From the resuls of the assay with mydriasis of mice eyes, is was shown that the antispasmodics by the antacid reduced the abesorption of these drugs from gastrointetinal tract, but practically this will not affect their pharmacological activity seriously, because gastric juice will facilitate the dissociation of the drug from antacid.

To examine the effects of the drugs on peptic ulcer, Shay rats were used. Ulcer formation on Shay rat's stomach was treated as the duantal response, and ED 50 of some drugs was calculated. By this method it was shown that synergism of antispasmodics with antacid was of the type of potentiation.

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207. Masao Nishikawa : Infrared Spectra of Thiourea and its Inclusion Compounds. IV.[*1] Investigations on Aggregational States of Some Cyclohexane Derivatives.

(*Research Laboratories, Takeda Chemical Industries, Ltd.*[*2])

In an earlier paper of this series,$^{1)}$ a method of investigations on infrared dichroism of thiourea adducts was described. This method would be also applicable for studies on hydrogen bonding of enclosed molecules having some polar groups.

Previously, Barlow and Corish$^{2)}$ found that the C=O stretching vibrations of hexanoic acid and pelargonic acid molecules trapped in urea channels absorbed at the same frequencies as those in the liquid states and they suggested that the carboxyl groups of these molecules were in similar environments in these two states. An identical phenomenon was observed also by Mima, *et al.*$^{3)}$ in the case of α-lipoic acid-thiourea adduct but more detailed studies did not appear to be published until the author measured the characteristic bands due to the OH out-of-plane bending vibrations of α-lipoic acid or hydnocarpic acid trapped in thiourea channels, and showed$^{1)}$ that these carboxylic acids formed dimers in channels just as they did in nonpolar solvents.

As for the molecular structure, either of these acids has a relatively long CH_2 chain between the five-membered ring and carboxylic group and therefore, because of the flexibility of the polymethylene chain, the carboxyl groups will be able to form dimers without much difficulty even the molecules are confined in thiourea channels. If however, the flexible chain is missing or the carboxylic group is linked directly to the ring, hydrogen bonding of the acid dimers might not occur since the conformation of the ring is somewhat restricted as shown in the previous paper.[*1] The present work is concerned with an analysis of aggregational states of cyclohexane derivatives having some polar groups directly attached to the six-membered ring. An outline of a part of this work was reported in a communication$^{4)}$ already.

[*1] Part Ⅲ : This Bulletin, **11**, 977 (1963).

[*2] Juso-nishino-cho, Higashiyodogawa-ku, Osaka (西川正夫).

1) M. Nishikawa : This Bulletin, **10**, 1205 (1962).

2) G.B. Barlow, P.J. Corish : J. Chem. Soc., **1959**, 1706.

3) H. Mima, Y. Asahi, H. Okuto, T. Kanzawa : Yakugaku Zasshi, **80**, 1233 (1960).

4) M. Nishikawa : Chem. & Ind. (London.), **1963**, 256.

Experimental

IR dichroic measurements and determinations of absorption frequencies of guest molecules in thiourea channels were conducted in the same way as reported in previous papers of this series.[*1,1,4,5]

Among the guest molecules treated in this work, cyclohexanecarboxylic acid, cyclohexanol, cyclohexylamine, and methylcyclohexane were obtained as commercial guaranteed reagents which were subsequently purified by several recrystallizations or redistillations. *trans*-2-Chlorocyclohexanol was synthesized by the method described by Newman and VanderWerf.[6] Cyclohexanemethanol was obtained by the reduction of methyl cyclohexanecarboxylate with $LiAlH_4$ in Et_2O, b.p$_{20}$ 90°.

Several compounds did not form adducts with thiourea by ordinary methods. For example, cyclohexylamine-thiourea adduct could not be prepared but with large excess of the amine in a small amount of solvent, MeOH. In this case it was difficult to remove excess amine completely from the adduct crystal without partial decomposition of the adduct. Me_2CO was found to be a good solvent for such case. In Me_2CO, adducts were formed even in a relatively large amount of solvent. The crystal grown from Me_2CO solution was washed with ice cooled Me_2CO and Nujol was applied immediately on it. By this procedure thiourea adducts satisfactorily pure for the present experiment were obtained. During these processes, Me_2CO molecules might also be forced to be enclosed in thiourea channels but the intensity of the carbonyl absorption of Me_2CO was so weak that the interpretation of the experimental results was not obscured.

A volumetric titration of cyclohexanecarboxylic acid enclosed in thiourea channels was conducted as follows. About 60 mg. of cyclohexanecarboxylic acid-thiourea adduct was dissolved in 20 ml. of neutralized EtOH and the solution was titrated with 0.1*N* KOH by the use of phenolphthalein as an indicator. From the amounts of the KOH solution consumed for the titration, the molar ratio of the host and guest molecules in the adduct was calculated by

$$[\text{molar riato}]=\left(\frac{[\text{adduct, mg.}]}{[0.1N\ \text{KOH, ml.}]}-12.8\right)\times\frac{1}{7.6}$$

Results and Discussion

a) Cyclohexanecarboxylic Acid

In Fig. 1 are shown the spectra of cyclohexanecarboxylic acid-thiourea adduct measured by the polarized lights with the electric vector parallel or perpendicular to the C-axis of the adduct crystal. There are three points which deserve attention. The first point is a marked low transmission in the region between 2700 and 1800 cm^{-1} (especially near 2600 cm^{-1}) of the polarized light with electric vector parallel to the C-axis. This is the region just where absorption bands due to the OH stretching vibrations of strongly hydrogen bonded carboxylic acid dimers are expected. The second point is the appearance of a characteristic broad and strong absorption band at 945 cm^{-1}. The

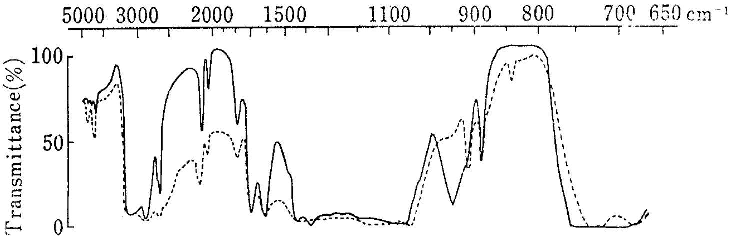

Fig. 1. Infrared Spectra of Cyclohexanecarboxylic Acid-Thiourea Adduct

—— Electric vector perpendicular to the C-axis of the crystal

------ Electric vector parallel to it

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5) M. Nishikawa, H. Mima, T. Kanzawa: This Bulletin, **10**, 1199 (1962).

6) M.S. Newman, C.A. VanderWerf: J. Am. Chem. Soc., **67**, 233 (1945).

frequency of this band is higher, by 10 cm^{-1}, than the OH out-of-plane bending frequency of the dimer in solution, in contrast with the case of α-lipoic acid reported before.[1] Nevertheless the band was definitely assigned to the OH bending vibration, since no other vibrations of this molecule will give rise to such a broad and strong band at this frequency. On the contrary to the OH stretching bands, this band showed strong perpendicular dichroism to the crystal axis.

The third point is concerned with the C=O stretching vibration, which is not clearly observed in this figure. A more detailed spectrum is shown in Fig. 2, in comparison with the spectra measured in solution. From the figure, it is apparent that the frequency of the C=O stretching vibration of cyclohexanecarboxylic acid trapped in thiourea channels coincides well with that of the acid dimer in carbon tetrachloride solution. In Table I the frequencies of this vibration as measured in various states are listed. These three points indicate the dimer formation of this acid in thiourea channels and, in addition, the dichroic behavior described above suggests that the O-H------O hydrogen bonds of the dimer is neary paralled to the C-axis of the adduct crystal.

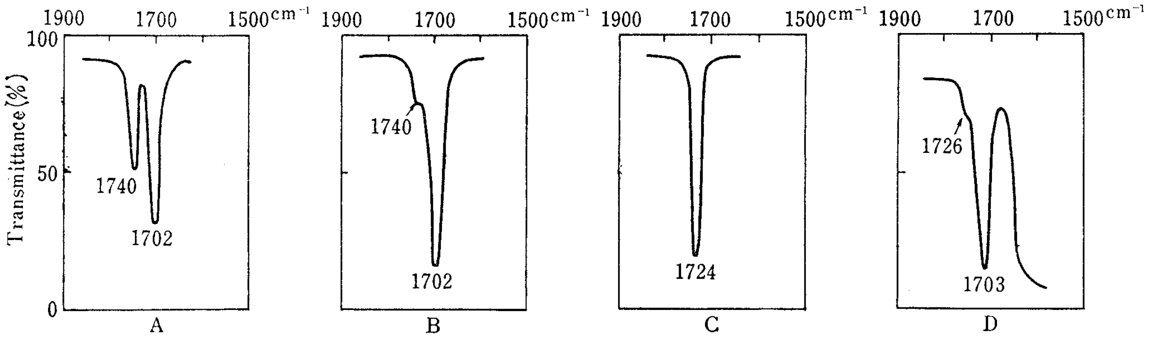

Fig. 2. C=O Stretching Vibration of Cyclohexanecarboxylic Acid in Various States

A : 0.0005 mole CCl_4 soln. C : 0.1 mole Dioxane soln.
B : 0.1 mole CCl_4 soln. D : Thiourea adduct

TABLE I. Frequencies of Carbonyl Stretching Vibrations and Hydroxyl Out-of-plane Bending Vibrations of Cyclohexanecarboxylic Acid in Various States

		$\nu_{C=O}$ (cm^{-1})		δ_{OH} (cm^{-1})
		Monomer	Dimer	Dimer
Thiourea adduct		—	1702	945
Solid state		—	1703	935
Solutions in	Hexane	1756	1707	940
	CCl_4	1750	1704	938
	CS_2	1750	1704	938
	$CHCl_3$	1726	1701	937
	Xylene	—	1703	942
	Chlorobenzene	—	1701	937
	Dichloroethane	1738	1702	939
	Dioxane	1729	—	—
	Acetonitril	1734	—	—

For the determination of the preferred conformation of cyclohexanecarboxylic acid molecules in thiourea channels, methods similar to that used previously for halocyclohexanes*[1] could not be applied, since the infrared absorption bands of the two conformational isomers of cyclohexanecarboxylic acid have not been established. However, the following considerations based on other standpoints would give some information concerning to this conformational problem.

The difference of the free energy between the two conformational isomers of cyclohexanecarboxylic acid, namely, the two chair forms with the axial and the equatorial C-COOH bond has been determined by Stolow in aqueous solution.[7] According to his results, ΔF for the undissociated acid is 1.7 ± 0.2 k cal/mole and that for the carboxylate anion is 2.4 ± 0.4 k cal/mole. These values are three to four times as large as those for halocyclohexanes and although they may be somewhat smaller in less polar solvents because of weaker solvation of the carboxyl group, it is questionable whether the axial conformation of cyclohexanecarboxylic acid molecules is preferred to the equatorial one in thiourea channels overcoming such large free energy difference of the two isomers.

The free energy difference for methylcyclohexane has also been estimated by several investigators and the values, 1.8,[8] 1.5[9] and 1.97[10]k cal/mole were obtained in the vapour state, in ether and in carbon disulfide solutions, respectively. The abundance ratio [equatorial]/[axial] calculated from these values is about $10\sim30$. Consequenly, bands associated only with the equatorial conformation have been clearly located by infrared spectroscopic analysis.[11] In the present work the thiourea adduct of methylcyclohexane was also prepared and its infrared absorption was measured by the present technique. The observed adduct spectrum of methylcyclohexane was identical with that of the liquid state or of solution, in contrast to the case of halocyclohexanes where remarkable intensity changes were observed between the spectra in thiourea adducts and the ones in the liquid state.[*1] Accordingly in the case of methylcyclohexane the equatorial conformation must be preserved even in thiourea channels. Cyclohexanecarboxylic acid molecules, ΔF of wihch is comparable with that of methylcyclohexane, would also exist in the equatorial conformation even though they are enclosed in thiourea channels.

Another support for the preservation of the equatorial conformation in thiourea channels is given by consideration of the molar ratio of the two components in the adduct.

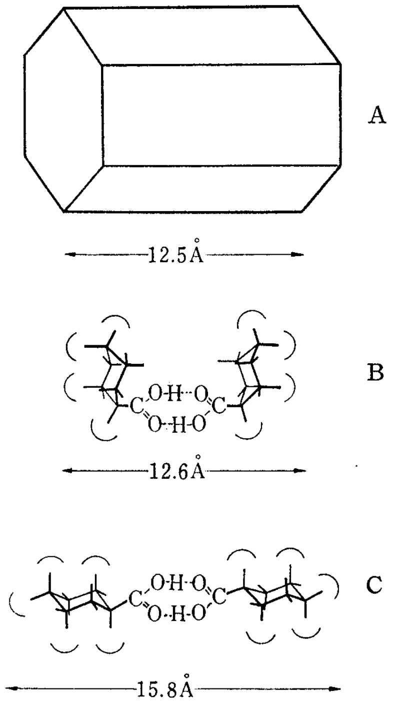

Fig. 3. Diagram of the Thiourea Channel and Cyclohexanecarboxylic Acid Dimer

A : The unit cell of thiourea adduct
B : Axial dimer of cyclohexanecarboxylic acid
C : Equatorial dimer of it

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7) R.O. Stolow : J. Am. Chem. Soc., **81**, 5806 (1959).
8) C.W. Beckett, K.S. Pitzer, R. Spitzer : J. Am. Chem. Soc., **69**, 2488 (1947).
9) E.L. Eliel, M.N. Rerick : *Ibid.*, **82**, 1367 (1959).
10) F.R. Jensen, L.H. Gale : J. Org. Chem., **25**, 2075 (1960).
11) M. Larnandie : Compt. rend., **235**, 154 (1952).

By volumetric titration of the adduct and by elementary analysis conducted in this work, the molar ratio [thiourea]/[cyclohexanecarboxylic acid] was found to be 3.8. However, from inspection of the molecular model, as shown in Fig. 3, the length of the dimer structure of cyclohexanecarboxylic acid in the axial conformation was roughly estimated to be 12.6 Å, which was equal to the length of a unit cell of the adduct crystal. Therefore, in this conformation the molar ratio should be 3,*[3] provided that channels are closely packed with guest molecules. On the contrary, if the equatorial conformation was taken in thiourea channels, the dimer would be about 15.8 Å long. This value is consistent with the observed molar ratio, 3.8.

It will be necessary, at this point, to know the origin of the force which changes the conformation of halocyclohexanes to the axial form on inclusion in thiourea channels. Formerly Schlenk[12] found that in the case of urea adducts the molar ratio [host]/[guest] increased uniformly with increasing chain length of guest molecules (*e.g.*, paraffins) but in the case of thiourea adducts the molar ratio changes stepwise with the length of CH_2 chains of alkylcyclohexanes or ω,ω'-dicyclohexylalkanes (guest molecules) and the adducts with ratios of 3, 6, 9, etc., were more stable than those with intermediate ratios. For example, pentylcyclohexane-, hexylcyclohexane- and heptylcyclohexane-thiourea adducts have the same molar ratio of 6 even though the numbers of CH_2 groups are different as many as two. Since there values of the molar ratios are multiples of the half of the number of thiourea molecules in unit cell,*[3] Schlenk presumed that there were two relatively large rooms in a unit cell. There, the potential energy of van der Waals' attractive forces were presumed to be minimum and so guest miolecules would be enclosed most stably. For guest molecules having slightly longer CH_2 chains than the length of these rooms, the chains are somewhat deformed so as to get accommodated in the rooms. These forces would be the same as the ones which change the conformation of halocyclohexanes on inclusion in thiourea channels. In the equatorial conformation, the shapes of halocyclohexane molecules are rather elliptical and will be a little too longer for the room in thiourea channels. So, in order to form stable adducts some forces must operate to change the conformation to the axial one in which the molecular shapes are spherical and one molecule of halocyclohexanes will be enclosed just in one room provided by thiourea. Thus, the molar ratio of halocyclohexane-thiourea adducts are 3, whereas the ratio of methylcyclohexane-thiourea adduct, where methylcyclohexane molecules take the equatorial conformation, is 3.5.[11] In the case of cyclohexanecarboxylic acid, the equatorial conformation in thiourea channels would be presumed even by the molar ratio of 3.8 only.

Qualitative coincidence of the infrared absorption bands of cyclohexanecarboxylic acid (between 1400 and 700 cm^{-1}) in thiourea adduct, measured as Nujol mull, with those in solution would also suggest the same conformation of this acid in these two states.

b) Cyclohexanol

The next problem to be solved is aggregational and conformational states of cyclohexanol which has an OH group substituted on a cyclohexane ring. Since OH groups form weaker hydrogen bond than do COOH groups, cyclohexanol may be situated at an intermediate position between halocyclohexanes and cyclohexanecarboxylic acid. Spectra of cyclohexanol-thiourea adduct were measured by the present technique and are shown in Fig. 4.

Aggregational state would be investigated most conveniently with absorption bands due to the hydroxyl group. In Fig. 4 there are two bands assignable to the stretching

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*[3] A unit cell consists of six molecules of thiourea.

12) W. Schlenk : Ann., **573**, 142 (1951).

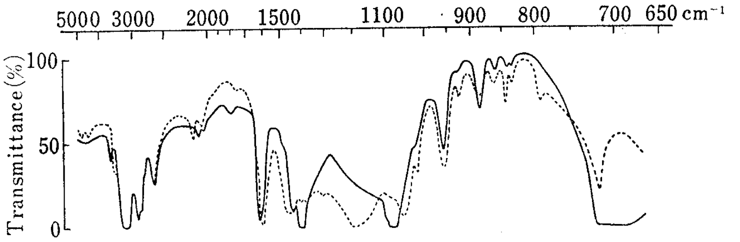

Fig. 4. Infrared Spectra of Cyclohexanol–Thiourea Adduct
—— Electric vector perpendicular to the C–axis of the crystal
------ Electric vector parallel to it

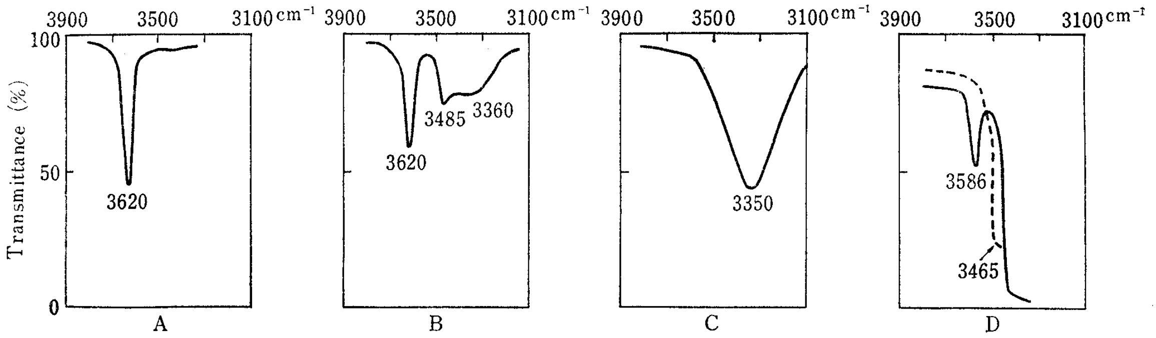

Fig. 5. O–H Stretching Vibration of Cyclohexanol in Various States
A : 0.0005 mole CCl_4 Soln. C : The liquid state
B : 0.1 mole CCl_4 Soln. D : Thiourea adduct

Table II. Frequencies of OH Stretching Vibrations of Some Cyclohexane Derivatives in Various States

	Solutions in							Thiourea adduct	
	CCl_4		Chlorobenzene		Xylene		Dioxane		
Cyclohexanol	3620	3485	3605	3485	3587	3491	3495	3586	3465
Cyclohexanemethanol	3641	3492	3621	3490	3603	3495	3500	3602	3400
2-Chlorocyclohexanol	3593	3475	3586	3482	3589	3480	3465	3574	

vibration of this group. In Fig. 5, the portion of the spectra associated with this vibration is expanded and is compared with those of spectra in other states. Absorption frequencies of this mode of vibration in various states are tabulated in Table II. Clearly the band at 3586 cm^{-1} in thiourea adduct arises from the free hydroxyl group and the frequency shift of 34 cm^{-1} from that in carbon tetrachloride solution may be attributed to environmental effects.[1,13] Such an absorption band has never been observed in the case of urea adducts with some alkanols.[14] The shoulder band at 3465 cm^{-1}, located on the high frequency side of the strong NH stretching bands of thiourea might be due to the dimer just like the band at 3486 cm^{-1} in carbon tetrachloride solution.[15]

The band at 3586 cm^{-1} exhibited perpendicular dichroism to the C-axis of the adduct crystal. On the contrary, the band at 3465 cm^{-1} exhibited the parallel polarization. The dichroisms of these two bands were unusually strong.

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13) W.C. Price, W.F. Sherman, G.R. Wilkinson : Proc. Royal Soc., Series A, **255**, 5 (1960).
14) A.R. Daniewski, U. Dabrowska, Z. Piasek, T. Urbański : J. Chem. Soc., **1962**, 2340.
15) R.N. Jones, C. Sandorfy : "Technique of Organic Chemistry IX, Chemical Applications of Spectroscopy," p. 418 (1956).

Possibly the band due to the stretching vibration of more strongly hydrogen-bonded OH group lies in lower frequency region but it was not recognized because of overlapping with the NH bands. Such a band, if existed, would be of little significance since the intensities of the above two bands were sufficiently strong when compared with those of other bands due to cyclohexanol observed in Fig. 4.

The conformations of cyclohexanol in solution have been investigated by earlier researchers[16,17] and the C-O stretching band at 1069 cm^{-1} has been assigned to the equatorial isomer and the band at 972 cm^{-1} to the axial isomer. From the intensity ratio of these two bands the isomer ratio [equatorial]/[axial] at 25° was calculated to be $1.68\sim1.95$[16] or $1.50\sim1.85$[17] which corresponds to the free energy difference of $300\sim400$ or $250\sim350$ cal/mole, respectively. These values are not much different from those obtained from rates of certain chemical reactions ($K=2.40$ and $\Delta F=520$ cal/mole).[18] From these small values of the equilibrium constants in solution, the axial conformation would be expected to be predominant over the equatorial one in thiourea channels. In thiourea adduct, the band at 1069 cm^{-1} overlaps with bands due to thiourea molecules and the conformational analysis could not be achieved by the use of this band. However, as the relative intensities of the bands in the region between 1000 and 750 cm^{-1} in thiourea adduct strongly resemble with those in the liquid state or in solution, the isomer ratio in thiourea channels appears, contrary to the above expectation, to be little different from that in the liquid state (Fig. 6).

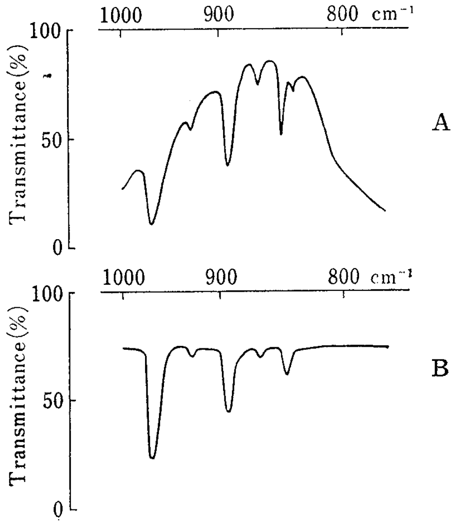

Fig. 6. Infrared Spectra of Cyclohexanol at $1000\sim750$ cm^{-1}

A : Thiourea adduct, Nujol mull
B : In the liquid state

This result may be explained by the information concerning the aggregational state obtained before, that is, appearance of the band due to the dimer. From the considerations of steric hindrance, the formation of the dimer seems to be much more favorable for the equatorial conformation than for the axial one, and because of the energy lowering due to the hydrogen bonding, the former would be stabilized in thiourea channels. Furthermore, the molar ratio [thiourea]/[cyclohexanol] has been determined to be 3.[12] This value indicates that even in the equatorial conformation, one molecule of cyclohexanol can be enclosed just in one room in a unit cell of the thiourea adduct. This would be possible since the hydroxyl groups of the two adjacent cyclohexanol molecules can approach closely one another by the dimer formation.

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16) R.A. Pickering, C.C. Price : J. Am. Chem. Soc., **80**, 4931 (1958).

17) G. Chiurdoglue, W. Masshelein : Bull. Soc. Chem. Belg., **69**, 154 (1960); *Idem* : *Ibid.*, **70**, 29 (1961); *Idem* : *Ibid.*, **70**, 307 (1961).

18) E.L. Eliel, C.A. Lukach : J. Am. Chem. Soc., **79**, 5986 (1957).

From these considerations it may be deduced that the intensity of the band attributed to the dimer may be mostly due to the equatorial isomer whereas that of the band attributed to the free hydroxyl group may arise mostly from the axial isomer. This deduction may be supported by observations described in the next section.

Appearance of the absorption band due to a free hydroxyl group would indicate considerably weak proton-accepting power of thiourea molecules which construct the channel wall. Similar observations were made in previous works,[1,4] where the proton-donating power of thiourea molecules was revealed to be weak from resemblance of absorption bands due to carbonyl groups of guest molecules in adduct with those in nonpolar solvents. These two facts would suggest that in the adduct crystal, thiourea molecules are strongly hydrogen bonded to one another and little ability is left for association with guest molecules except that due to van der Waals' forces even though thiourea itself is a polar compound.

Dichroic behavior of the OH stretching bands could not be explained at present but it might suggest ordered orientation of cyclohexanol in thiourea channels, perhaps due to the cyclic dimer formation. Actually, on the contrary to the case of halocyclohexanes, almost all observable bands of cyclohexanol in the adduct exhibited fairly strong dichroism as shown in Fig. 4.

c) Some other Derivatives of Cyclohexane

In the case of cyclohexanemethanol, the band attributable to the free hydroxyl group ($3620\,cm^{-1}$ in Table II) was much weaker and the shoulder band on the high frequency side of NH bands was stronger and shifted to lower frequency by about $65\,cm^{-1}$ as compared with the case of cyclohexanol. Since the substituent CH_2OH is as large as COOH or CH_3, it would exist mostly in the equatorial conformation in the liquid state as in the case of cyclohexanecarboxylic acid or methylcyclohexane. This conformation would be preserved also in thiourea channels as the relative intensities of bands in the region between 1000 and $750\,cm^{-1}$ in the adduct were nearly the same as those in the liquid state. Therefore, the intensity changes of the hydroxyl stretching bands may be easily understood if the deduction described in section (b) is correct.

The dichroisms of the absorption bands due to hydroxyl stretching vibrations were qualitatively the same as those of cyclohexanol. The bands in the region between 1000 and $750\,cm^{-1}$ in the adduct also exhibited fairly strong dichroism; that is, the bands at 990 and $844\,cm^{-1}$ exhibited parallel dichroism and the bands at 953 and $867\,cm^{-1}$ perpendicular dichroism to the C-axis of the crystal. Only the dichroism of the band at $892\,cm^{-1}$ was not clear.

In the case of *trans*-2-chlorocyclohexanol, the OH stretching frequencies in less polar solvents (Table II) indicate that the hydroxyl group and its adjacent chlorine atom form intramolecular hydrogen bond similar to the case of *trans*-cyclohexane-1,2-diol.[19] Since this hydrogen bond cannot be formed in the diaxial conformation, it suggests that *trans*-2-chlorocyclohexanol molecules exist almost exclusively in the diequatorial conformation in these solutions. This conformation seems to be retained also in thiourea channels as the OH stretching frequency ($3574\,cm^{-1}$) in the adduct is too low for a free hydroxyl group and should be assigned to the intramolecularly hydrogen bonded one.

From the examination of the spectrum of cyclohexylamine-thiourea adduct, little information could be obtained, but the conformational change did not seem to take place in this case either.

As mentioned before, the interactions between the guest and host molecules in adducts seem to arise primarily from van der Waals' forces. Since the energies of van der

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19) R. N. Jones, C. Sandorfy : *loc. cit.*, p. 423.

Waals' forces are usually much smaller than those of hydrogen bonds, the equatorial conformation would be favored even in thiourea channels if this conformation is stabilized by intermolecular or intramolecular hydrogen bonds. These will be the cases of cyclohexanol and *trans*-2-chlorocyclohexanol. On the other hand the axial conformation is preferred for halocyclohexanes and 1,2-*trans*-dihalocyclohexanes which do not have functional groups for the hydrogen bond formation.

The author wishes to thank Dr. S. Tatsuoka, director of Research Laboratories, for his permission to publish this work and Dr. H. Mima for his guidance throughout the course of this work. He is also grateful to Mr. A. Takabatake and Miss Kasahara for experimental assistance.

Summary

Aggregational states of cyclohexanecarboxylic acid, cyclohexanol, cyclohexanemethanol and *trans*-2-chlorocyclohexanol, when they were enclosed in thiourea channels were investigated by the method described in the previous papers of this series. In the case of cyclohexanecarboxylic acid, the dimer structure similar to that found in the liquid states or in solution in less polar solvents was detected. The conformation of this acid could not be determined by this technique but the equatorial form, expected from stereochemical consideration, was ascertained by some other experimental evidences.

Two OH stretching bands were found in cyclohexanol-thiourea adduct, one arising from the free hydroxyl group and the other from the dimer. The dimer formation seemed to stabilize the equatorial conformation so that the tendency of increasing the axial conformation in thiourea channels was not observed in this case. The intramolecular hydrogen bond of *trans*-2-chlorocyclohexanol was found to persist even in the thiourea adduct.

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