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Jack Hine,* M. Niyaz Khan
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210
Received February 17, 1977

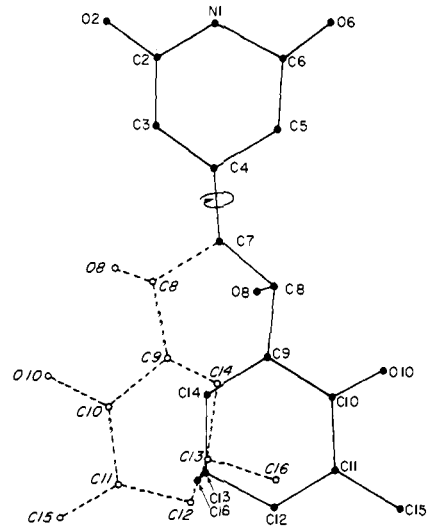

Figure 1. Superposition of molecules A (solid bonds, block lettering) and B (dashed bonds, italic lettering) over their geometrically common portions showing the striking difference in the orientation around the exocyclic bond C(4)-C(7). View is parallel to the c^* axis.

Simultaneous Occurrence of a Chair and a Boat Conformation in Crystalline Cycloheximide

Sir:

As part of our investigation of protein synthesis inhibitors, we have determined the crystal structure of the antibiotic cycloheximide (4-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]-2,6-piperidinedione) (Figure 1). Cycloheximide inhibits the translocation step of eucaryotic ribosomal protein synthesis, possibly by blocking the release of deacylated tRNA from the ribosome.[1] The molecule consists of the two saturated rings, glutarimide and dimethylcyclohexanone, connected by a two carbon chain. There are two crystallographically independent cycloheximide molecules in the asymmetric part of the unit cell and these are found to have markedly different conformations. The most interesting difference occurs in the cyclohexanone moiety which exhibits the chair conformation in one molecule and the twist boat conformation in the other. As far as we are aware, this is the first observation of the coexistence of a chair and boat conformation in a crystal. Another unusual feature of this structure is that the hydroxyl group of one of the molecules is not involved in hydrogen bonding.

Crystals of cycloheximide ($C_{15}H_{23}NO_4$) are monoclinic, with space group $P2_1$, and cell dimensions a = 15.151 (5) Å, b = 7.761 (2) Å, c = 14.012 (4) Å, and β = 113.56 (5)°. The observed density of 1.24 g cm^{-3} indicated the presence of two crystallographically independent molecules in the asymmetric unit. The structure was solved by direct methods[2] and refined by full-matrix least-squares methods to a final R value of 3.5% using 2325 unique reflections collected on a Picker FACS-I diffractometer. All 46 hydrogen atoms were located by difference electron density synthesis. A table of atomic coordinates is available; see paragraph at end of paper regarding supplementary material. The details of the crystallographic work will be reported elsewhere.

The cycloheximide molecule could be expected to have considerable conformational freedom because of the presence of three carbon-carbon single bonds linking the glutarimide and dimethylcyclohexanone rings. The crystal structure analysis has shown that the two molecules have very different overall conformations, resulting not only from the rotations of the linkage bonds, but also from differences in the puckering of the dimethylcyclohexanone rings. The exocyclic torsion angle C(5)-C(4)-C(7)-C(8) is gauche (−63°) in molecule A and trans (174°) in molecule B, so that the glutarimide and dimethylcyclohexanone rings have different orientations in the two molecules (Figure 1). Despite this very pronounced difference, the torsion around the central C(7)-C(8) bond is in the apparently preferred trans conformation in both molecules (Table I), thereby forcing them into an extended rather than a folded configuration. Likewise, the torsion angle around the third exocyclic bond (C(8)-C(9)) is similar in both molecules.

Table I. Torsion Angles in Cycloheximide

Atoms	Exocyclic torsions Molecule A	Molecule B
C(5)-C(4)-C(7)-C(8)	−62.8 (3)	174.1 (2)
C(3)-C(4)-C(7)-C(8)	175.5 (2)	52.9 (3)
C(4)-C(7)-C(8)-C(9)	179.0 (2)	160.1 (2)
C(7)-C(8)-C(9)-C(10)	−164.7 (2)	174.8 (2)
C(7)-C(8)-C(9)-C(14)	70.1 (3)	49.9 (3)

Atoms	Endocyclic torsions (cyclohexanone) Molecule A chair	Molecule B twist boat	(Ideal) twist boat[3]
C(9)-C(10)-C(11)-C(12)	46.9 (3)	24.5 (3)	33.2
C(10)-C(11)-C(12)-C(13)	−50.6 (4)	38.6 (3)	33.2
C(11)-C(12)-C(13)-C(14)	55.0 (4)	−67.7 (3)	−70.6
C(12)-C(13)-C(14)-C(9)	−55.9 (4)	30.8 (3)	33.2
C(13)-C(14)-C(9)-C(10)	52.4 (4)	28.9 (3)	33.2
C(14)-C(9)-C(10)-C(11)	−48.1 (3)	−59.7 (3)	−70.6

The dimethylcyclohexanone rings differ in the two molecules in that the familiar chair conformation is adopted in molecule A and the twist boat conformation in molecule B (Figure 2). A comparison of their endocyclic torsion angles is given in Table I. In the chair form, one of the methyl groups is axial and the other equatorial resulting in some unfavorable 1,3 nonbonded interactions between the axial methyl group and the axial hydrogen atoms at C(9) and C(11). These interactions

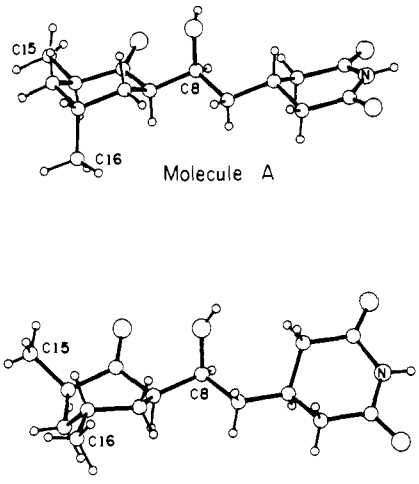

Figure 2. End-on views of the overall conformations of the two independent cycloheximide molecules illustrating the chair (molecule A) and twist boat (molecule B) dimethylcyclohexanone rings.

are relieved in the twist boat conformation, and perhaps act as the driving force for the transition from the chair to the twist boat where the C(16) methyl becomes pseudoequatorial (from axial), the C(15) methyl becomes isoclinal (from equatorial), and the C(8) carbon leading to the glutarimide portion of the molecule becomes pseudoequatorial (from equatorial). Thus, there is a delicate balance between ring strain (1,4 nonbonded interactions) in the boat form and the steric (1,3 nonbonded) interactions in the chair. Our estimate is that the twist boat structure is probably 2-3 kcal/mol higher in energy than the chair. Molecular mechanics calculations comparing the relative intramolecular energetics of the two structures would be of interest.[4] Besides the intramolecular nonbonded interactions mentioned above, the crystal packing forces may also play a role in stabilizing the twist boat conformation.

The occurrence of more than one independent molecule in the asymmetric unit of a crystal is not uncommon, and conformational variation between them is frequently observed.[5,6] However, the existence of both the chair and twist boat conformations in chemically identical rings in the same crystal, as observed here, is unique and quite unexpected. It should be pointed out that the dimethylcyclohexanone moiety presents a good case for this phenomenon since it contains a trigonal carbon atom C(10) in the ring which would be expected to reduce the energy barrier between the chair and boat forms in comparison to cyclohexane.[7,8] As expected,[9] the cyclohexanone chair is flattened around the ring bonds of the trigonal carbon atom and buckled most around the bonds involving C(13) at the opposite end of the ring (Table I). The torsions around the central bonds have intermediate values. In the twist boat, the C(9)-C(10) and C(12)-C(13) bonds on opposite sides of the ring exhibit the greatest pucker (−59.7 and −67.7°), while the torsions around the remaining ring bonds range from 24.5 to 38.6°.

The cycloheximide molecules are closely packed in the crystal with molecules A and B lying on interleaving planes separated by 3.5 Å. Within the planes, the glutarimide portions of screw axis related molecules are linked through hydrogen bonds between the ring nitrogen and the carbonyl oxygen O(2) to form an infinite ribbon along the screw axis. The O(6) carbonyls do not participate in hydrogen bonding. The molecular layers are cross-linked by a hydrogen bond between the hydroxyl group of molecule A and the glutarimide carbonyl oxygen O(2) of molecule B. Thus, the carbonyl oxygen O(2) of molecule B is involved in an intralayer as well as an interlayer hydrogen bond. The hydroxyl group of *molecule B* is not involved in any hydrogen bonding, although an intramolecular hydrogen bond between this hydroxyl and the carbonyl oxygen O(10) of the cyclohexanone ring is geometrically possible. Steric interference from the C(16) methyl group of a neighboring molecule B rotates the hydroxyl hydrogen away from the carbonyl function (Figure 2) preventing the formation of the intramolecular hydrogen bond. In *molecule A* the above intramolecular hydrogen bond is again not formed due now to the rotation around the C(8)-C(9) and C(9)-C(10) bonds (Table I).

The biological activity of cycloheximide is probably a result of its specific binding to a ribosomal or soluble protein involved in translocation.[1] The chair conformation would preferably be involved in such an interaction because of its inherent stability compared to the twist boat. Besides these two cycloheximide conformations found in the solid state, the possibility of an alternative conformation being involved in the interaction with the protein synthesis machinery cannot be precluded. Knowledge of the solution conformation of cycloheximide would also be of interest in this regard.[10] Further information on the biologically active conformation could be gleaned through crystallographic studies of the active cycloheximide analogues, streptimidone and streptovitacin A, which are currently in progress in our laboratory.

Acknowledgments. We gratefully acknowledge Dr. Julian Davies of this department for his enthusiastic interest in the work. This research was supported by Grant GM-17378 from the National Institutes of Health of the United States Public Health Service and the College of Agricultural and Life Sciences, University of Wisconsin-Madison.

Supplementary Material Available: A table of atomic coordinates (1 page). Ordering information is given on any current masthead page.

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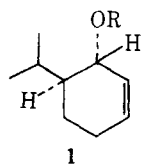
J. Sayers, D. Schindler, M. Sundaralingam*
Department of Biochemistry
University of Wisconsin-Madison
Madison, Wisconsin 53706
Received December 27, 1976

Concerning the Stereochemistry of the S_N2' Reaction in Cyclohexenyl Systems

Sir:

Over 20 years ago,[1] we examined the stereochemistry of the S_N2' reaction of piperidine with the 2,6-dichlorobenzoate of *trans*-6-isopropyl-2-cyclohexen-1-ol (**1**, R = 2, 6-dichlorobenzoyl). We have now reexamined this reaction and have further extended the inquiry to a variety of other situations. We can now report the following: (1) The detailed scrutiny now possible with analytical tools which were unavailable at the time of the original study has confirmed the conclusion that S_N2' displacement on cyclohexenyl esters **1** with piperidine leads to (predominant) syn entry of the displacing group with formation of the amine **2.** (2) Extension of the study to the cis isomer of **1,** shows exclusive syn entry of the piperidine in the S_N2' product (**3**, R = aroyl → **4**). (3) When the displacing



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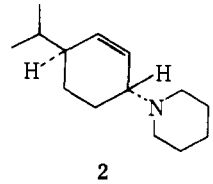

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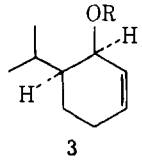

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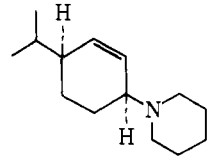

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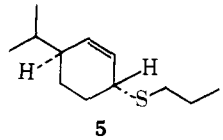
group was changed from piperidine to propanethiolate, a major product was the sulfide from simple S_N2 displacement. The rearranged sulfide component was again largely formed by syn displacement (**1** → **5**). Remarkably, however, this was accompanied by varying amounts of the epimer **6** from anti displacement: the ratio of **5** to **6** varied from ~10:1 down to ~2:1,



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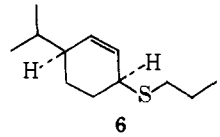

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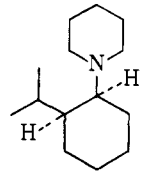
depending on the departing aroyl group R in **1** and on the reaction solvent. (4) The cis isomer **3,** R = aroyl, in striking contrast to its clean syn allylic displacement with piperidine (**3** → **4**) led, in 1-butanol, to either a predominance of anti S_N2' product (**3** → **5, 6**) with the sodium salt of propanethiol (**5:6** ~65:35), or to essentially equal amounts of syn and anti displacement with the corresponding lithium salt.

We now report the experimental evidence and correlations which form the basis for these conclusions.

trans 6-Isopropyl-2-cyclohexen-1-ol (**1,** R = H) was prepared by lithium aluminum hydride reduction[2] of the corresponding enone and purified as reported[1] (NMR: δ 0.83, 3 H, d, *J* = 7 Hz; 0.94, 3 H, d, *J* = 7 Hz; 5.63, 2 H, s). The 2,6-dichlorobenzoate **1,** R = 2,6-dichlorobenzoyl, mp 65–67 °C (reported[1] 66.5–67.2 °C), had NMR: δ 0.92, 3 H, d, *J* = 6 Hz; 0.99, 3 H, d, *J* = 6 Hz; 5.83, 2 H, s. The liquid mesitoate **1** (R = 2,4,6-trimethylbenzoyl) from the lithium salt of **1,** R = H, and mesitoyl chloride (−20 °C → room temperature overnight, 78%)[3] had NMR: δ 0.88, 3 H, d, *J* = 6 Hz; 0.97, 3 H, d, *J* = 6 Hz; 5.78, 2 H bs.

cis-6-Isopropyl-2-cyclohexen-1-ol (**3,** R = H) was best prepared from the corresponding enone with triisobutylaluminum in toluene to give a 92/8 mixture of **3** and **1,** R = H. The pure **3,** R = H, mp 43–45 °C,[3] had NMR: δ 0.93, 3 H, d, *J* = 6 Hz; 0.97, 3 H, d, *J* = 6 Hz. The structure was confirmed by reduction with diimide to *cis*-2-isopropylcyclohexanol,[4] also obtained by lithium tri-*sec*-butylborohydride (L-Selectride)[5] reduction of 2-isopropylcyclohexanone. The mesitoate **3,** R = 2,4,6-trimethylbenzoyl, mp 71–73 °C,[3] had NMR: δ 0.93, 3 H, d, *J* = 6 Hz; 0.98 3 H, d, *J* = 6 Hz; 5.45, 1 H, m; 6.02 2 H, m (CH=CH).[6]

A reference mixture of the two 1-piperidinoisopropylcyclohexanes was prepared starting with the catalytic hydrogenation of 2-isopropylcyclohexanone oxime (platinum oxide in acetic acid) to a mixture (largely cis)[7] of the primary amines (kugelrohr 110 °C/35 mm, 71% yield) which were then cycloalkylated with 1,5-dibromopentane (40 h reflux in ethanol with potassium carbonate). The product (kugelrohr 100 °C/0.5 mm, 60% yield) was an 86:14 mixture of the cis and trans isomers of 1-piperidino-2-isopropylcyclohexane, **7** and **8,** respectively.[8] The cis and trans 4-piperidinoisopropylcyclohexanes **9** and **10** were synthesized, as previously described,[1] by displacement with piperidine of the tosylates of trans and cis 4-isopropylcyclohexanol. The latter were prepared from 4-isopropylcyclohexanone with lithium aluminum hydride[9] (trans:cis = 80:20) or with L-Selectride[5] (trans:cis = 7:93).



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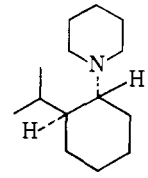

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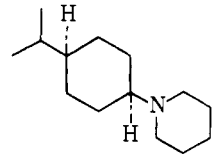

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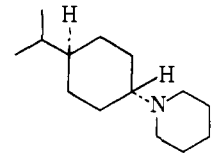

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The authentic *trans*- and *cis*-3-isopropyl-6-propylthiocyclohexene, **5** and **6,** were prepared via the stereospecific Mislow rearrangement[10] of the propylsulfenates of **1** and **3,** R = H, to the sulfoxides, followed by lithium aluminum hydride reduction to the desired thioethers (A → B → C → D). The *trans*- and *cis*-4-isopropyl-3-propylthiocyclohexenes **13** and **14**[11] were prepared similarly from *trans*- and *cis*-4-isopropyl-2-cyclohexen-ols, themselves made by the lithium aluminum hydride reduction of the corresponding enone.[12] Separation on silica gel gave the more rapidly eluted cis alcohol[13] (~20%) **11,** followed by the trans isomer **12** (~80%).

Displacement of the ester **1,** R = 2,6-dichlorobenzoyl, in neat piperidine (24 h, 130 °C), as previously described,[1] did indeed result in the formation of the product of syn allylic displacement, the unsaturated amine **2.** It was, however, accompanied by the isomer **4** (**2:4** = 61:23). We suspected that the correct ratio might be more in favor of the syn product **2**