directionality in cyclamers.

VI   **VI:B**
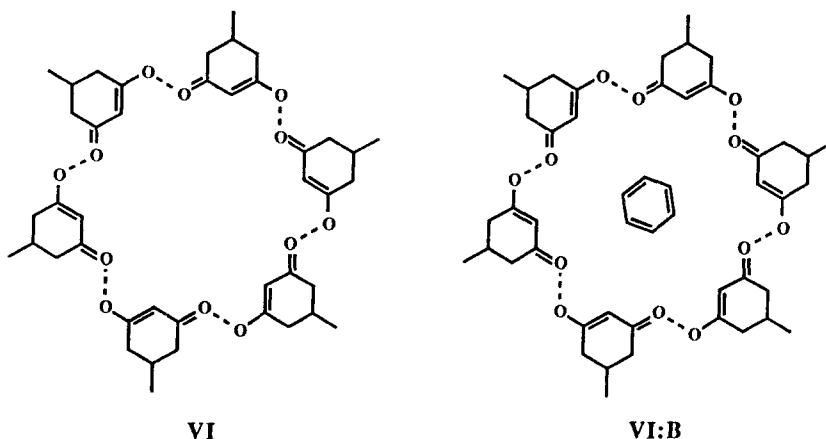
2. Experimental

2.1. SYNTHESIS OF V

5-Methyl-1,3-cyclohexanedione (**V**) was prepared by condensing the sodium salt of ethyl acetoacetate with ethyl 2-butenoate, according to the literature method [7]. The product, a dione salt, was dissolved in KOH and water, refluxed, and acidified to form crude **V**. The product, recrystallized from ethyl acetate, was obtained in 70% yield: mp 129–130°C (lit. mp 128°C) [7b], ^{1}H NMR (CDCl$_3$): δ1.08 (t, 3H, $J = 6$ Hz.), 2.07–2.73 (m, 5H) 3.36 (s, 0.5H), 5.46 (s,1.5H).

2.2. PREPARATION OF CYCLAMER (VI)

The cyclamer (**VI**), composed of six molecules of **V** and one molecule of benzene, was prepared by slow recrystallization of **V** from benzene (**B**) according to the previously reported method [1]. Crystals of **VI:B** are large and hexagonal (Figure 1a), with a morphology identical to the hexagonal crystals of **III:B** (Figure 1b). The crystals turn slightly cloudy when removed from the mother liquor but they continue to diffract well nonetheless.

2.3. X-RAY CRYSTAL STRUCTURE OF VI

A single crystal of **VI** (C$_8$H$_{11}$O$_2$), $0.16 \times 0.18 \times 0.40$ mm^3, was used for data collection (Enraf-Nonius CAD4 diffractometer. MoKα radiation, $\lambda = 0.71069$Å, -85°C). Lattice parameters were obtained from least squares analysis of 25
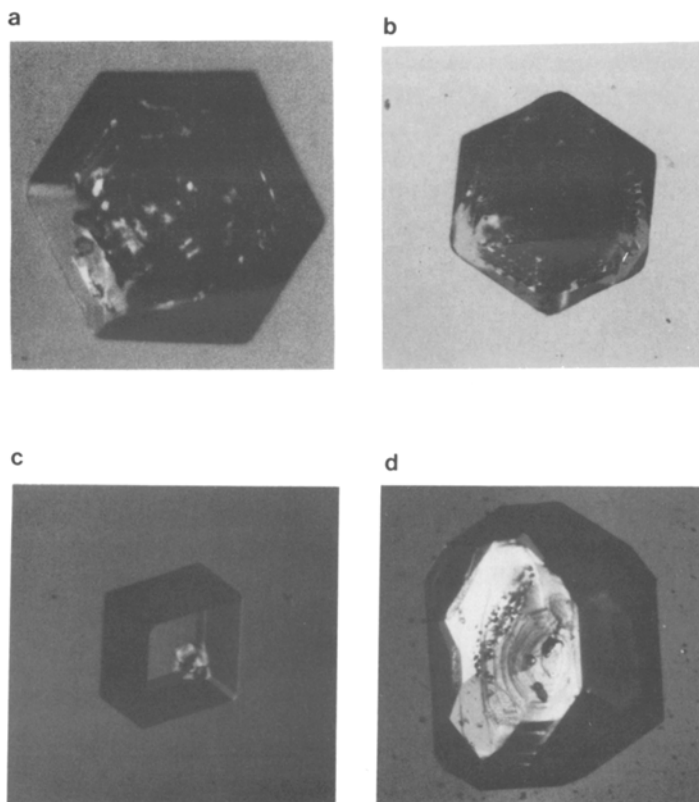
Fig. 1. Typical single crystals of cyclamers of 1,3-cyclohexanedione and 5-methyl-1,3-cyclohexanedione: (a) hexagonal crystal of **VI:B**, (b) hexagonal crystal of **III:B**, (c) rhombohedral crystal of **III:B**, (d) crystal of **III:B,T**.

reflections in the range $7° < \theta < 14°$. Unit cell parameters: $a = b = 19.19(2)$Å, $c = 10.545(9)$Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $R\bar{3}$, $Z = 18$, $V = 3362(6)$Å^3, $\rho_{calc} = 1.23$ g/cm^3, $\mu(MoK\alpha) = 0.9$ cm^{-1}. Data were collected in the 2θ range 0–44° to give 912 measured reflections and 717 unique reflections. The $I/\sigma(I)$ cutoff was 1σ. Lorentz and polarization corrections were applied. The structure was solved using direct methods procedures from the SDP package [8]. All heavy atoms and the enolic proton were found from difference Fourier maps; all other protons were placed in idealized positions. Atoms C(5) and C(7) are disordered, with an occupancy factor that refines to 0.65/0.35. Thermal parameters for the heavy atoms, except for the disordered carbon atoms were refined anisotropically, while those for the protons were fixed at values of 4 for the protons on the cyclohexanedione ring, 5 for the phenyl protons, 7 for the protons on the disordered methyl groups, and 9 for the enolic proton.

Final R and R_w in the last cycle were 0.062 and 0.066 respectively, with $w = 1/\sigma^2(F_0)$ based on counting statistics. Max shift/err = 0.06. The highest peaks on the final difference density maps were less than 0.2e Å^{-3}. Scattering factors were taken from standard tables [9]. Atomic positional parameters, thermal

parameters, structure factor tables, intra- and intermolecular bond distances, angles, and esds are available as supplementary material.

2.4. CRYSTAL GROWTH STUDIES OF III:B

Crystals of **III:B** are grown by slow evaporation of benzene solvent (about 60 mL) and previously recrystallized **I** (about 0.5 g) at room temperature in a crystallization dish. Crystals appear with two different morphologies. One form is a large (5 mm diameter) flat hexagonal crystal (Fig 1b). The largest face (001), usually has clearly visible etch pits. This crystal type transforms slowly over several hours or days in solution into a smaller brilliant crystal (2 mm on a side) with rhombohedral morphology, Figure 1c. Occasionally only crystals of rhombohedral morphology are obtained from the crystallization. Crystals of both morphologies have the same crystal structure, as confirmed by X-ray powder pattern analysis.

2.5. INCLUSION OF THIOPHENE INTO THE CAVITY OF III

Various attempts were made to obtain **III** with thiophene (T) included as the guest species. Recrystallization of **I** from pure thiophene yielded the nonsolvated crystal form, **II**. If **I** is recrystallized from a mixed solvent of benzene and thiophene, however, thiophene can be incorporated into the cyclamer. The amount of thiophene incorporated is proportional to the amount of thiophene in the solvent mix, with a maximum of 33% (measured as the percent of cavities that contained thiophene), obtained from a solution of 75% thiophene/25% benzene. Raising the percent of thiophene in the solution above 75%, however, results in the exclusive formation of **II**. The presence of thiophene in the solid state was confirmed by ^{13}C CP/MAS NMR spectra [10]. A quantitative measure of the amount incorporated was determined by solution ^{1}H NMR of solutions of air-dried crystals ($(CD_3)_2SO$).

Crystals of **III:B,T** that contain 33% thiophene, Figure 1d, have a distinctly different morphology than crystals of **III:B** from pure benzene. To determine if these crystals were isomorphous with **III:B**, the space group and unit cell parameters were obtained using single crystal X-ray diffraction methods. The unit cell parameters of the thiophene/benzene crystal compared to those of a crystal of **III:B** are: **III:B,T**: $R\bar{3}$, $a = b = 18.106$ (20), $c = 10.466$ (11)Å, $Z = 18$; **III:B**: $R\bar{3}$, $a = b = 18.127$ (7)Å, $c = 10.542$ (3)Å, $Z = 18$ [1].

2.6. CRYSTALLIZATION OF III:B FROM TOLUENE AND BENZENE

Various attempts to recrystallize **I** from mixed toluene and benzene solutions were made. Solutions with more than 70% toluene produced only the unsolvated crystal form **II**, while solutions with less than 70% toluene produced hexagonal or rhombohedral crystals of type **III:B**. No toluene was detected in the ^{1}H NMR of solutions of air-dried crystals.

2.7. RATE OF LOSS OF BENZENE FROM III:B

Since the rate of loss of benzene from **III:B** is a measure of the binding strength of the cyclamer host, we carried out a series of studies on the rate of loss of benzene as a function of temperature and of crystal size.

By varying the rate at which crystals are formed, batches of crystals with nearly homogeneous particle size were obtained in the size ranges of 0.15–0.20 mm, 0.25–0.30 mm, and 1.90–2.10 mm. The crystals were spread in a uniform monolayer on the bottom of an open beaker that was placed in a variable temperature oven (temperature stability, $\pm 2°C$). Samples of the crystals were removed from the oven at various time intervals, weighed, and dissolved in $CDCl_3$ for the determination of a ^1H solution NMR spectrum. Each set of experiments was repeated at room temperature, 50°C, 60°C, and 70°C. The integrated intensity of the benzene proton peak in the NMR spectrum, relative to the intensity of the aliphatic proton peaks of 1,3-cyclohexanedione, was used to monitor the rate of loss of benzene from the samples. The overall precision of each measurement was estimated from a series of standards to be $\pm 10\%$.

The data obtained are shown in Figure 2. The rate of loss of benzene increases with decreasing crystal size and with increasing temperature. There was no detectable loss of benzene at room temperature, even though the crystals were visibly cloudy after being removed from the mother liquor. The energy of activation for the loss of benzene was calculated to be 25–30 kcal/mol from the data for crystals 0.50 mm in diameter [11].

2.8. SOLID-STATE TRANSFORMATIONS OF III:B

To determine whether cyclamers with empty cavities remain after loss of benzene in the solid state, X-ray powder diffraction patterns were recorded on samples with different amounts of desolvation (70% and 100%). X-ray powder diffraction patterns of I, II, and III:B were obtained as standards.

To our surprise, we found that the 100% desolvated sample of III:B gave an X-ray powder pattern identical to that of II prepared independently. The powder pattern of the 70% desolvated sample showed predominantly the peaks of II, but peaks for III:B were still visible. No unidentified X-ray diffraction peaks were seen in either sample.

To confirm that a transformation from III:B to II was occurring in the solid state, a large single crystal of III:B was mounted on a goniometer and the change in its oscillation pattern (about [001]) was followed as a function of temperature. The crystal and the goniometer were heated in an oven at 60°C, and oscillation patterns were recorded intermittently until 100% conversion was obtained.

The single crystal oscillation pattern of III:B disappeared as the powder pattern of II grew in intensity over the period of time that the crystal was observed. We found that the single crystal slowly sublimed when heated for extended periods of time so the relative intensities of diffraction spots of III:B and diffraction rings of II could not be readily evaluated. These studies give no evidence that the cyclamer ring is retained when most of the benzene is lost from the crystal.

The heat of transformation of III:B to II was measured using a Mettler FP 84 differential scanning calorimeter microscope cell mounted on a Nikon SMZ-10 stereomicroscope. A 1.2 mg single crystal sample of III:B was observed through the microscope during the course of heating (5°C/min). At 80°C, the bp of benzene, an endotherm of 8 kcal mole^{-1} of cyclamer was observed. After melting at 103°C the sample was cooled and reheated. No peak was observed at 80°C on reheating.

LOSS OF BENZENE AS A FUNCTION OF CRYSTAL SIZE
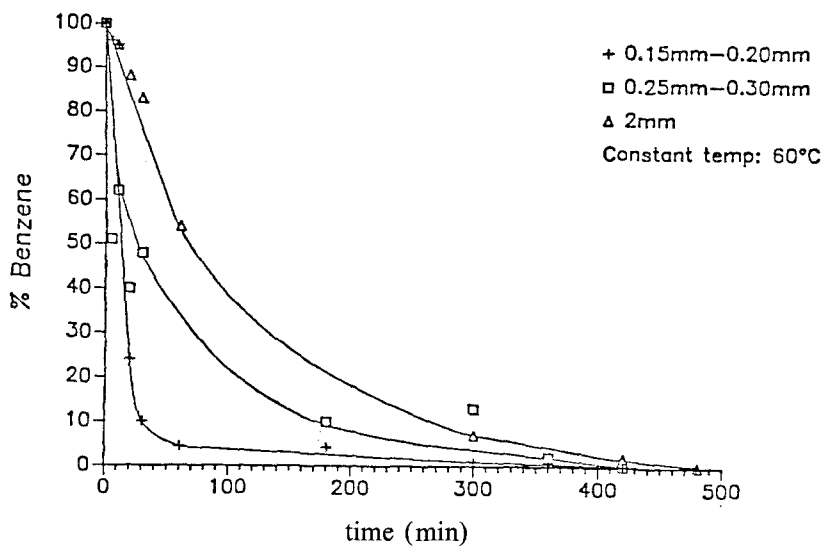
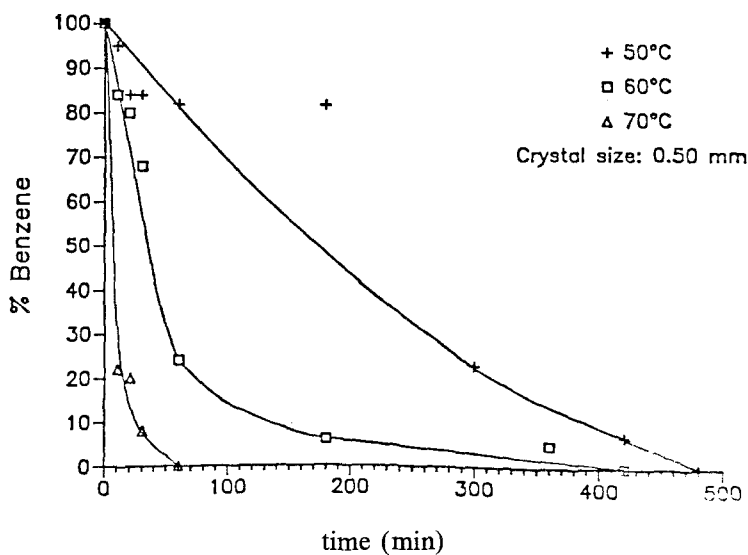LOSS OF BENZENE AS A FUNCTION OF TEMPERATURE

Fig. 2.   Results of study of loss of benzene from **III** on heating. *Top*: loss of benzene as a function of crystal size. *Bottom*: loss of benzene as a function of temperature.

2.9. GENERAL PROCEDURES

Melting points were determined on a Fisher-Johns melting point apparatus. Infrared spectra were recorded on a Nicolet 5DXB FT-IR Spectrometer as Nujol mulls. ^{1}H NMR spectra were recorded on an IBM NR200AF spectrometer at 200 MHz in deuterochloroform. ^{13}C NMR spectra were also recorded on an IBM NR200AF spectrometer operating at a carbon frequency of 50.323 MHz. X-ray powder diffraction measurements were done on a Siemens-D500 automated diffractometer with CuKα radiation.

3. Results and Discussion

Cyclohexanedione (I) and 5-methylcyclohexanedione (V) crystallize from benzene and closely related solvents as cyclic hexameric aggregates, called cyclamers. Cyclamers behave like crown ether macrocycles in their ability to selectively bind neutral molecules, yet they differ from crown ethers in their structures, which have hydrogen-bonded rather than sigma-bonded backbones. The present study was undertaken to explore the solid-state properties of these unusual host molecules and to evaluate the likelihood that other small organic molecules might also aggregate into cyclic structures with crown ether-type properties.

3.1. CRYSTAL STRUCTURE OF VI:B

The crystal structure of VI is essentially isomorphic with that of III. In both structures, six monomers are linked by very short hydrogen bonds which have a *syn-anti* stereoelectronic orientation. The molecules have little conformational flexibility. Positioning the enolic proton in a *syn* or *anti-* position and choosing the *syn* or *anti-* nonbonded electron pair of the carbonyl group as the proton-acceptor site predetermines the configuration of the aggregate.

The methyl groups on molecules of VI are equatorial, allowing the cyclohexanedione ring to be nearly planar. Atoms C(5) and C(7) are disordered in the crystal structure in a manner analogous to that of the disordered C(5) atom in the nonsolvated crystal form of I [1]. An edge-on view of V shows the disorder pattern, Figure 3. At any one site, 65% of the molecules are in one configuration and 35% are in the other; however, since the two configurations are enantiomers and the crystal is centric, there are an equal number of both configurations in the crystal.
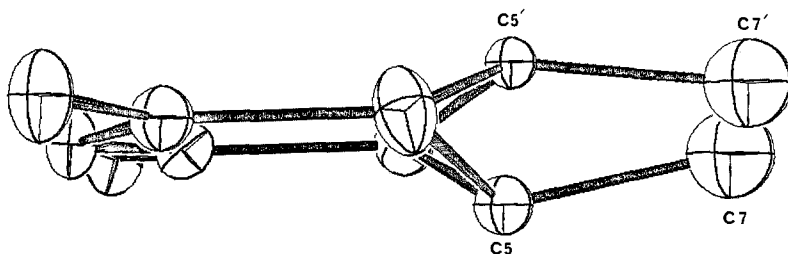

Fig. 3. Edge-on view of a molecule of V showing disorder at C5. The disordered molecules both have equatorial methyl substituents and are enantiomers of one another.

Whether the disorder is from monomer to monomer, or whether any particular cyclamer is ordered internally but disordered with respect to the other cyclamers, cannot be answered from the X-ray data.

All intramolecular bond lengths and angles are within normal limits [12]. The only intermolecular contact shorter than van der Waals distance occurs between the hydrogen-bonded oxygens. The distance is 2.579(3)Å, and the O—H---O angle is 176 (3)° (compared to 2.579(1) and 174(2)° for comparable distances in the crystal structure of **III**) [1]. Despite the very short length of this contact, the proton is ordered and is 0.2 Å nearer to one oxygen than to the other. Infrared patterns of **I** and **VI** and of the nonsolvated form of **I** show the expected low frequency broad OH stretching bands around 2500 cm^{-1} characteristic of strong asymmetric hydrogen bonds [13].

3.2. ROLE OF BENZENE AS A CYCLAMER GUEST

The cavities in both **III** and **VI** have hexagonal symmetry and are about 8Å in diameter. Both the symmetry of the cavities and their size are conducive to incorporation of benzene molecules. Structures **III:B** and **VI:B** have stoichiometric amounts of benzene incorporated in their cavities. The packing patterns of the host-guest complexes are graphitic with adjacent planes displaced from one another so benzene molecules are trapped in pockets rather than in channels. Two views of the packing pattern of **VI** are shown in Figure 4.

Thermal studies show that benzene is lost from crystals of **III:B** at rates that depend inversely on particle size and directly on temperature. At room temperature there is essentially no detectable loss of benzene, but at 50°C, all the benzene has escaped from crystals of 0.5 mm diameter after 8 hours. A detailed study was made of the phase changes that accompanied the loss of benzene in hopes of detecting the presence of empty cyclamers. X-ray powder pattern measurements showed clearly, however, that loss of 50% or more of the benzene is accompanied by a non-reversible structural reorganization in which the aggregate rings open and the molecules recrystallize within the solid state into the nonsolvated crystal structure, **II** [1]. The molecular motions required for this rearrangement are enormous. Even if most of the hydrogen bonds remain intact, neighboring molecules need to reorient in order to change from *syn-anti* to *anti-anti* hydrogen-bond stereochemistry.

Cyclamers with guest molecules other than benzene or deuterobenzene have proven difficult to prepare. Attempts to incorporate thiophene molecules (which are known to form solid solutions with benzene) [14] by crystallizing **I** from pure thiophene gave only crystals of the nonsolvated form, **II**. Crystallizing **I** from mixed solvents of thiophene and benzene, however, gave crystals of the cyclamer with up to one third of the cavities occupied by thiophene molecules. These guest molecules are disordered throughout the structure. The incorporation of thiophene into these cavities is an example of induced molecular recognition since thiophene is not incorporated in the absence of the second guest, benzene. Crystals could not be made to incorporate more than 33% thiophene guest. When mixed solutions of benzene and thiophene containing more than 75% thiophene are employed as the recrystallization solvent only crystals of **II** are obtained.
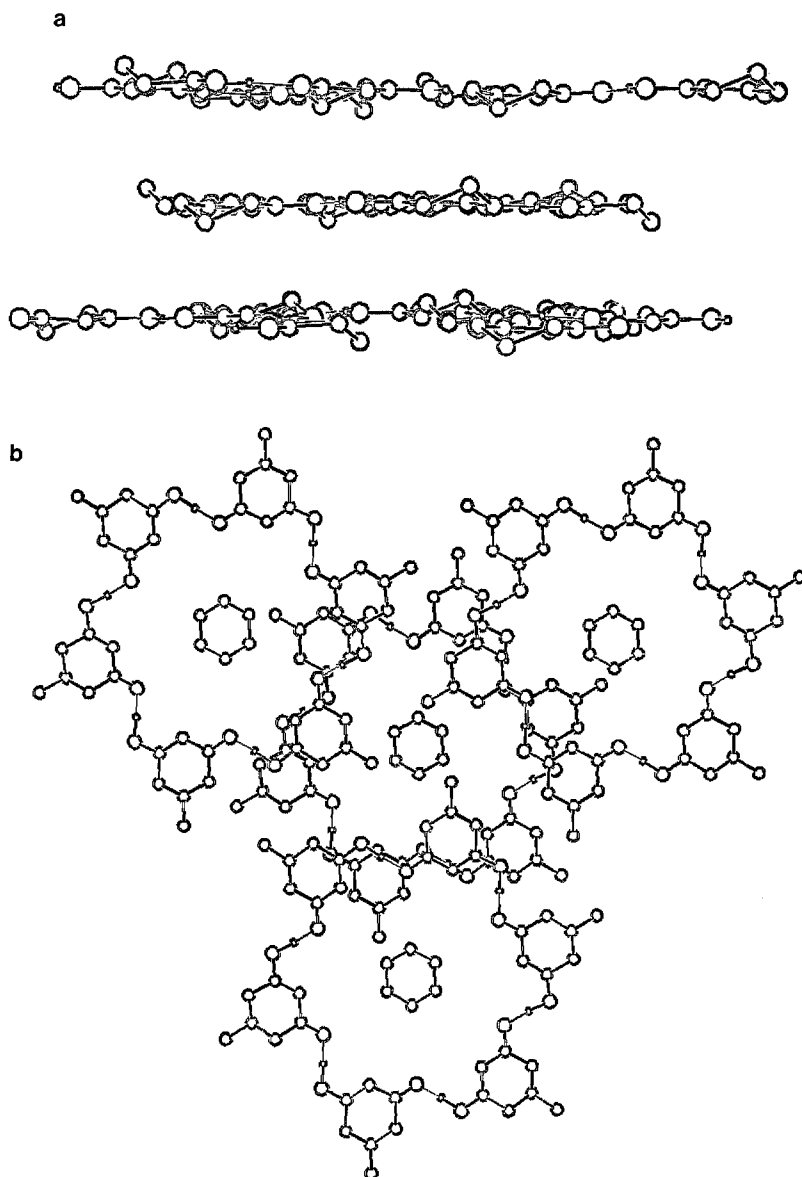
a

b

Fig. 4. ORTEP views of **VI:B** showing how cyclamer rings in neighboring planes are oriented: (a) projection along [001], (b) view perpendicular to [001].

Crystallization of **I** from mixed benzene and toluene produces crystals of **III:B** when the percentage of benzene is greater than 25–30% and crystals of **II** when it is less. No toluene is incorporated into the cyclamer ring, probably due to its larger size. The results of crystallization of **I** from both mixed solvent systems imply that a minimum amount of benzene is needed for cyclamer rings to form.

3.3. CYCLIC DIRECTIONALITY AND CYCLOSTEREOISOMERISM IN VI

Structures **III** and **VI** are directed cycles. Travelling around either ring in a clockwise direction is distinguishable from travelling in a counterclockwise direction. Mislow has recently analyzed the stereochemical consequences of ring directionality for cyclic structures composed of stereogenic subunits [15]. In **III** [16] and **VI** the C(5) carbon atoms are stereogenic, with R and S configurations alternating around the cyclamer ring. In the schematic diagrams of **III** and **VI** shown above, C(5) has an R configuration when it is pointing up out of the figure, and an S configuration when it is pointing behind the figure. A schematic representation of these rings showing their S_6 symmetry and cyclic directionality is given below.

A   B
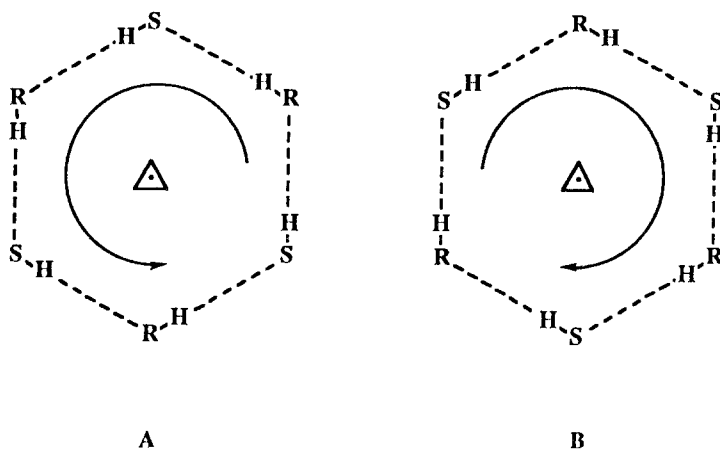
Switching ring directionality results in inversion of the absolute configuration of every C(5) atom in **A** to give the homomeric structure, **B**. A mechanism by which ring directionality could be reversed in **III** or **VI** would be proton hopping from the enol oxygen of one molecule to the carbonyl oxygen of a neighbor [17].

R   S   S   R
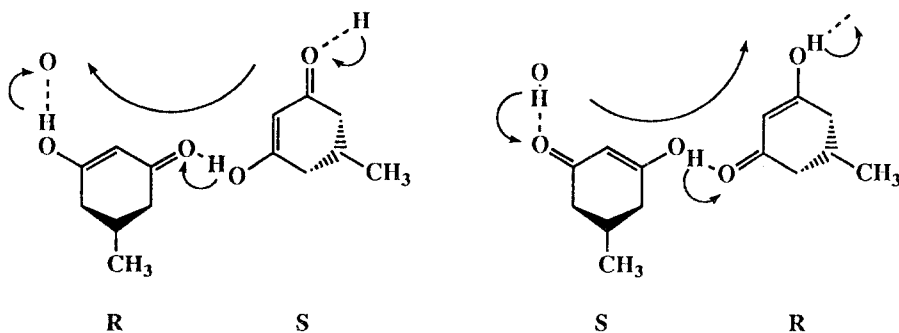
The proton would have to move only about 0.2Å to effect the change. If such a change occurred for one cyclamer unit in a hypothetical crystal, the new ring with reversed directionality would *not* be homomeric with the original ring for two

reasons. The most significant reason is that the cyclamer is fixed in an anisotropic environment in the crystal so the crystal lattice imposes diastereomeric properties on **A** and its reversed cycle **B**. The conversion would be homomeric only if all **A** switched direction simultaneously. The second reason is specific to the cyclamer structure and involves different orientation of O(1)and O(3) [18].

3.4. STRUCTURAL CONSIDERATIONS IN DESIGNING CYCLAMERS

One of the most remarkable features of these cyclamers is that they form at all given the severe entropic constraints imposed by organizing six molecules into an array. Most host-guest chemistry involves use of macrocyclic sigma-bonded hosts, where the stabilizing role of prearranged cavities in determining binding constants has been well documented [19]. The structural features that contribute to the formation of stable cyclic arrays of **I** and **V** involve both intra- and intermolecular considerations. Cyclohexanedione molecules have limited conformational freedom and their topography is nearly planar. Planar arrays appear to be important since dimedone (**V**) does not crystallize as a cyclamer. The aggregate structures have hexagonal symmetry, which is the most common symmetry for organic solid-state inclusion complexes [20]. The hydrogen bonds that form are not only very short, but also participate in resonance assisted hydrogen bonding throughout the 36-membered ring [21]. The benzene guest molecule has the same symmetry and size as the host cavity, so it may be functioning as a template for organizing the formation of aggregates. Additional stabilizing features may be very weak interactions between the aromatic CH protons of the benzene and the *syn*-nonbonded electron pairs of the carbonyl groups [22].

Acknowledgements

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10. Spectrum was run by the Colorado State University Regional NMR Center.

11. The rate constant for the loss of benzene was calculated according to several equations derived from different mechanisms for solid state reactions (S. R. Byrn: *The Solid-State Chemistry of Drugs*, Academic Press (1982)). An Arrhenius plot of ln(k) (using k from the Prout-Tompkins equation, which gave the best fit) vs $1/T$ gave the energy of activation. The correlation coefficients for the rate equations were approximately 0.90, reflecting the difficulties inherent in quantifying reactions in the solid state.

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16. At first glance, it appears that C(5) in **III** cannot be stereogenic since it has two attached identical groups (hydrogens). Upon further consideration, however, it is recognized that the axial and equatorial hydrogens are chemically different in the solid state where conformational interconversions are not taking place.

17. Concerted proton hopping similar to the mechanism proposed here has been observed for porphyrins in photochemical hole burning experiments (S. Volker and J. H. van der Waals: *Mol. Phys.* **32**, 1703 (1976)).

18. The enol and keto oxygens occupy diastereomeric positions in the cyclamers, so proton hopping is not a degenerate process, as it would be in **A** and **B**.

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