VIBRATIONAL ANALYSIS OF GLUTARIMIDE AND β,β-DIMETHYL GLUTARIMIDE

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ABSTRACT

VIBRATIONAL ANALYSIS OF GLUTARIMIDE AND β,β-DIMETHYL GLUTARIMIDE

By

John Wiley Thompson, Jr.

This thesis describes a study, employing infrared and Raman spectroscopy, of glutarimide, 3,3-dimethyl glutarimide and the N-deuterated derivatives of these molecules. In particular the N-H and carbonyl motions were monitored in solution in order to examine changes in the glutarimide-solvent and glutarimide-glutarimide interactions as the solvent is changed. In addition, a vibrational analysis of the molecules was performed. The study was initiated in order to examine whether there is any correlation between the states of the molecule in solution and their physiological activity.

Spectra of these compounds were examined at various concentrations in deuterochloroform and acetonitrile. In deuterochloroform the major solute-solvent interaction was found to occur by hydrogen bond formation through the carbonyl groups of the glutarimides. The formation of hydrogen bonds through the carbonyl groups rather than the N-H group allows the measurement of the N-H and N-D frequencies in a relatively free state.

In acetonitrile, as one would expect, the strongest interaction

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between solute and solvent was found to take place through the N-H (N-D) group of the glutarimides. In this case the N-H----N$\equiv$CCH$_3$ hydrogen bond frees the carbonyl groups from strong solvent interaction and allows the frequencies of these fundamentals to be measured in a relatively free state.

The concentration study indicates that the strongest interaction in solution is between solute molecules resulting in the formation of dimers. On the basis of this study it would appear that dimers form more readily in deuterochloroform than in acetonitrile, since dimer bands appear at lower solute concentration in deuterochlorform.

Assignments are proposed for the observed vibrational bands which are not highly mixed, based on group frequencies and the normal coordinate analysis. In addition, the calculation predicts a large degree of mixing for those fundamentals whose frequencies occur below 1300 cm^{-1}.

It is noted that the frequencies of the fundamentals in most cases are the same for both glutarimide and 3,3-dimethyl glutarimide, and that any differences in frequency can be explained in terms of mass effects. Thus, it is concluded that there is no correlation between the vibrational spectra of the compounds studied and their physiological activities.

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By

John Wiley Thompson, Jr.

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1974

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HISTORICAL

HISTORICAL

The glutarimides are six-membered heterocyclic ring compounds, with five carbon and one nitrogen atoms in the ring. The carbon atoms adjacent to the nitrogen are doubly bonded to oxygen. The general structure of the β-disubstituted glutarimides is shown in Figure 1.

A homologous series of compounds possessing varying pharmacological action is generated by substituting various organic moieties for the hydrogens of glutarimide at the β-position of the ring. The literature contains several examples of methods used to synthesize glutarimide and the β-disubstituted glutarimides (1-12). The physiological activity of these drugs has been examined by several investigators and is reported in the literature (13-21). Table 1 lists some members of this series and their pharmacological activity. It may be noted that as the R groups are changed from hydrogen to hydrocarbon radicals the physiological activity progresses through the sequence inactive, convulsant, dual activity, anticonvulsant.

In addition to studies involving the determination of the drug activity of these compounds, several investigators have attempted to explain the variation in the physiological activity in this series of drugs. It was assumed by most of these investigators that the glutarimides and other narcotic drugs produce their effects by a single mechanism. Such theories attempt to explain the pharmacological action of chemical substances in terms of parameters such as lipid solubility, surface activity, vapor pressure, colloid dispersion, thermodynamic activity, membrane permeability, pore-fit, tissue asphyxia, and depression of enzyme action and energy production of cells (2).

Figure 1. The General Structure of Glutarimide.

Table 1. Activity of β-Disubstituted Glutarimides

Drug	Activity
Glutarimide	Inactive
β,β- Dimethyl glutarimide	Convulsant
β-Methyl-β-ethyl glutarimide	Convulsant
β-Methyl-β-n-propyl glutarimide	Dual activity
β-Methyl-β-n-butyl glutarimide	Anti-convulsant
β-Methyl-β-n-pentyl glutarimide	Anti-convulsant

In 1927 Sircar (22) determined the stability of the rings for several substituted glutarimides by comparing the relative rates of hydrolysis. He reported an unusual instability for glutarimide itself, with a steady increase of the stability of the following series, with substitution at the β-positions of the ring. H,H < Me, H < Et, H < Me, Me < Me, Et < Et, Et < cyclopentane < cyclohexane.

Popov and Holm (23) and Lee and Dumler (24) studied the dipole moments of glutarimide and several β-substituted glutarimides in 1961. Lee and Dumler (25) later compared these moments with those of cyclic anhydrides and aromatic cyclic imides. The differences in dipole moments were shown to be due to differences in degree of resonance, with the resonance in the glutarimides being moderate; greater than in the cyclic anhydrides, but less than for the aromatic cyclic imides. The resonance structures for the glutarimides are shown in Figure 2.

A molecular orbital calculation by Andrews (26) in 1968 attempted to link the electron distribution in the heterocyclic ring to the drug activity, but with little success. Andrews found no correlation between the calculated atomic charges and observed activity, indicating that hydrogen-bonding ability, in terms of net atomic charges, has little effect on the types or extent of physiological activity. He proposed that the activity of the drugs may be due to a strong and specific hydrogen-bonding complex with a cellular substrate, where the type of action is controlled by the size and position of substituent groups.

Shulman, in 1963 (5), and again in 1964 (2), proposed a mass-action theory whereby convulsant and anticonvulsant drugs produce their opposed action at common sites in the central nervous system. In terms of rate theory the convulsant drugs have high values of k_2,

Figure 2. Resonance Structures of Glutarimide.

the dissociation rate constant for the receptor-drug complex, anticonvulsant drugs have low values of k_2, and drugs of dual activity have intermediate values of k_2. This theory considers that convulsive and anticonvulsive drugs differ primarily in their affinity for the common receptor surfaces. The common site hypothesis is supported by the N-allylation of β- methyl, β-ethylglutarimide (convulsant), and β-spiro-cyclohexaneglutarimide (anticonvulsant). N-allylation of these compounds of opposite central nervous system action produces drugs with dual activity. It is very difficult to explain this change in activity in terms of hypnotic and convulsive action taking place at separate sites, but this behavior is understandable in terms of action at common sites. Shulman reports (14) that in some cases the change in drug activity can be linked to relative changes in the flexibility of the ring system. Several other experimental facts are presented to support the theory, and processes involved in the central nervous system related to drug action are suggested.

In 1969 Buchanan and Shulman (18) determined air-solution surface tension isotherms for several drugs with central nervous system stimulant action. Several of the β-disubstituted glutarimides were among the drugs for which isotherms were obtained. The results indicate that convulsive drugs tend to populate the aqueous bulk phase while the anticonvulsive drugs tend to accumulate at the air-solution interface. The surface activities of the drugs with dual action appeared to be related to their depressant activities. Buchanan and Shulman suggested that a crude analogy could be drawn between the two phases of the simple air-solution system and the protein and lipid phases of a responsive neuronal membrane. The neuronal membrane is, of course, much more complicated than the air-solution system, and in such a complicated environment there must be many other factors involved. However, the same types of forces which regulate the phase of accumulation of the drug in the simple air-solution system may also make a significant contribution to its distribution between the protein and lipid phases of the membrane.

Andrews and Buchanan (27) studied the self association of a series of β-disubstituted glutarimides and their association with 9-ethyladenine. In both cases the association was measured in chloroform, and the N-H stretching region was monitored by infrared spectroscopy to determine the degree of association. The self association of the glutarimide molecules produces cyclic dimers, i.e., the molecules orient themselves in such a way that two hydrogen bonds are formed in the dimer (see Figure 14), such as in the formic acid dimer. The association with 9-ethyladenine was also cyclic, with two hydrogen bonds per heterodimer. Changes in the substituent groups at the β-position, which markedly affect physiological activity, did not significantly influence the observed association constants. However, as Andrews and Buchanan point out, the strength of the associations are consistent with the hypothesis that such an association may be occurring in the central nervous system, with a second variable determining the type and degree of activity.

Several investigators have recorded the infrared spectra of glutarimide and several of the β-substituted glutarimides. Hall and Zbinder (31) recorded the IR spectrum of glutarimides in the solid state and in carbon tetrachloride solution. They assigned the N-H

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stretch, the C=O stretch, and four of the six C-H stretches. However, a complete analysis of the spectrum was not attempted.

Bassignana et al. (32) recorded the infrared spectra of a large number of imides, including glutarimide, with the emphasis on the carbonyl stretching region. Again, no detailed analysis was attempted.

Borisevich and Khovratovich studied the infrared spectra of a number of phthalimides (33), a five-membered ring imide fused to a benzene ring. They reported finding bands which were absent in the spectra of compounds with alkyl groups on the imide nitrogen. These bands were assigned to the N-H bending motions, and occurred at approximately 1620-1650 cm^{-1}.

The crystal structure of glutarimide has been determined by Petersen (34). He reported a puckered conformation of the molecule, with the carbon at the β position being 0.5 Å out of the planar system formed by the other five ring atoms. In the solid phase the molecules are linked together by N-H---O bonds in infinite chains, in contrast to solution where they form dimers.

Mass spectra of several glutarimides obtained from vaporized solids by Maquestiau and Lejeune (35) do not indicate the presence of dimers. The fragmentation patterns suggest preferential ionization of the oxygen rather than the nitrogen atom. The authors suggest that the explanation for such behavior is to be found in the conjugation of the molecular orbitals, and resonance structures such as illustrated in Figure 2.

In summary, we note that there have been many investigations into the physiological activity of the β-disubstituted glutarimides and the cause of the change in activity. However, the latter has not been elucidated. The vibrational spectra, both infrared and Raman, have not been analyzed completely in the past. It was felt that a detailed analysis of the vibrational spectrum of the glutarimides, with emphasis on the motions of the N-H and C=O groups as well as the ring skeletal modes, could provide useful information, and that possibly a correlation could be found between the vibrational spectra of the β-disubstituted glutarimides and their physiological activities.

CHAPTER I

EXPERIMENTAL

CHAPTER I

EXPERIMENTAL

COMPOUNDS

Glutarimide and 3,3-dimethyl glutarimide were obtained from the Eastman Kodak Company and were used without further purification. The N-deuterated compounds were prepared by dissolving glutarimide and 3,3-dimethyl glutarimide in deuterium oxide (Columbia Organic). The solutions were left standing for 72 hours, with intermittent agitation. The solutions were then evaporated to dryness over calcium sulfate (Drierite), and the composition of the residue was analyzed by mass spectrometry. Mass spectra show that deuteration was 50 and 60% complete for glutarimide and 3,3-dimethyl glutarimide, respectively.

SOLVENTS

Chloroform and deuterochloroform (Aldrich) were dried over freshly activated Linde 4A molecular sieves for 24 hours. Acetonitrile (J. T. Baker) was fractionally distilled over granulated calcium hydride (Matheson, Coleman and Bell) after refluxing for 24 hours. The solvents were then stored in a dry box under a nitrogen atmosphere.

SAMPLE PREPARATION

For the Raman and infrared studies stock solutions of approximately 0.2 M were prepared by weighing out the desired amount of compound into a 2 ml volumetric flask and diluting to volume with the solvent.

The mixed solvent solutions were prepared by weighing out the desired amount of solvent A into a volumetric flask along with the compound and diluting to volume with solvent B.

INSTRUMENTAL

The far infrared spectra were taken on a Digilab FTS-16 Fourier transform spectrometer. For the theory and operation of this instrument consult the Thesis of P. Handy (36). The spectra were obtained with an average resolution of 2 cm^{-1}. The samples were contained in a Beckman variable path liquid cell with polyethylene windows. Path lengths used were between 0.2 and 0.5 mm.

A Perkin-Elmer 225 grating infrared spectrometer was used to obtain spectra in the mid infrared, 4000-200 cm^{-1}. The samples were contained between CsI salt plates in a sealed cell. All the mid-infrared spectra were solvent compensated, with the solvent placed in the reference beam, contained in the Beckman variable path length cell. The path length was approximately 0.2 mm. The average resolution of the instrument was 1 cm^{-1} (slit program 4), and on a scale of zero to ten the gain was set at 0.5 for each spectrum.

The Raman spectra were recorded with the instrument built in Dr. Leroi's laboratory. The instrument is described fully in a technical report (37). Briefly, the Raman instrument consists of a Spex 1400 double monochromator, an RCA C31034 selected photomultiplier tube, a Victoreen VTE-1 dc amplifier, and either a Spectra-Physics Model 164 argon ion laser (providing a maximum output of 1.5 watts of 5145 and 4880 Å radiation) or a Spectra-Physics Model 165 krypton ion laser (with a maximum output of 0.76 watts of 6471 Å radiation), and a Spectra-Physics Model 265 exciter. The spectrum of each compound was taken with at least two different laser lines to insure location of the laser plasma lines. The slits of the monochromator were varied to maintain an average resolution of 3 cm^{-1} for each laser line used. This instrument was used in the dc mode, with an amplification of 1×10^{-9} - 1×10^{-10} amps for full scale deflection on the strip chart recorder, and 1900V on the photomultiplier tube. Several Raman spectra were also recorded on the Spex Ramalog 4 laser-Raman system described by M. Greenberg (38). The samples analyzed by Raman spectroscopy were contained in sealed 1.6 - 1.8 x 90 mm melting point capillary tubes.

The mass spectra were obtained with a Hitachi Perkin-Elmer model RMU-6 mass spectrometer. The samples were run by Mrs. Guile of the instrument service department.

NMR spectra were obtained with a Varian T-60NMR spectrometer in D_2O solution.

The solutions of glutarimide examined by Raman spectroscopy were 0.5 M, all other solutions analyzed by Raman were 0.2 M. The solutions prepared for far-infrared ranged from 0.2 M - 0.01 M, and solutions analyzed by the Perkin-Elmer 225 infrared spectrometer were 0.2 M and 0.1 M.

CHAPTER II

VIBRATIONAL ANALYSIS OF GLUTARIMIDE AND 3,3-DIMETHYL GLUTARIMIDE

CHAPTER II

VIBRATIONAL ANALYSIS OF GLUTARIMIDE AND 3,3-DIMETHYL GLUTARIMIDE

INTRODUCTION

In this chapter the analysis of the vibrational spectra of glutarimide, 3,3-dimethyl glutarimide, and their N-deuterated derivatives is presented. The spectra are of the compounds in deuterochloroform and acetonitrile solution. The vibrational frequencies for these molecules have been calculated using valence force constants derived from paraffins (39), ring compounds (40), and various other sources (41,42). These force constants were further refined in this analysis.

For most small molecules the vibrational assignment is well established. Additional information is often available, such as the assignments for several isotopic species, molecular geometry, Coriolis coupling and centrifugal distortion constants. The consequence of this situation is that research, in this case, is oriented towards the determination of a complete potential function, with emphasis on the validity of the harmonic approximation.

For large molecules the vibrational assignment is normally not completely established and only in a few cases are frequencies of a deuterated species available. The essential focus of this kind of work is, therefore, the search for approximate potential functions including a limited number of terms. The emphasis, in this case, is on the power of such a potential function to aid in establishing vibrational assignments and in predicting frequencies of related molecules.

Glutarimide and 3,3-dimethyl glutarimide can easily be considered large molecules in terms of normal coordinate calculations. As a consequence the calculation is used here as a qualitative tool to aid in the vibrational assignment.

The normal coordinate analysis employed the computer programs written by Shimanouchi and coworkers (43). The calculation used here consists of three programs, one for the calculation of the cartesian coordinates of each atom, a second which is a preparatory program giving all the matrix elements needed for the normal coordinate calculation in the form of punched cards, and finally a third program for the calculation of normal frequencies and the potential energy distribution. The third program (LSMA) will adjust force constants by a least squares method to give the best fit of calculated frequencies to observed frequencies. These programs employ the method outlined by Wilson (44) for setting up and solving the vibrational secular equation. These programs were adopted to run on the CDC 6500 computer.

Examples of solvent compensated infrared spectra are shown in Figures 3-10. Raman spectra were very difficult to obtain, and measured depolarization ratios were unreliable. As a consequence the Raman spectra were of minimum value for vibrational assignments. They are not shown here, and are not listed in any of the tables.

MOLECULAR STRUCTURE AND SYMMETRY CONSIDERATIONS

The crystal structure of glutarimide has been determined (34) and is given in Figure 11. This structure was used in the calculations

Figure 3. IR Spectra of Glutarimide in $CDCl_3$

A - 0.1 $\underline{M}$
B - 0.2 $\underline{M}$

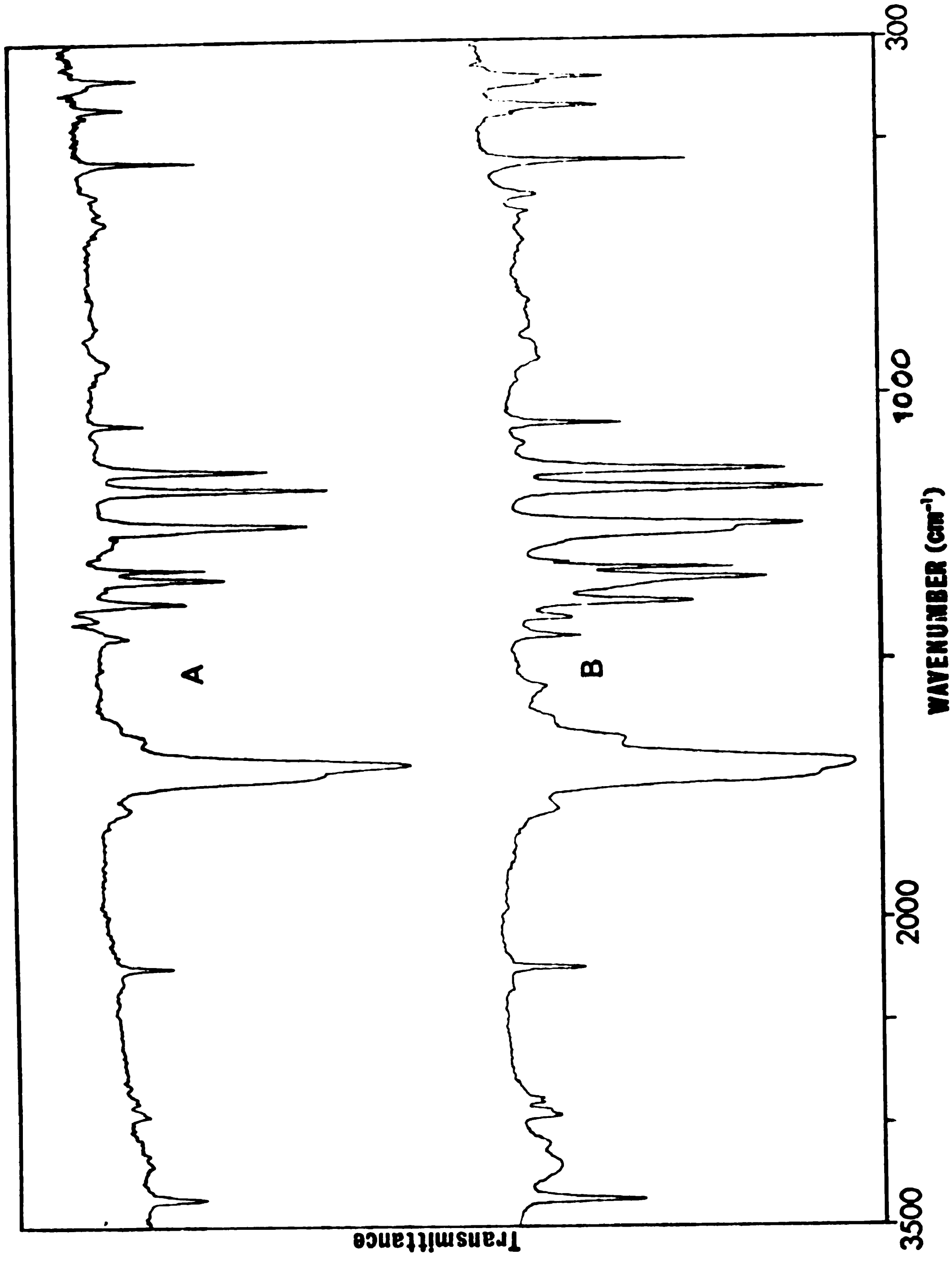


Figure 3

Figure 4. IR Spectra of Glutarimide in CH_3CN.

A - 0.1 M
B - 0.2 M

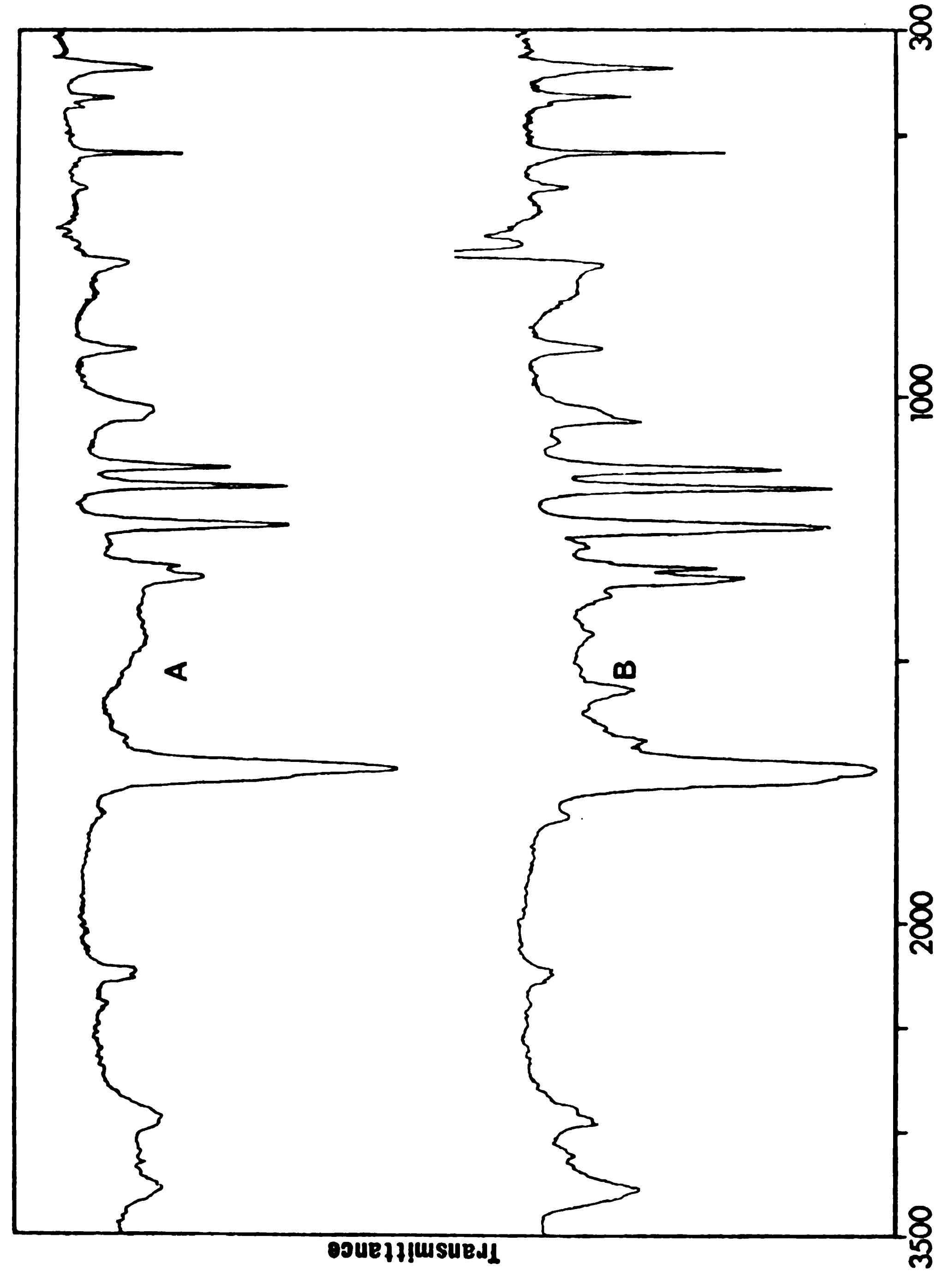


Figure 4

Figure 5. IR Spectra of N-D Glutarimide in $CDCl_3$.

A - 0.1 M
B - 0.2 M

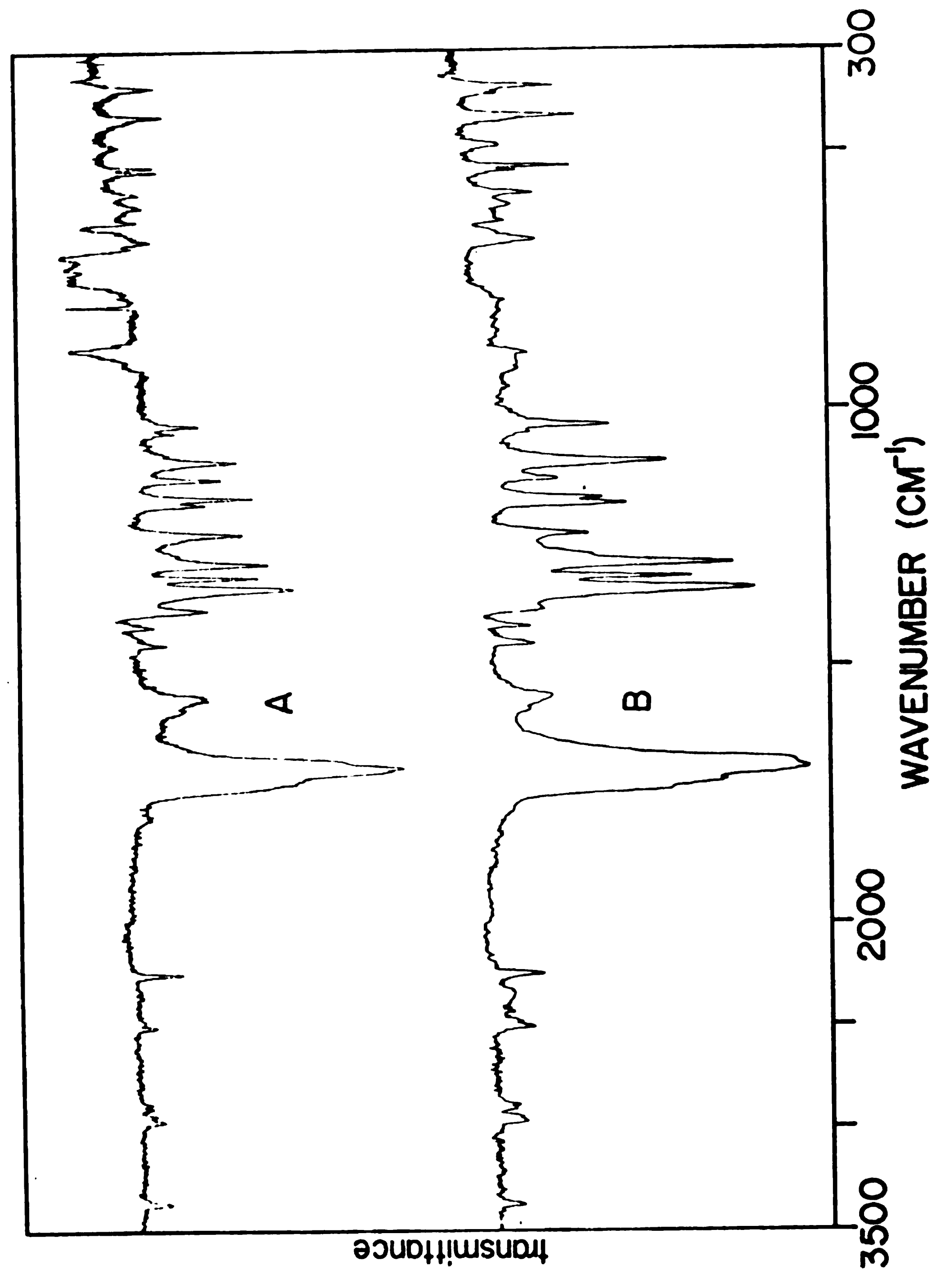


Figure 5

Figure 6. IR Spectra of N-D Glutarimide in CH_3CN.

A - 0.1 <u>M</u>
B - 0.2 <u>M</u>

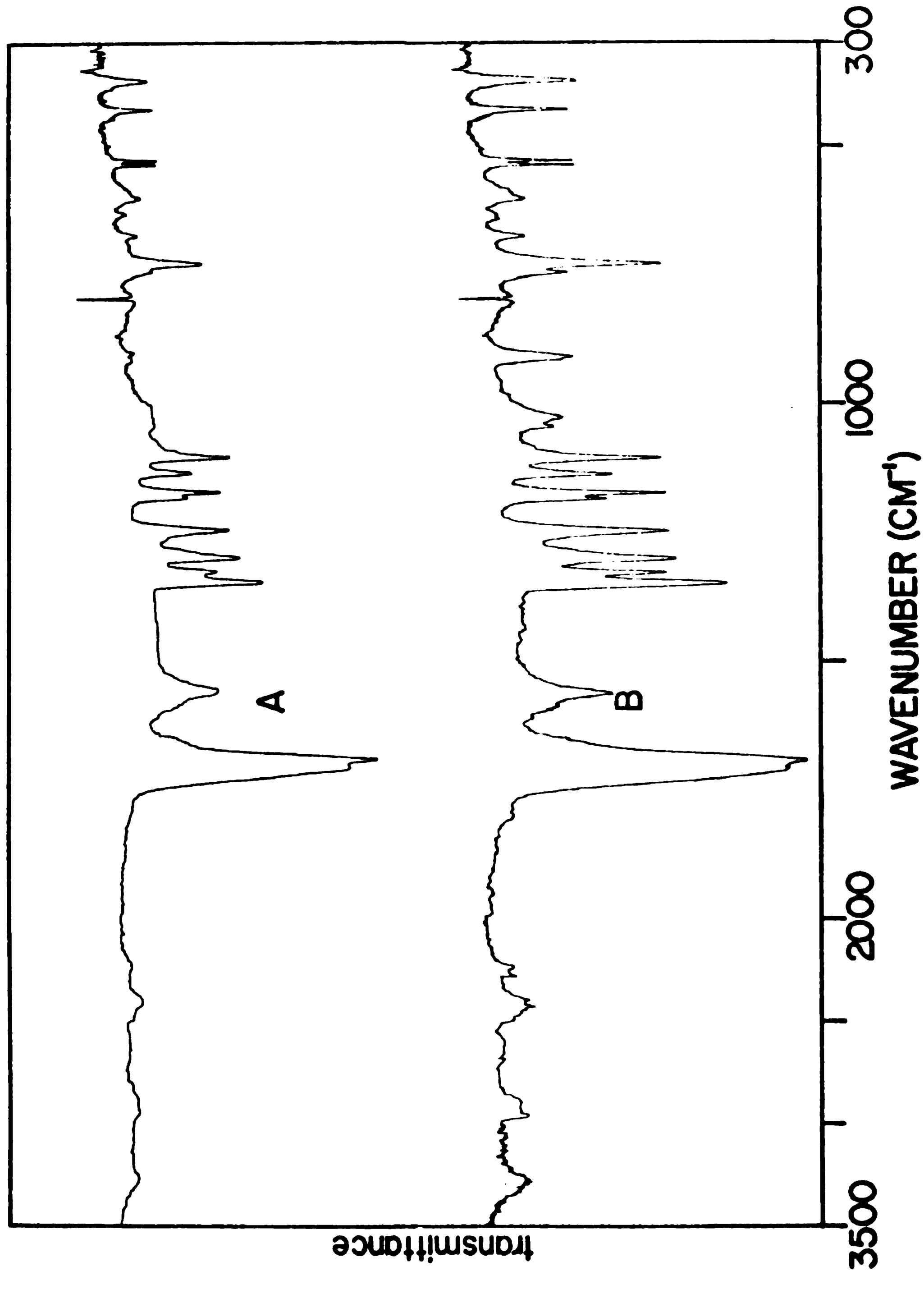


Figure 6

Figure 7. IR Spectra of 3,3-Dimethyl Glutarimide in $CDCl_3$.

A - 0.1 M
B - 0.2 M

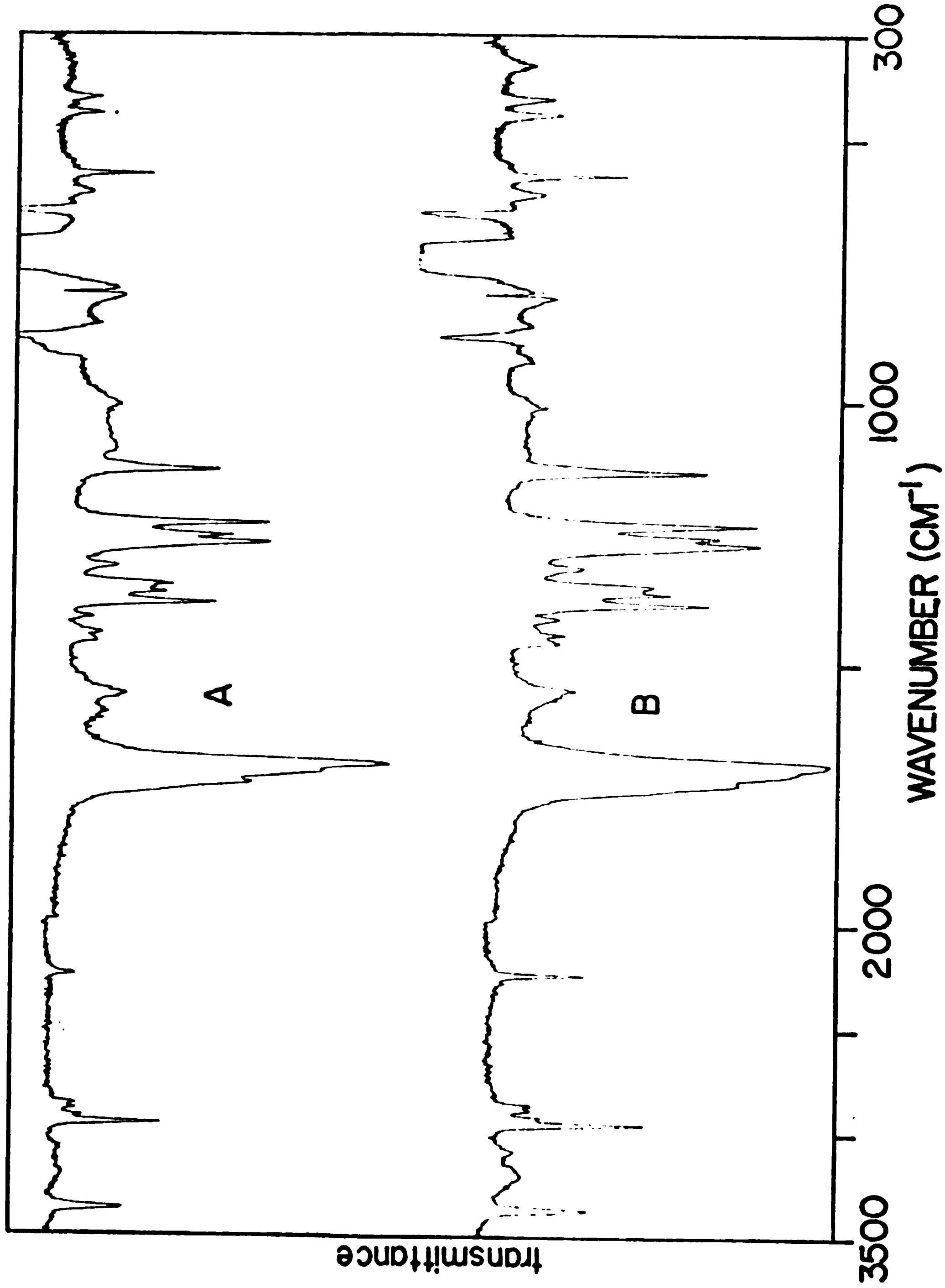


Figure 7

Figure 8. IR Spectra of 3,3-Dimethyl Glutarimide in CH_3CN.

A - 0.1 <u>M</u>
B - 0.2 <u>M</u>

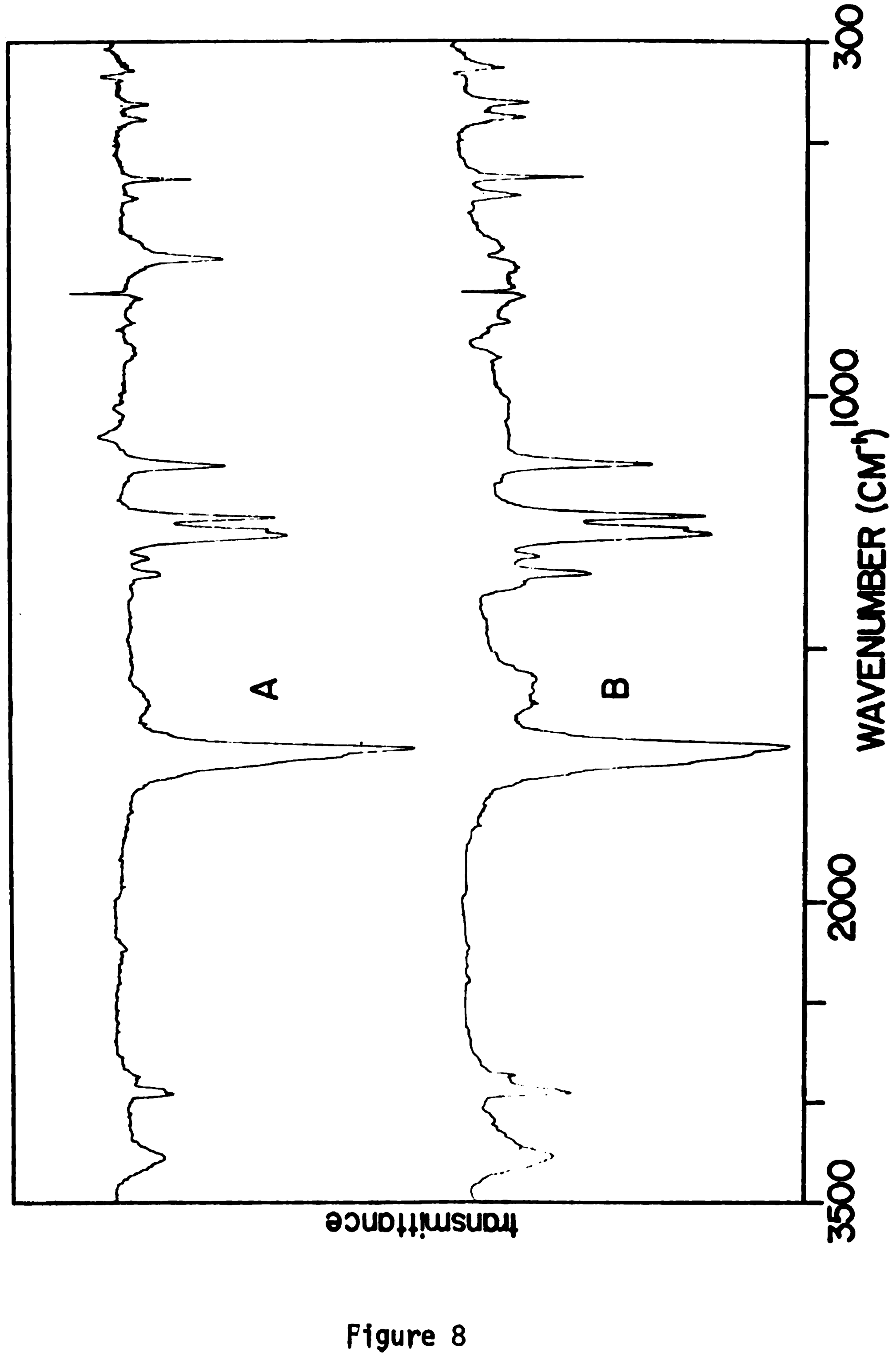


Figure 8

Figure 9. IR Spectra of N-D 3,3-Dimethyl Glutarimide in $CDCl_3$.

A - 0.1 <u>M</u>
B - 0.2 <u>M</u>

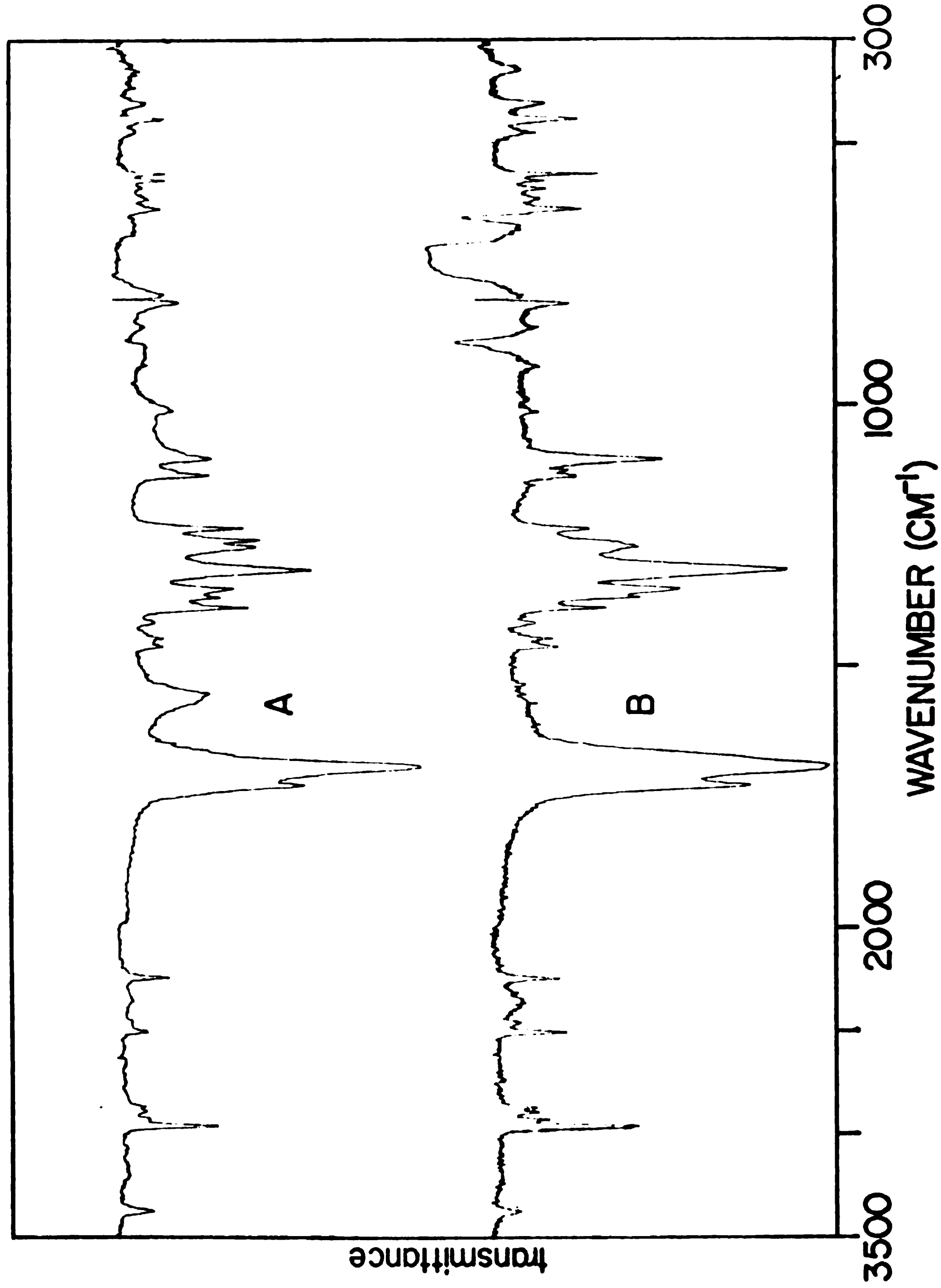


Figure 9

Figure 10. IR Spectra of N-D 3,3-Dimethyl Glutarimide in CH_3CN.

A - 0.1 M
B - 0.2 M

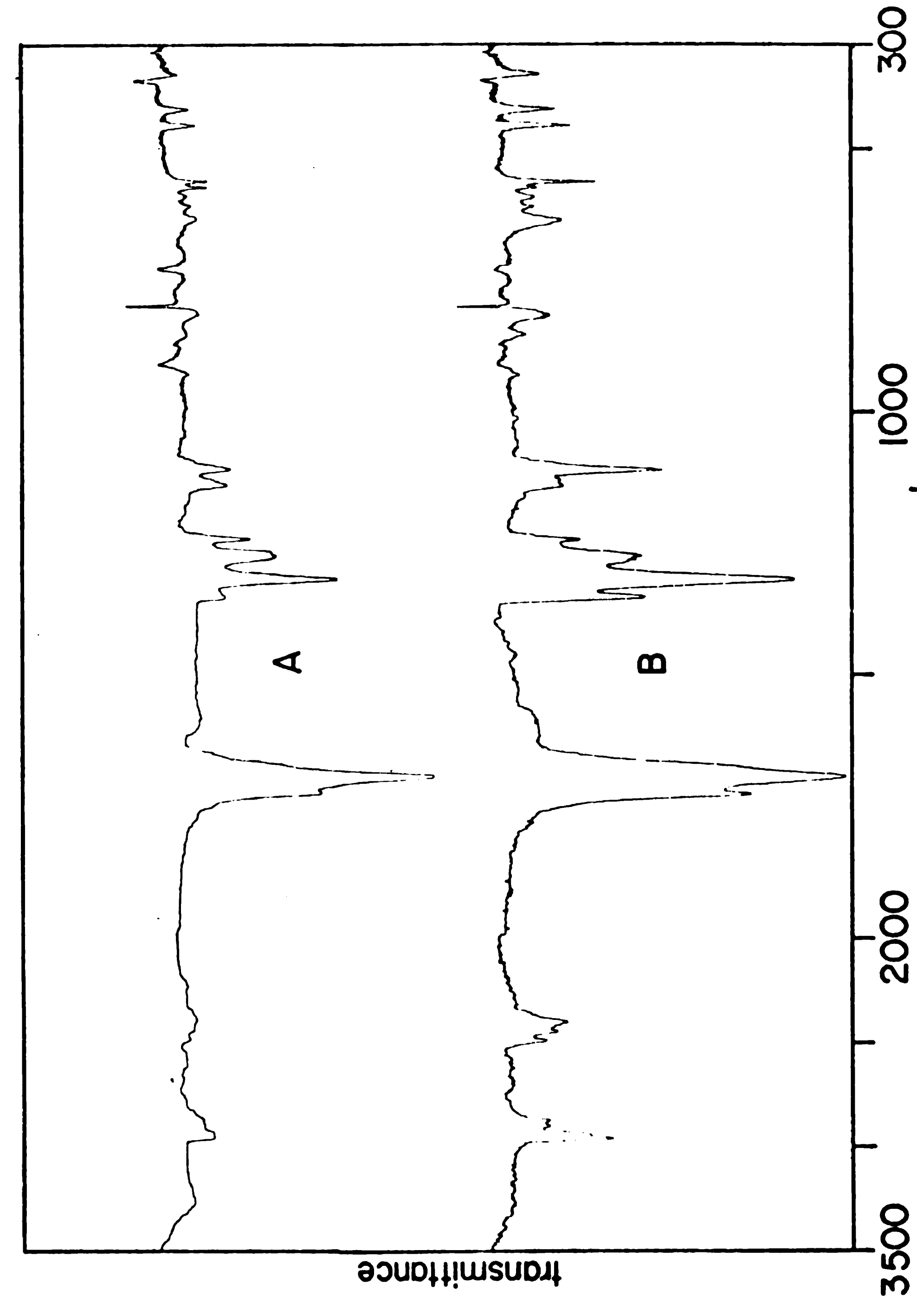
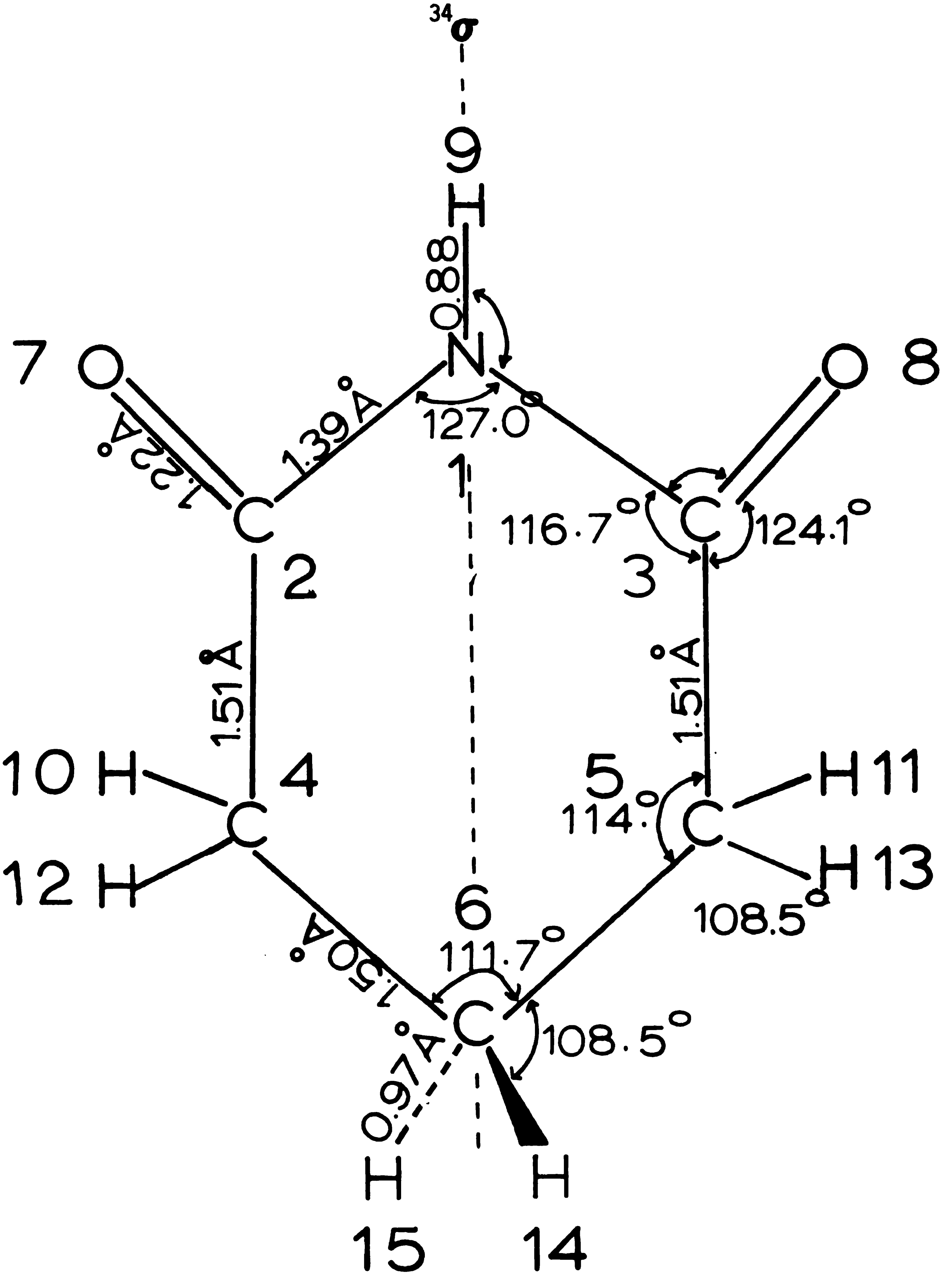


Figure 10

Figure 11. Geometric Parameters and Symmetry for the Glutarimides.



$^{34}\sigma$
9
H
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7
O
N
O
8
1.39Å
127.0°
1.22Å
1
C
2
116.7°
C
124.1°
3
1.51Å
1.51Å
10 H
4
5
H 11
C
114°
C
12 H
H 13
6
108.5°
1.50Å
111.7°
C
108.5°
0.97Å
H
H
15
14

Figure 11

on glutarimide and N-deuterated glutarimide. For 3,3-dimethyl glutarimide the structure given in Figure 11 was altered slightly. The hydrogens on carbon number 6 were changed to point-mass methyl groups, and the C-H distances on carbon atom 6 were changed to $C-CH_3$ distances.

All the ring atoms except carbon atom 6 lie in one plane. Thus the only element of symmetry possessed by these molecules is the plane illustrated in Figure 11. This places the molecule in the symmetry group C_s. The character table for this group is listed in Table 2.

All the molecules considered here have 15 atoms, and therefore a total of 39 normal modes of vibration (3N-6). From group theory considerations, there will be 22 vibrations of A' symmetry and 17 vibrations of A" symmetry for each molecule. Of these 39 vibrations, 9 will be stretches involving only one ring atom, i.e., the N-H stretch (A'), 2C=O stretches (A' and A"), and 6 C-H stretches (4A' and 2 A"). Of the remaining 30 normal modes 4 will be motions involving bending of the carbonyl, 2 bendings of the N-H group, 12 bending motions of the CH_2 groups, and 12 ring modes. All vibrations are allowed in both the Raman and the infrared spectra.

Internal and Symmetry Coordinates

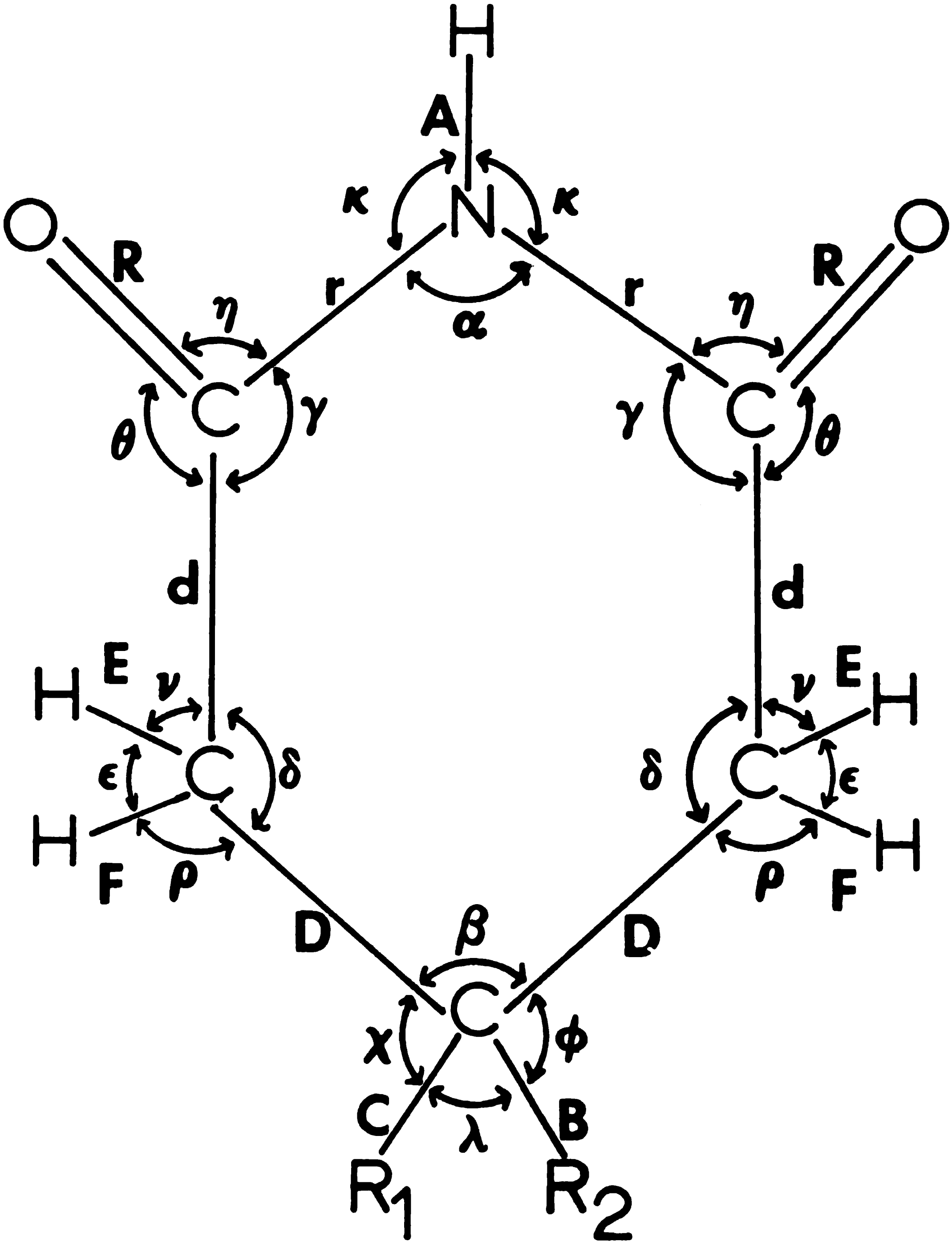
The internal coordinate basis set and numbering of the atoms are shown in Figures 12 and 13. Table 3 lists the internal coordinates, while the symmetry coordinates are listed in Table 4.

The lone plane of symmetry passes through atoms 9-1-6-14-15, with the following atoms forming mirror-pairs across the plane: 2 and 3, 4 and 5, 7 and 8, 10 and 11, 12 and 13. The internal coordinates

Table 2. Character Table for Symmetry Group C_s.

C_s	E	σn		
A'	1	1	X,Y,R_Z	$X^2,Y^2,$ Z^2,XY
A"	1	-1	Z,R_X,R_Y	YZ,XZ

Figure 12. Internal Coordinates of Glutarimide.


H
A
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C
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d
d
H
E
ν
ν
E
H
ϵ
C
δ
δ
C
ϵ
H
F
ρ
ρ
F
H
D
β
D
χ
C
ϕ
C
λ
B
R1
R2

Figure 12

Figure 13. Internal Coordinates of Glutarimide (cont.).

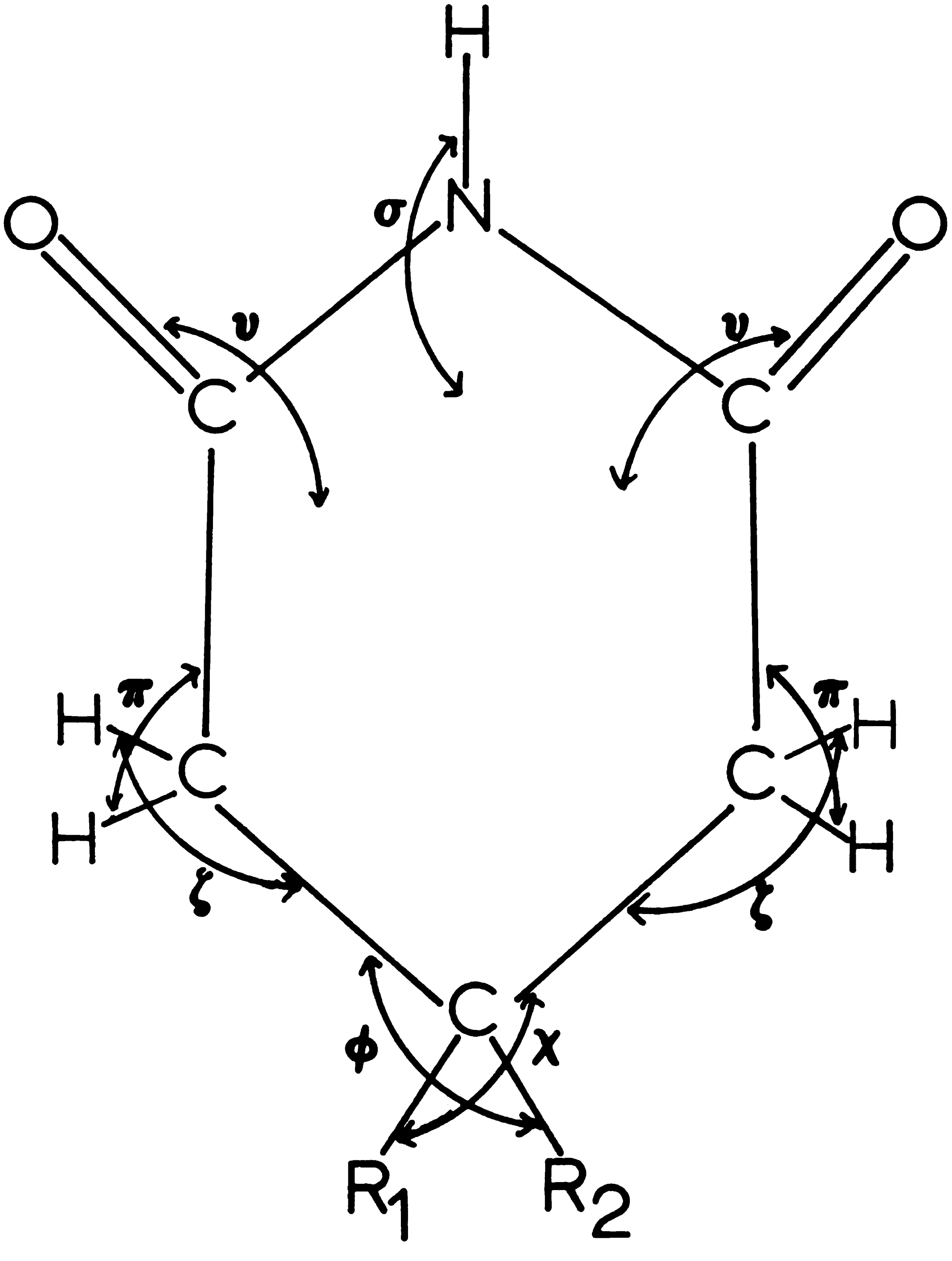

Figure 13

Table 3. List of Internal Coordinates

Symbol	Atoms Involved	Description
A	1,9	N-H distance
r_1	1,2	N-C distance
r_2	1,3	" "
d_1	2,4	C-C distance
d_2	3,5	" "
D_1	4,6	" "
D_2	5,6	" "
R_1	2,7	C=O distance
R_2	3,8	" "
E_1	4,10	C-H distance
E_2	5,11	" "
F_1	4,12	" "
F_2	5,13	C-H distance
B	6,15	" "
C	6,14	" "
α	2,1,3	C-N-C angle
κ_1	2,1,9	C-N-H angle
κ_2	3,1,9	" "
γ_1	4,2,1	C-C-N angle
γ_2	5,3,1	" "
η_1	1,2,7	O=C-N angle
η_2	1,3,8	" "
σ_1	7,2,4	O=C-angle

Table 3 - Continued

Symbol	Atoms Involved	Description
σ_2	8,3,5	O=C-C angle
μ_1	2,7	C=O bend
μ_2	3,8	" "
σ	1,9	N-H bend
δ_1	2,4,6	C-C-C angle
δ_2	3,5,6	" "
β	4,6,5	" "
ν_1	10,4,2	C-C-H angle
ν_2	11,5,3	" "
ξ_1	10,4,6	" "
ξ_2	11,5,6	" "
ε_1	10,4,12	H-C-H angle
ε_2	11,5,13	" "
π_1	12,4,2	C-C-H angle
π_2	13,5,3	" "
ρ_1	12,4,6	" "
ρ_2	13,5,6	" "
χ_1	14,6,4	" "
χ_2	14,6,5	" "
λ	14,6,15	H-C-H angle
ϕ_1	15,6,4	C-C-H angle
ϕ_2	15,6,5	" "
τ_1	4,2,1,3	Ring Torsion

Table 3 - Continued

Symbol	Atoms Involved	Description
τ_2	5,3,1,2	Ring Torsion
τ_3	6,4,2,1	" "
τ_4	6,5,3,1	" "
τ_5	5,6,4,2	" "
τ_6	4,6,5,3	" "

Table 4. List of Symmetry Coordinates

A' Coordinates		A" Coordinates	
Coordinate	Description	Coordinate	Description
$S_1=A$	N-H stretch		
$S_2=1/\sqrt{2}(r_1+r_2)$	C-N "	$S_{30}=1/\sqrt{2}(r_1-r_2)$	C-N stretch
$S_3=1/\sqrt{2}(d_1+d_2)$	C-C "	$S_{31}=1/\sqrt{2}(d_1-d_2)$	C-C "
$S_4=1/\sqrt{2}(D_1+D_2)$	C-C "	$S_{32}=1/\sqrt{2}(D_1-D_2)$	C-C "
$S_5=1/\sqrt{2}(R_1+R_2)$	C=O "	$S_{33}=1/\sqrt{2}(R_1-R_2)$	C=O "
$S_6=1/\sqrt{2}(E_1+E_2)$	C-H "	$S_{34}=1/\sqrt{2}(E_1-E_2)$	C-H "
$S_7=1/\sqrt{2}(F_1+F_2)$	C-H "	$S_{35}=1/\sqrt{2}(F_1-F_2)$	C-H "
$S_8=B$	C-H "		
$S_9=C$	C-H "		
$S_{10}=\alpha$	CNC angle bend		
$S_{11}=1/\sqrt{2}(\kappa_1+\kappa_2)$	CNH " "	$S_{36}=1/\sqrt{2}(\kappa_1-\kappa_2)$	CNH angle bend
$S_{12}=1/\sqrt{2}(\gamma_1+\gamma_2)$	CCN " "	$S_{37}=1/\sqrt{2}(\gamma_1-\gamma_2)$	CCN " "
$S_{13}=1/\sqrt{2}(\eta_1+\eta_2)$	OCN " "	$S_{38}=1/\sqrt{2}(\eta_1-\eta_2)$	OCN " "
$S_{14}=1/\sqrt{2}(\sigma_1+\sigma_2)$	OCC " "	$S_{39}=1/\sqrt{2}(\sigma_1-\sigma_2)$	OCC " "
$S_{15}=1/\sqrt{2}(\delta_1+\delta_2)$	CCC " "	$S_{40}=1/\sqrt{2}(\delta_1-\delta_2)$	CCC " "
$S_{16}=\beta$	CCC " "		
$S_{17}=1/\sqrt{2}(\nu_1+\nu_2)$	CCH " "	$S_{41}=1/\sqrt{2}(\nu_1-\nu_2)$	CCH " "
$S_{18}=1/\sqrt{2}(\xi_1+\xi_2)$	CCH " "	$S_{42}=1/\sqrt{2}(\xi_1-\xi_2)$	CCH " "
$S_{19}=1/\sqrt{2}(\varepsilon_1+\varepsilon_2)$	CH_2 " def.	$S_{43}=1/\sqrt{2}(\varepsilon_1-\varepsilon_2)$	CH_2 angle def.
$S_{20}=1/\sqrt{2}(\pi_1+\pi_2)$	CCH angle bend	$S_{44}=1/\sqrt{2}(\pi_1-\pi_2)$	CCH angle bend
$S_{21}=1/\sqrt{2}(\rho_1+\rho_2)$	CCH angle bend	$S_{45}=1/\sqrt{2}(\rho_1-\rho_2)$	CCH " "
$S_{22}=1/\sqrt{2}(\chi_1+\chi_2)$	CCH " "	$S_{46}=1/\sqrt{2}(\chi_1-\chi_2)$	CCH " "
$S_{23}=\lambda$	CH_2 angle def.		

Table 4 - Continued

A' Coordinates		A" Coordinates	
Coordinate	Description	Coordinate	Description
$S_{24}=1/\sqrt{2}(\phi_1+\phi_2)$	CCH angle bend	$S_{47}=1/\sqrt{2}(\phi_1-\phi_2)$	CCH angle bend
$S_{25}=1/\sqrt{2}(\mu_1+\mu_2)$	C=O wag	$S_{48}=1/\sqrt{2}(\mu_1-\mu_2)$	C=O wag
$S_{26}=\sigma$	N-H "		
$S_{27}=1/\sqrt{2}(\tau_1+\tau_2)$	Ring Torsion	$S_{49}=1/\sqrt{2}(\tau_1-\tau_2)$	Ring Torsion
$S_{28}=1/\sqrt{2}(\tau_3+\tau_4)$	" "	$S_{50}=1/\sqrt{2}(\tau_3-\tau_4)$	" "
$S_{29}=1/\sqrt{2}(\tau_5+\tau_6)$	" "	$S_{51}=1/\sqrt{2}(\tau_5-\tau_6)$	" "

also occur in pairs and have been labelled as such, i.e., r_1-r_2, d_1-d_2, etc. When projection operators are applied to internal coordinates not lying on the plane, the operation E carries each coordinate into itself and σ takes each coordinate either into the positive or negative of its partner. If the internal coordinate lies on the plane, both E and σ take it into itself. Applying the projection operators with this procedure generates the symmetry coordinates listed in Table 4.

VALENCE FORCE FIELD

The Wilson F and G matrix method (44) was used with a valence force field. G matrix formulation, solution of the secular equations, and determination of the best values of the force constants were done by digital computer, using FORTRAN programs (43). The main program is designed to adjust the values of the force constants until calculated and observed frequencies are in the best agreement possible. The initial force field was diagonal, with 18 constants. A set of starting values of the 18 constants was chosen, and all except four (or six) were held fixed while the best values of the others were found by allowing them to vary. Then the fixed and variable constants were interchanged and the best values of the new variable constants found. This was continued with different combinations of constants held fixed until calculated and observed frequencies agreed. At this point interaction constants were introduced and the procedure repeated. Interaction constants which did not produce a significant improvement in the agreement between calculated and observed frequencies were discarded. In the final analysis all 20 force constants were allowed to vary simultaneously. This procedure cannot lead to reliable values for all the constants, since the final values will depend to some degree upon the starting values chosen. However, the prime reason for the normal coordinate calculation was to aid in the vibrational assignments, and this was satisfactorily accomplished.

Table 5 lists the initial and final values of the force constants and their dispersions. The observed and calculated frequencies along with the assignments are listed in Table 6. For comparison, the assignments of Hall and Zbinder (31) are listed in Table 7.

N-H AND N-D STRETCHING REGIONS

The observed N-H and N-D stretching frequencies for glutarimide, 3,3-dimethyl glutarimide and their dimers in deuterochloroform and acetonitrile solutions are listed in Table 8, along with the positions of the corresponding vibrations in acetonitrile. The frequencies observed in deuterochloroform were used in the normal coordinate calculation.

For glutarimide and N-deuterated glutarimide in $CDCl_3$ the relatively free N-H and N-D stretching frequencies come at 3373 cm^{-1} and 2510 cm^{-1}, respectively. At higher concentrations, two additional bands appear in each spectrum at 3219, 3108 cm^{-1} and 2480, 2360 cm^{-1}, respectively. These bands have been assigned to dimers on the basis of the N-deuterated glutarimide spectrum and a mixed solvent study (dimers might have cyclic (Figure 14) or open structures). One or both of the bands could be due to overtones or combination bands involving the carbonyl stretching fundamentals. However, both bands shift to lower frequency in the spectrum of N-deuterated glutarimide even though the carbonyl shift is only slight. These bands could also be due to interaction of the relatively positive proton on

Table 5. Initial and Final Values of the Force Constants and Their Dispersions

	Initial	Final	Dispersion
K(N-H)	6.0	6.36	0.04
K(C-C)	4.47	3.41	0.14
K(C=O)	9.4	8.50	0.31
K(C-H)	4.5	4.71	0.01
K(C-N)	5.5	4.54	0.18
H(CNC)	0.8	1.64	0.23
H(CNH)	0.5	0.35	0.01
H(CCN)	0.8	1.46	0.16
H(OCN)	0.4	0.38	0.22
H(OCC)	0.4	0.60	0.23
H(CCC)	1.0	0.74	0.06
H(CCH)	0.68	0.47	0.01
$H(CH_2)$	0.53	0.44	0.01
H(C=O-OOP)	0.5	0.89	0.05
H(N-HWag)	0.6	0.71	0.04
T(CN)	0.1	0.08	0.04
T(CC)	0.1	0.28	0.02
F(CO-CN)	0.02	-0.27	0.13
F(CO-CC)	0.02	-0.04	0.19

K: Stretching constant (10^5 dyne/cm);
F: Interaction constant (10^5 dyne/cm);
H: Bending constant (10^{-11} dyne cm);
T: Bond twisting constant (10^{-11} dyne cm).

Table 6. Observed and Calculated Frequencies of Glutarimide, 3,3-Dimethyl Glutarimide and Their N-D Compounds

Glutarimide, A' Block

Obs. (cm^{-1})	Rel. Int.	Calc. (cm^{-1})	Solvent	Assignment
3374	med	3397	$CDCl_3$	N-H str.
2980	w	2981	$CDCl_3$	C-H str.
2970	w	2972	$CDCl_3$	C-H str.
2943	w	2905	$CDCl_3$	C-H str.
2886	w	2902	$CDCl_3$	C-H str.
1714	s	1704	CH_3CN	62% C=O str., 10% CC str.
1462	w	1472	$CDCl_3$	65% CH_2 def., 21% CCH bend
1427	w	1438	$CDCl_3$	73% CH_2 def., 15% CCH bend
1395	med	1389	$CDCl_3$	47% CCH bend, 17% CH_2 def.
1330	s	1348	$CBCl_3$	59% N-H wag, 14% C=O-OOP bend
1247	s	1238	$CDCl_3$	33% C-N str., 22% CCH bend
1178	s	1170	$CDCl_3$	CCH bend
1050	med	1014	$CDCl_3$	42% CCH bend, 21% N-H wag
		857		26% CCH bend, 16% CCC bend, 15% C-C str.
		836		48% C-C Str., 18% CCH bend
734	med	725	CH_3CN	46% CCH bend, 29% C=o-OOP bend
648	w	634	CH_3CN	49% CCH bend, 17% C-C str.
544	med	559	CH_3CN	23% C-N str., 20% C-C str.
453	w	455	$CDCl_3$	52% CCC bend, 19% CCH bend
382	w	350	$CDCl_3$	50% ring tor., 19% CCH bend
255	w	263	CH_3CN	C=O wag
		170		ring tor.

Table 6 - Continued.

Obs. (cm^{-1})	Rel. Int.	Calc. (cm^{-1})	Solvent	Assignment
		A" Block		
2970	w	2973	$CDCl_3$	C-H str.
2905	w	2904	$CDCl_3$	C-H str.
1731	s	1731	CH_3CN	50% C=O str., 18% C-N str.
1462	w	1466	$CDCl_3$	40% CH_2 def., 32% CCH bend
1427	w	1438	$CDCl_3$	32% CCH bend, 25% CH_2 def.
1350	s	1360	$CDCl_3$	54% CCH bend, 14% CH_2 def.
1330	s	1304	$CDCl_3$	44% N-H - oop, 30% CCH bend
		1205		26% N-H - oop, 25% C-N str.
1178	s	1165	$CDCl_3$	CCH bend
1142	s	1146	$CDCl_3$	CCH bend
		936		47% C-C Str., 43% CCH bend
916	med	910	CH_3CN	44% C=O - oop bend, 37% CCH bend
758	med	772	CH_3CN	39% C-C str., 25% C-N str.
610	w	620	CH_3CN	59% CCH bend, 31% C=O - oop bend
437	med	442	CH_3CN	42% CCN bend, 15% C=O wag
394	w	387	$CDCl_3$	C=O wag
151	w	181	$CDCl_3$	ring tor.
		N-D Glutarimide A' Block		
2980	w	2982	$CDCl_3$	C-H str.
2970	w	2971	$CDCl_3$	C-H str.
2943	w	2904	$CDCl_3$	C-H str.
2886	w	2901	$CDCl_3$	C-H str.
2509	w	2501	$CDCl_3$	N-D str.
1696	s	1702	CH_3CN	62% C=O str., 10% C-C str.
1462	w	1471	$CDCl_3$	66% CH_2 def., 21% CCH bend
1427	w	1437	$CDCl_3$	CH_2 def.

Table 6 - Continued.

Obs. (cm^{-1})	Rel. Int.	Calc. (cm^{-1})	Solvent	Assignment
1395	w	1386	$CDCl_3$	52% CCH bend, 17% CH_2 def.
1247	med	1254	$CDCl_3$	36% N-H wag, 25% C=O - oop bend
1178	med	1226	$CDCl_3$	31% C-N str., 23% CCH bend
1143	w	1167		CCH bend
		947		45% CCH bend, 29% N-H wag
		848		31% CCH bend, 18% C-C str.
752	med	832	CH_3CN	32% C-C str., 18% CCN bend
683	w	685	CH_3CN	57% CCH bend, 11% N-H wag and C=O - oop bend
586	w	601	CH_3CN	29% C=O - oop bend, 25% CCH bend
544	w	558	CH_3CN	27% C-C str., 22% C-N str.
445	w	452	CH_3CN	50% CCC bend, 19% CCH bend
371	med	348	CH_3CN	50% ring tor., 18% CCH bend
255	w	262	$CDCl_3$	C=O - wag
		158		ring tor.
		A" Block		
2970	w	2974	$CDCl_3$	C-H str.
2905	w	2903	$CDCl_3$	C-H str.
1713	s	1720	CH_3CN	53% C=O str., 18% C-N str.
1462	w	1465	$CDCl_3$	43% CH_2 def., 31% CCH bend
1427	w	1432	$CDCl_3$	36% CCH bend, 23T CH_2 def.
1350	med	1355	$CDCl_3$	CCH bend
1247	med	1252	$CDCl_3$	31% CCH bend, 31% C-N str.
1190	med	1165	$CDCl_3$	CCH bend
1177	med	1149	$CDCl_3$	CCH bend
		996		N-H - oop wag
		934		47% C-C str., 42% CCH bend
914	med	910	CH_3CN	44% C=O - oop bend, 37% CCH bend

Table 6 - Continued.

Obs. (cm^{-1})	Rel. Int.	Calc. (cm^{-1})	Solvent	Assignment
736	med	714	CH_3CN	30% C-C str., 26% N-H-oop wag
610	w	619	CH_3CN	59% CCH bend, 31% C=O-oop bend
437	w	442	CH_3CN	42% CCN bend, 14% C=O wag
391	w	382	$CDCl_3$	C=O wag
151	w	184	$CDCl_3$	ring tor.
3,3-Dimethyl Glutarimide A' Block				
3375	med	3397	$CDCl_3$	N-H str.
2964	w	2977	$CDCl_3$	C-H str.
2884	w	2903	$CDCl_3$	C-H str.
1701	s	1704	CH_3CN	C=O str.
1452	w	1448	$CDCl_3$	CH_2 def.
1423	med	1433	$CDCl_3$	38% CH bend, 14% CH_3 def.
1395	med	1381	$CDCl_3$	30% N-H wag, 28% C-CH_3 str.
1325	w	1313	$CDCl_3$	33% N-H wag, 28% C-CH_3 str.
1243	med	1240	$CDCl_3$	36% C-N str., 17% C-C str.
		1159		53% CCH bend, 33% C-CH_3 str.
		1104		49% CCH bend, 27% C-CH_3 str.
864	w	888	CH_3CN	29% CCH bend, 18% C-O-oop bend
		834		22% CCN bend, 20% C-C str.
		749		48% C-C str., 18% C-CH_3 str.
638	w	633	CH_3CN	43% CCH bend, 30% C=O-oop bend
578	med	548	CH_3CN	27% C-C str., 23% C-N str.
432	w	423	CH_3CN	43% CCC bend, 13% CH_3 bend
364	w	390	CH_3CN	33% CCH bend, 30% ring tor.
		276		C=O - wag
		235		CH_3-C-CH_3 def.
		170		ring tor.
		115		C-C-CH_3 bend

Table 6 - Continued.

Obs. (cm^{-1})	Rel. Int.	Calc. (cm^{-1})	Solvent	Assignment
		A" Block		
2964	w	2974	$CDCl_3$	C-H str.
2904	s	2903	$CDCl_3$	C-H str.
1733	s	1731	CH_3CN	50% C=O str., 20% C-N str.
1452	w	1446	$CDCl_3$	CH_2 def.
1423	w	1426	$CDCl_3$	41% CCH bend, 34% C-C str.
1279	s	1312	$CDCl_3$	46% N-H-oop bend, 27% C=O str.
1243	med	1212	$CDCl_3$	31% N-H-oop bend, 24% C-N str.
1142	med	1175	$CDCl_3$	CCH bend
		1106		47% CCH bend, 42% C-C str.
934	w	922	CH_3CN	43% C=O-oop bend, 36% CCH bend
810	w	790	CH_3CN	41% C-C str., 24% C-N str.
614	w	622	CH_3CN	60% CCH bend, 33% C=O-oop bend
462	w	466	CH_3CN	30% CCN bend, 25% C=O wag
		412		C=O wag
		286		C-C-CH_3 bend
		212		C-C-CH_3 bend
		140		ring tor.
		N-D 3,3-Dimethyl Glutarimide A' Block		
2964	w	2977	$CDCl_3$	C-H str.
2884	w	2903	$CDCl_3$	N-D str.
2514	w	2501	$CDCl_3$	N-D str.
1700	s	1702	CH_3CN	C=O str.
1452	w	1448	$CDCl_3$	CH_2 def.
1422	w	1432	$CDCl_3$	40% CCH bend, 12% CH_2 def.
1359	med	1360	$CDCl_3$	C-CH_3 str.
1266	med	1242	$CDCl_3$	38% CCH bend, 25% N-H wag
1243	w	1226	$CDCl_3$	34% C-N str., 20% C-C str.

Table 6 - Continued.

Obs. (cm^{-1})	Rel. Int.	Calc. (cm^{-1})	Solvent	Assignment
1143	w	1148	$CDCl_3$	44% $C-CH_3$ str., 35% CCH bend
		1082		47% CCH bend, 23% $C-CH_3$ bend
855	w	841	CH_3CN	30% CCH bend, 16% CCN bend
819	w	804	CH_3CN	N-D wag, (highly mixed)*
		745		50% C-C str., 20% $C-CH_3$ str.
578	w	588	CH_3CN	35% C=O-oop bend, 32% CCH bend
567	w	547	CH_3CN	C-N str., (highly mixed)*
429	w	420	CH_3CN	CCC bend
364	w	389	$CDCl_3$	33% CCH bend, 30% ring tor.
		275		46% C-O wag, 24% CH_3CCH_3 bend
		235		40% CH_3CCH_3 bend, 20% C=O wag
		158		ring tor.
		114		62% $CCCH_3$ bend, 24% ring tor.
		A" Block		
2964	w	2974	$CDCl_3$	C-H str.
2904	w	2903	$CDCl_3$	C-H str.
1730	s	1719	CH_3CN	54% C=O str., 18% C-N str.
1452	w	1446	$CDCl_3$	CH_2 def.
1422	w	1417	$CDCl_3$	46% CCH bend, 40% C-C str.
1277	med	1263	$CDCl_3$	34% C-N str., 24% C=O str.
1161	w	1175	$CDCl_3$	CCH bend
1111	med	1110	$CDCl_3$	45% CCH, 44% C-C str.
1019	w	998	$CDCl_3$	N-D-oop wag
933	w	922	CH_3CN	42% C=O-oop bend, 36% CCH bend
		729		30% C-C str., 28% N-D-oop wag
614	w	622	CH_3CN	60% CCH bend, 33% C=O oop bend
460	w	465	CH_3CN	31% CCN bend, 22% C=O wag

Table 6 - Continued.

Obs. (cm^{-1})	Rel. Int.	Calc. (cm^{-1})	Solvent	Assignment
		406		C=O wag
		286		$CCCH_3$ bend
		212		$CCCH_3$ bend
		140		ring tor.

Abbreviations used: s, med, w, str, def, tor, and oop denote strong, medium, weak, stretch, deformation, torsion, and out-of-plane respectively.

*These bands are mixtures of four or more vibrational modes, the one listed is the most prominent.

Table 7. Assignments of Glutarimide Due to Hall and Zbinder[a]

Frequency (cm^{-1})	Assignment
3386	Free N-H stretch
2964	Asymmetric C-H stretch
2941	Asymmetric C-H stretch
2907	Symmetric C-H stretch
2883	Symmetric C-H stretch
1742	
1730	C=O stretching
1718	

[a] Less than 1% in CCl_4 solution.

Figure 14. Structure of the Dimer of Glutarimides.

Table 8. Frequencies of N-H and N-D Stretching Motions

Glutarimide		N-D Glutarimide	
$CDCl_3$	CH_3CN	$CDCl_3$	CH_3CN
3373 cm^{-1} (3397)[a]		2510 cm^{-1} (2501)	
	3279 cm^{-1}		
3219		2480	2432 cm^{-1}
3108		2360	
3,3-Dimethyl Glutarimide		N-D 3,3-Dimethyl Glutarimide	
3375 cm^{-1} (3397)		2514 cm^{-1} (2501)	
	3280 cm^{-1}		
3211		2470	2411 cm^{-1}
3098		2366	

[a] Indicates calculated frequencies.

glutarimide with the deuterochloroform solvent. Spectra of glutarimide solutions in acetonitrile-deuterochloroform mixtures were obtained in the 3100-3500 cm^{-1} spectral region. The solutions were 0.2 M in glutarimide and 0.1-1.0 M in acetonitrile. If the bands in question were due to interaction with the solvent ($CDCl_3$), then, as the concentration of acetonitrile increases, they should decrease in intensity and a band would grow in around 3280 cm^{-1} (position of the N-H stretch in CH_3CN). However, the 3373 cm^{-1} band decreased in intensity instead, and a shoulder grew in on the high frequency side of the 3219 cm^{-1} band at the position of the N-H stretch in acetonitrile. The results indicate that the two solvents are competing for the glutarimide molecules instead of the competition being between the acetonitrile-glutarimide association and the glutarimide dimer. Thus neither of the broad bands at 3219 cm^{-1} and 3108 cm^{-1} are due to interaction of $CDCl_3$ and the N-H group of glutarimide, but are due to formation of dimers of glutarimide in solution. The greater shift of the N-H stretching frequency in the dimer than in CH_3CN solution (3280 cm^{-1}) indicates that it is the strongest interaction in the system, and only the huge excess of solvent present enables one to detect the monomer of glutarimide. This discussion is continued in Chapter III.

For 3,3-dimethyl glutarimide and N-deuterated 3,3-dimethyl glutarimide in $CDCl_3$ the results were the same, with the free N-H and N-D stretches occurring at 3375 cm^{-1} and 2514 cm^{-1}.

In acetonitrile, where the major solute-solvent interaction occurs through the N-H of the glutarimide ring, the N-H and N-D stretching vibrations are shifted to lower frequency. The magnitude of the shift is an indication of the strength of the hydrogen bonds formed (45).

For this reason these frequencies were not used in the normal coordinate analysis. In glutarimide and 3,3-dimethyl glutarimide in CH_3CN the N-H stretch was observed at 3279 cm^{-1}. In the deuterated compounds the N-D stretches are tentatively assigned to bands at 2432 cm^{-1} and 2411 cm^{-1} for glutarimide and 3,3-dimethyl glutarimide respectively. The larger shift from the "free" N-D frequency for N-D 3,3-dimethyl glutarimide is interesting, since this indicates the acetonitrile, N-deuterated dimethyl glutarimide interaction is stronger than the corresponding interaction with N-deuterated glutarimide. The same trend is also found in D_2O solution, where the N-H, N-D exchange in deuterium oxide was more complete for the dimethyl compound.

THE C-H STRETCHING REGION

The observed and calculated frequencies for glutarimide, 3,3-dimethyl glutarimide and their N-deuterated derivatives in deuterochloroform are listed in Table 9. The frequencies of the C-H stretches in acetonitrile were not measured due to the low transmittance of the solutions in this region.

In the Raman spectrum of 0.2 M glutarimide in $CDCl_3$ a band appears at 2980 cm^{-1}. This is one of the two symmetric stretches of the methylene group at the 3 position of the ring, illustrated in Figure 15A. Internally (i.e., within the methylene group), the vibration is antisymmetric. However, the plane of symmetry of the molecule is conserved, since all atoms involved in the vibration lie in that plane.

The methylenes at the 2 and 4 positions of the ring can vibrate antisymmetrically internally in two modes (Figure 15 B and C);one with

Table 9. Observed and Calculated Frequencies in the C-H Stretching Region

Observed Frequencies (cm^{-1})	Calculated (cm^{-1})	Symmetry
	Glutarimide	
2980	2981	A'
2970	2972	A'
2970	2973	A"
2943	2905	A'
2905	2904	A"
2886	2902	A'
	3,3-dimethyl glutarimide	
2964	2976	A'
2964	2973	A"
2904	2904	A"
2884	2904	A'

Figure 15. Vibrations of the Methylenes.

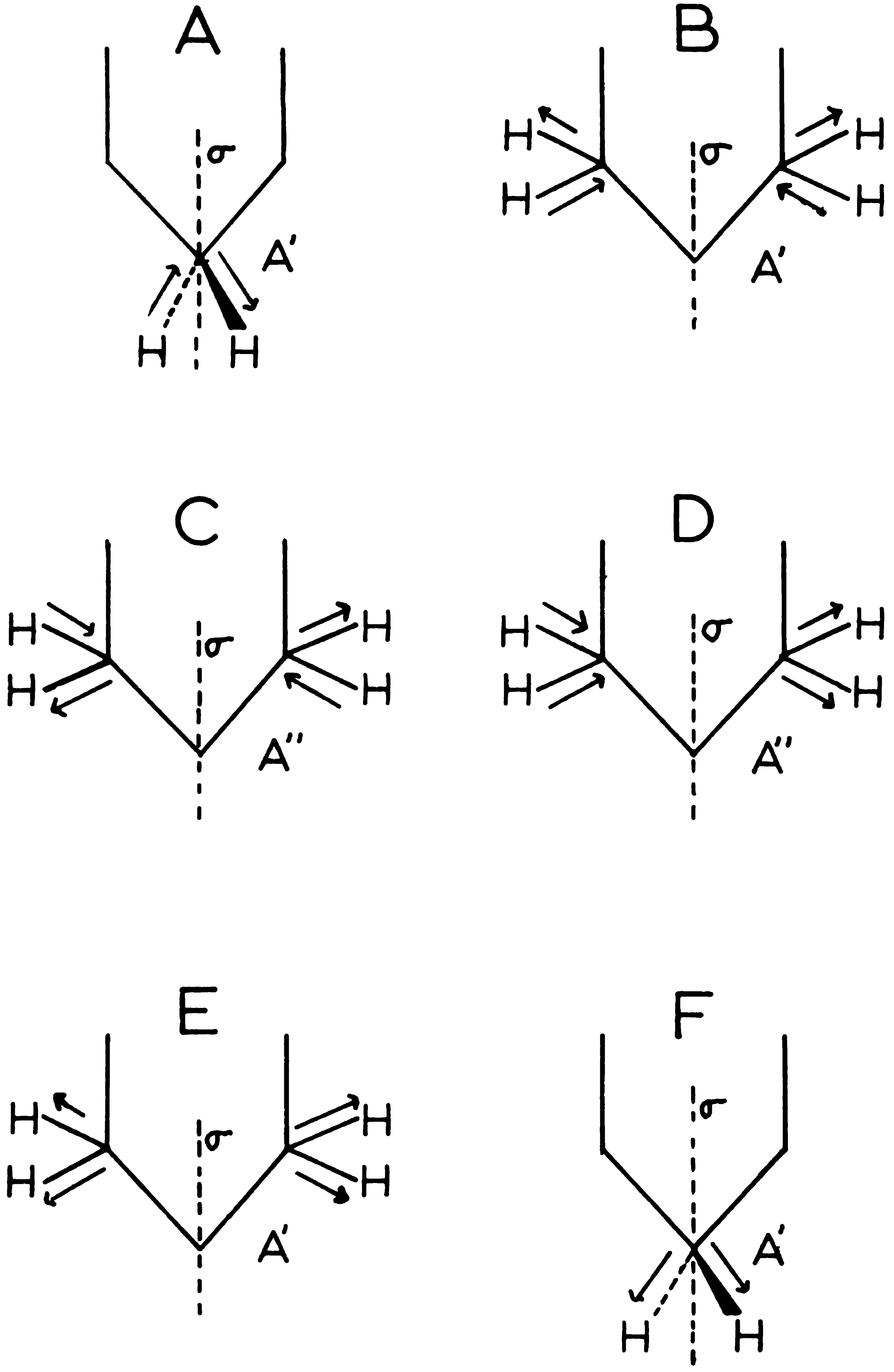

Figure 15

A' symmetry and one with A" symmetry. These vibrations are expected to be degenerate, and are assigned to the band at 2970 cm^{-1} in the infrared spectrum of 0.1 M glutarimide in deuterochloroform.

The other three bands observed in this region, at 2943 cm^{-1}, 2905 cm^{-1}, and 2886 cm^{-1} agree only qualitatively with calculated frequencies. The normal coordinate calculation gives three bands between 2905 cm^{-1} and 2910 cm^{-1}. Two of these vibrations involve the methylenes at the 2 and 4 positions (Figure 15D and E). In this case each methylene group is vibrating symmetrically when considered alone, but when coupled together they give rise to two vibrations, one of A' symmetry and one of A" symmetry. Again, this is expected to produce a doubly degenerate band. The third of these three modes is the internally symmetric C-H stretch of the methylene at the 3 position (Figure 15F). The frequency of this vibration is expected to fall near the two modes, (Figure 15D and E) of the methylenes at the 2 and 4 positions. This vibration has A' symmetry. A plausible result of having these three bands very near each other, two of A' symmetry and one of A" symmetry is illustrated in Figure 16. The two bands of A' symmetry can interact by Fermi Resonance which causes a splitting, one band moving to higher frequency (2943 cm^{-1}) and the other to lower frequency (2886 cm^{-1}).

For 3,3-dimethyl glutarimide and N-deuterated 3,3-dimethyl glutarimide, the methyls at the 3 position were assumed to be point masses in the normal coordinate calculation. This leaves four C-H stretches to be calculated, two symmetric and two antisymmetric, as shown in Figure 15B, C, D and E. The frequencies of these vibrations are not expected to change appreciably from those of glutarimide,

Figure 16. Suggested Fermi Resonance in the C-H Stretching Region.

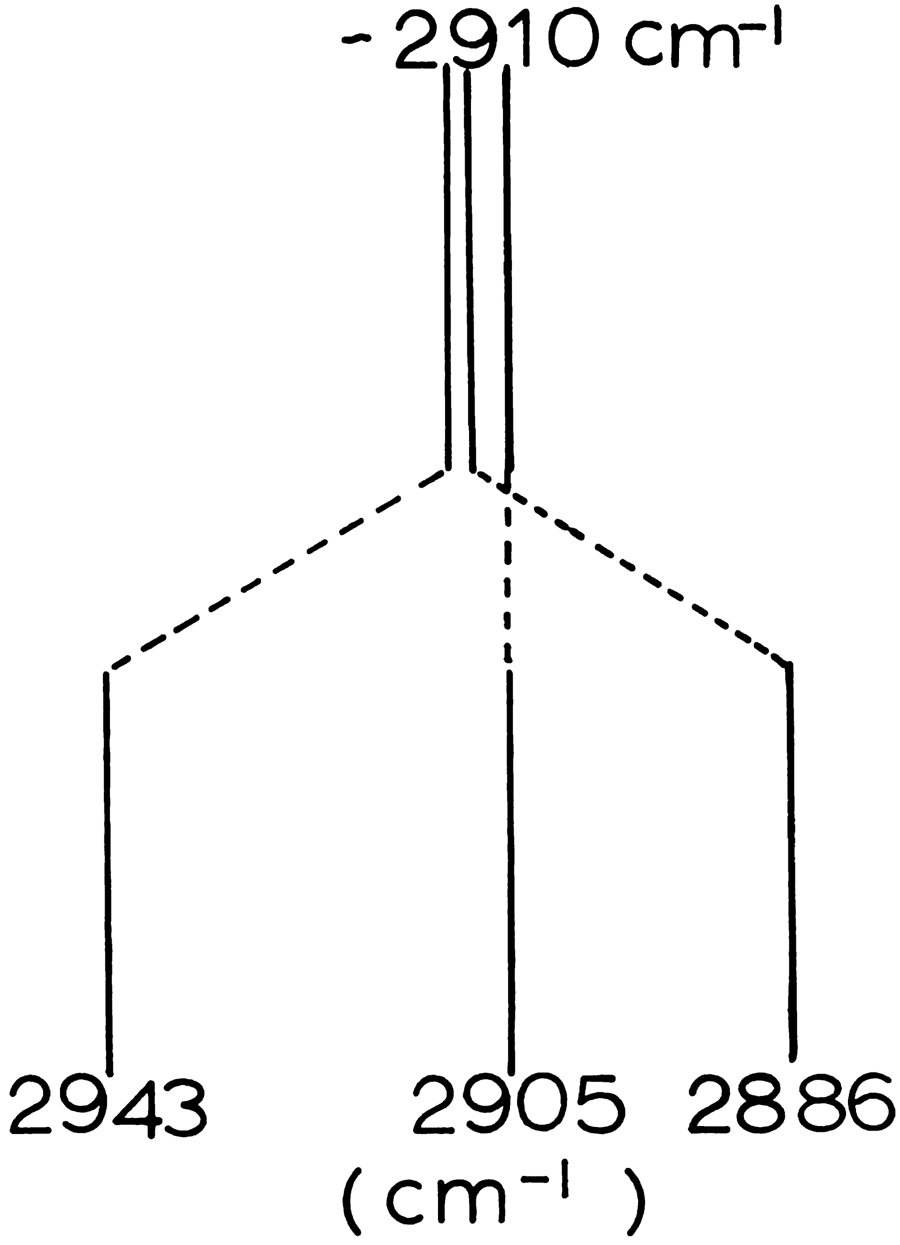

Figure 16

which they do not, the same four bands appearing but shifted to lower frequency. The band at 2964 cm^{-1} also increases in intensity, due to the symmetric methyl stretches. Since the methylene at the three position is no longer present, thus removing two C-H stretching vibrations of A' symmetry, one might expect the vibrations of the methylenes at the 2 and 4 positions (Figure 15D and E) to occur at approximately 2910 cm^{-1}. However, the addition of the two methyl groups introduces several new C-H stretches. One or more of the stretches of A' symmetry may well fall near 2910 cm^{-1}, causing a similar Fermi resonance effect as postulated for glutarimide.

THE CARBONYL STRETCHING REGION

If the motions of the carbonyl groups were strongly coupled during the stretching vibrations, two C=O stretching vibrations would be expected. If the coupling were non-existent the C=O stretching vibrations would be degenerate and only one would be observed. The infrared spectra (Table 10, Figures 3-10) show considerably more than two vibrations in the region expected for the C=O stretching vibrations.

Glutarimide and N-deuterated Glutarimide

In the carbonyl stretching region of the infrared spectra of glutarimide three bands are observed in CH_3CN solution, and four bands in $CDCl_3$ solution. Deuterochloroform is expected to hydrogen bond to the carbonyls, and these bands are observed to be shifted to lower frequencies by 1-10 cm^{-1}, relative to their values in CH_3CN solution. Based on the large decrease in the relative intensities of the bands at 1795 and 1660 cm^{-1} as the concentration of glutarimide decreases these bands have been assigned to dimeric vibrations. Also, the 1660

Table 10. Observed and Calculated Frequencies for the Carbonyl Region

CH_3CN	$CDCl_3$	Calculated	Assignment
Glutarimide			
	1795 cm^{-1}		dimer
1731 cm^{-1}	1731	1731 cm^{-1}	antisymmetric stretch
1714	1710	1704	symmetric stretch
1660	1660		dimer
N-D Glutarimide			
	1730		glutarimide antisymmetric stretch
1713	1706	1720	antisymmetric stretch
1696	1690	1702	symmetric stretch
1660			dimer
3,3-Dimethyl Glutarimide			
1754			dimer
1733	1735	1731	antisymmetric stretch
1714	1714	1704	symmetric stretch
N-D 3,3-Dimethyl Glutarimide			
1730	1734		antisymmetric stretch (N-H)
1719		1719	antisymmetric stretch
1700	1698	1702	symmetric stretch
1670			dimer

cm^{-1} band is observed in N-D glutarimide/CH_3CN solution, and therefore is not an N-H bending frequency. Raman depolarization ratios and Raman intensities for the remaining two bands, at 1731 cm^{-1} and 1714 cm^{-1} (IR frequencies) give no indication of the symmetry species for these bands. In the infrared spectra (Figure 3), the lower frequency band is the most intense. This band could be assigned to the asymmetric C=O stretch, based on intensity consideration. However, the lower frequency band is assigned to the symmetric stretch (1714 cm^{-1}), and the asymmetric stretch is assigned to the 1731 cm^{-1} band. These assignments are based on frequency positions and the normal coordinate analysis.

The infrared spectra of N-deuterated glutarimide in $CDCl_3$ and CH_3CN are shown in Figures 5 and 6. Three bands are observed in each solvent, and are listed in Table 10 along with the calculated frequencies and the assignments. In N-deuterated glutarimide the asymmetric and symmetric stretches shift to lower frequency, 1713 and 1696 cm^{-1}, respectively. The normal coordinate analysis indicates that this shift is the result of mixing between the C=O stretches, C-C stretches and the C-N stretches (see Table 6).

The band at 1730 cm^{-1} in the infrared spectrum of N-D glutarimide is assigned to the asymmetric stretch of the "light" compound; deuteration being only approximately 55% complete. The band at 1660 cm^{-1} in the N-D glutarimide/CH_3CN solution is assigned to the dimer of the light compound.

3,3-Dimethyl Glutarimide and N-Deuterated 3,3-Dimethyl Glutarimide

The observed and calculated frequencies and assignments for the dimethyl compounds are also listed in Table 10. The bands at 1733 and 1714 cm^{-1} in the infrared spectrum of the 3,3-dimethyl glutarimide/ CH_3CN solution are assigned to the asymmetric and symmetric stretching vibrations respectively, whereas the comparable vibrations in N-D dimethyl glutarimide are assigned to bands at 1719 and 1700 cm^{-1} (see Figures 8 and 10, and Table 10).

The band observed at 1754 cm^{-1} in the infrared spectrum of the "light" compound in CH_3CN is assigned to one of the C=O vibrations of the dimer. The band at 1730 cm^{-1} in the infrared spectra of N-D dimethyl glutarimide is assigned to the asymmetric stretch of the "light" compound, since deuteration was approximately 65% complete.

The normal coordinate analysis predicts mixing of the carbonyl stretching vibrations with the C-C and C-N stretches, similar to the glutarimide calculations.

In the infrared spectra (Figure 3-9) of most of the compounds studied, a weak to medium intensity band is observed at approximately 1550 cm^{-1}. Similar bands have been observed in amide compounds (46-50) and have been assigned to various vibrations of the O=C-N-H group. However, in the infrared spectra of the imides investigated in the present study, this band does not appear in all of the spectra, and could be removed by careful cleaning of the sample cell. The behavior of the 1550 cm^{-1} band is not consistent with any assignment. Therefore, it was not included in the normal coordinate analysis.

REMAINING VIBRATIONS

In the frequency region expected for the methylene deformations two bands are observed in each of the spectra: for glutarimide and N-D glutarimide these bands appear at 1462 and 1427 cm^{-1} (see Table 6), in the dimethyl compounds these bands occur at 1452 and 1422 cm^{-1}. From symmetry considerations the glutarimide compounds and dimethyl glutarimide compounds will have three and two methylene deformations respectively. For the glutarimide compounds the band at 1462 cm^{-1} is assigned to two degenerate deformations, one of A' and one of A" symmetry. The remaining deformation of A' symmetry is assigned to the band at 1427 cm^{-1}. The dimethyl compounds have only two methylene deformations, one symmetric and one asymmetric. These are assigned to the band at 1452 cm^{-1}. The band at 1422 cm^{-1} is a mixture of CH_2 deformation and CCH angle bending.

There are nine C-H bending modes yet to be assigned in the two glutarimide molecules, and six for the dimethyl compounds. The frequencies of these modes are expected to occur between 1400 and 600 cm^{-1}. In addition to these modes the N-H bending vibrations are yet to be assigned. Several bands are observed in this frequency region; the majority are expected to arise from mixing of the C-H, N-H and ring stretching modes. The reader is referred, therefore, to Table 6 which lists the assignments of these bands. These assignments are taken from the normal coordinate analysis. It should be noted that mixing of the C-H bending vibrations (normally referred to as CH_2 "twist, wag, and rock") is not surprising since each of the vibrations is a combination of C-C-H angle bending, C-N-H angle bending, and C-C, C-N stretching. The few exceptions are essentially pure CCH bending motions involving the methylene group at the β position of the ring.

The N-H and N-D bending modes have been collected and are listed in Table 11. The in-plane (symmetry plane of the molecule, Figure 11) N-H wagging motion in both glutarimide and dimethyl glutarimide is highly mixed, although this band is mixed to a higher degree in the dimethyl compound. The small (100-130 cm^{-1}) shift of these wagging motions from the N-H to N-D compounds is a consequence of the mixing. The N-H and N-D out-of-plane bending vibrations are also mixed to a large degree. This high degree of mixing of the N-H and N-D bending motions for both glutarimide and 3,3-dimethyl glutarimide inhibits any correlations between the positions of the frequencies for these vibrations and the physiological activities of the drugs.

The frequencies of the carbonyl bending modes have also been collected and are listed in Table 12. There will be four of these bends per molecule, two of A' and two of A" symmetry. These vibrations can also be classified as in-plane and out-of-plane with respect to the plane of the molecule (defined by atoms 1, 2, 3, 4, 5, 7, 8, 9; see Figure 11). The out-of-plane carbonyl bending vibrations are highly mixed in all four molecules studied. In all cases this mixing involves the N-H (or N-D) and CCH bending vibrations. The carbonyl in-plane bending motions are generally not mixed to any great extent, and when mixing does occur the motions involved are the CCN angle bendings. The positions of the in-plane carbonyl bending motions are approximately the same for all four molecules, since the slight variations in the positions of these bands is well within the error limits of the normal coordinate calculations. Thus, it can be noted that the frequencies of the carbonyl motions show no correlation with the physiological

Table 11. N-H and N-D Bending Vibrations

Glutarimide		N-D Glutarimide	
Frequency (cm^{-1})	% N-H Bend	Frequency (cm^{-1})	% N-D Bend
1330	59	1247	36
1050	21	(947)	29
1330*	44	(996)*	>60
(1205)*	26	736*	26
3,3-Dimethyl Glutarimide		N-D 3,3-Dimethyl Glutarimide	
1395	30	1266	25
1325	33	819	20
1279*	46	1019*	60
1243*	31	(729)*	28

( ) indicates a calculated frequency.

* frequencies associated with the N-H out-of-plane bending.

Table 12. C=O Bending Vibrations

Frequency (cm^{-1})	%C=O Bend	Frequency (cm^{-1})	% C=O Bend
Glutarimide		N-D Glutarimide	
1330^a	14	1247^a	36
734^a	29	683^a	11
255*^{a}	60	586^a	29
		255*^{a}	60
916	44	914	44
610	31	610	31
437*	15	437*	14
394*	60	391*	60
3,3-Dimethyl Glutarimide		N-D 3,3-Dimethyl Glutarimide	
864^a	18	578^a	35
638^a	30		
(276)^a*	60	(275)^a*	46
		(235)^a*	20
934	43	933	42
614	33	614	33
462*	25	460*	22
(412)*	60	(406)*	60

( ) indicates a calculated frequency.

* indicates an in-plane bend.

[a] indicates A' symmetry.

activities of the compounds analyzed in the present study.

The frequencies of those ring torsional modes which are not heavily mixed are listed in Table 13. It can be noted that the modes of A' symmetry have the same frequency in both glutarimide and dimethyl glutarimide. These modes involve twisting of the C-N bonds, whereas the torsional vibrations of A" symmetry represent twisting of the C_2-C_4 and C_3-C_5 carbon-carbon bonds. The frequency of these modes are predicted to appear at lower wave number in the dimethyl compound. This shift to lower frequency in the dimethyl compound is not surprising, since the methyl groups on carbon atom 6 move during the vibration. It is difficult to determine if the flexibility of the ring changes when methyl groups replace the hydrogens at the β-position of the ring. However, it appears the flexibility has not changed since the torsions about the C-N bonds of both glutarimide and 3,3-dimethyl glutarimide occur at the same frequency. This would indicate that there is no relation between the frequency positions of the ring torsions and the physiological activities of glutarimide and 3,3-dimethyl glutarimide.

SUMMARY AND CONCLUSIONS

A normal coordinate analysis has been completed on the molecules: glutarimide, 3,3-dimethyl glutarimide, and their deuterated derivatives. The assignments of the bands related to non-mixed vibrational modes have been discussed with the intention of establishing correlations between the frequencies of these vibrations in glutarimide, 3,3-dimethyl glutarimide, and the physiological activities of these molecules. In each case changes in the frequency position were either non-existent or could be explained by mass effects, and it is concluded that no correlations can be made in the present limited study.

Table 13. Ring Torsions

Frequency (cm^{-1}), A' Symmetry	Molecule	Frequency (cm^{-1}), A" Symmetry	
(170)	Glutarimide	151	(181)
(158)	N-D Glutarimide	151	(184)
(170)	Dimethyl Glutarimide		(140)
(158)	N-D Dimethyl Glutarimide		(140)

( ) indicates a calculated frequency.

CHAPTER III

INTERACTIONS OF THE GLUTARIMIDES IN SOLUTION

CHAPTER III

INTERACTIONS OF THE GLUTARIMIDES IN SOLUTION

INTRODUCTION

One of the most difficult problems encountered when studying solutions of any type is the elucidation of the interactions between various chemical species which exist in solutions. In the present study interactions which may occur include self-association of the solute molecules, interactions between the solvent and the solute, and interactions between the molecules of the solvent. In order to more clearly understand the vibrational analysis of our solutions the first two types of interactions were examined in some detail.

INTERACTIONS IN DEUTEROCHLOROFORM

Solute-Solvent Interactions

When glutarimide is dissolved in deuterochloroform, deuterium bonding is expected to occur between the solvent and the solute.

The dipole moment of $CDCl_3$ is directed toward the chlorine end of the molecule. Consequently, the deuterium atom in $CDCl_3$ has a partial positive charge. Thus deuterium bonding is expected to occur with the carbonyls of glutarimide.

In the infrared spectrum of glutarimide in $CDCl_3$, the band due to the N-H stretch is sharp and well defined, and is shifted to higher frequency, relative to its N-H stretching frequency in CH_3CN solutions. This is an indication that association of $CDCl_3$ with glutarimide does not occur through the N-H group. Other evidence for this conclusion will be given in the following section. The bands due to the symmetric and antisymmetric C=O stretches are rather broad and complex, with several absorption maxima. However, in $CDCl_3$ solution, the bands assigned to the symmetric and antisymmetric stretches are in most cases 1-5 cm^{-1} lower in frequency relative to their values when measured in CH_3CN solution, which supports the conclusion that hydrogen bonding occurs through the carbonyls.

Solute-Solute Interactions

The infrared spectra of both glutarimide and the dimethyl compound contain broad, weak bands 150-260 cm^{-1} below the "free" N-H stretch, at 3219 and 3108 cm^{-1}. These bands cannot be assigned as overtone or combination bands, and in the spectra of both the N-D compounds these broad bands shift to the 2300 to 2500 cm^{-1} region.

These bands could arise from interactions between the partially positive N-H proton of the glutarimides with the Cl_3 portion of the deuterochloroform solvent. Therefore, these bands were studied in mixed solvents of deuterochloroform and acetonitrile, with a large excess of deuterochloroform relative to acetonitrile. If the bands were due to interaction between the glutarimides and $CDCl_3$, then the competition between deuterochloroform and acetonitrile for the glutarimide molecules should result in the decreased intensity of the bands at 3219 and 3108 cm^{-1}. Another band should appear in the infrared spectrum at approximately 3280 cm^{-1} due to interaction of glutarimide with acetonitrile (Figure 4). On the other hand, if these bands are due to dimers of glutarimide, then the competition between the two solvents for the glutarimide monomer molecules would result in the decreased intensity of the monomer N-H stretching band at 3373 cm^{-1} (the position of the N-H fundamental in $CDCl_3$). As the concentration of acetonitrile is increased from 0.2 M to 1.0 M while the concentration of glutarimide remains constant at 0.2 M, the 3373 cm^{-1} band decreases in intensity and the 3280 cm^{-1} band, due to the association of glutarimide and acetonitrile, becomes apparent. However, there is no decrease in the intensity of either the 3219 cm^{-1} or the 3108 cm^{-1} bands. These bands therefore, are assigned to the dimers of glutarimide and the dimethyl compound, and do not indicate an interaction with deuterochloroform. The 150 and 260 cm^{-1} shift in the frequency of the N-H stretch between the monomer and dimers of glutarimide in $CDCl_3$ solution indicates that the interactions involved in the self association of the glutarimide molecules are strong. There are other indications that dimers of glutarimide exist in $CDCl_3$ solution. Three bands appear in the spectrum of 0.2 M glutarimide which do not appear at 0.1 M. These bands occur at approximately 1370, 1310 and 1250 cm^{-1} and can be seen in Figure 3B.

The self-association of glutarimide and 3,3-dimethyl glutarimide in chloroform has been measured by Andrews and Bunchanan (27). Although the solvent used in the present study was deuterochloroform, the self association is not expected to vary appreciably. The concentration range used in their study was 0.01-0.04 M, and the self-association constants measured were 1.6-2.2 M^{-1} and 2.0-2.7 M^{-1} for glutarimide and 3,3-dimethyl glutarimide respectively. However, we find that the band at 3680 cm^{-1}, which appears in all of their spectra and which they attribute to the solvent, is due to water. This band was also seen during this work, but was removed by allowing the $CDCl_3$ to stand over activated molecular sieves, and storing the solvent in a dry box under a nitrogen atmosphere. The concentration of water found in off-the-shelf bottles of deuterochloroform is at least as high as the most concentrated glutarimide solution used in the study by Andrews and Buchanan, and in most cases the amount of water present was greater than the amount of glutarimide (or 3,3-dimethyl glutarimide) present. Thus, the reported self-association constants are probably too low.

INTERACTIONS OF THE GLUTARIMIDES IN ACETONITRILE

Solute-Solvent Interactions

The dipole moment in CH_3CN is directed in such a way that the nitrogen atom has a partial negative charge. This negative end of acetonitrile is expected to form a hydrogen bond with the N-H group of glutarimide, i.e., a $CH_3CN \cdots\cdot$ H-NR hydrogen bond. The large shift (relative to $CDCl_3$) and broadness of the N-H stretching band of glutarimide and 3,3-dimethyl glutarimide in the infrared spectra of these compounds indicate that as expected, hydrogen bonds are formed through the N-H group.

The magnitude of the shift of the N-H stretching frequency of glutarimide in CH_3CN solution, approximately 100 cm^{-1}, is an indication of the strength of the solvent-glutarimide complex. In the previous section, the formation of dimers was noted to shift the N-H stretching frequency to 3219 cm^{-1} and 3108 cm^{-1}. The large shift of the frequency of the N-H stretching bands in the dimers relative to acetonitrile solution is believed to indicate that the self-association of the glutarimide molecules is the strongest interaction in any of the solutions investigated in the present study.

Solute-Solute Interactions in CH_3CN.

In acetonitrile solutions of glutarimide and 3,3-dimethyl glutarimide there is no appearance of the dimer N-H stretching bands at 3219 cm^{-1} and 3108 cm^{-1}, or any of the other bands attributed to the dimer of glutarimide in $CDCl_3$ solution (compare Figures 3 and 4). The formation of dimers in acetonitrile solution was not detectable at the concentrations studied.

The main factor for the absence of dimers in acetonitrile solutions is probably the strength of the acetonitrile-glutarimide interaction. In the presence of a large excess of acetonitrile the glutarimide molecule prefers to bind with the solvent rather than form a dimer, even though the self-association of glutarimide molecules is the strongest interaction in solution. If the relevant formation constants were known, one could calculate the relative equilibrium concentration of dimer and glutarimide-acetonitrile complex. In solution we have the following equilibria,

$$2\,G \quad G_2 \text{ (dimerization) } K_d = \frac{[G_2]}{[G^2]} \tag{1}$$

$$G + S \quad GS \text{ (solvation) } K_c = \frac{[GS]}{[G][S]} \quad (2).$$

Where: $[G]$ = the concentration of glutarimide.

$[G_2]$ = the concentration of self-associated glutarimide molecules (dimer).

$[S]$ = the concentration of the solvent, estimated to be 10 M for acetonitrile.

$[GS]$ = the concentration of the acetonitrile-glutarimide "complex".

K_d = the equilibrium constant for formation of dimers.

K_c = the equilibrium constant for formation of the solute-solvent "complex".

The highest concentration of glutarimide in CH_3CN studied was 0.2 M. The molarity of acetonitrile in this solution is estimated to be approximately 10. If we take the ratio $[GS]/[G_2]$,

$$\frac{[GS]}{[G_2]} = \frac{K_c}{K_d}\,\frac{[G][S]}{[G]^2}$$

$$\frac{[GS]}{[G_2]} = \frac{K_c}{K_d}\,\frac{[S]}{[G]} \qquad (3).$$

The N-H stretching bands of glutarimide are detectable in $CDCl_3$ at 0.2 M with a path length of 0.2 mm. Using the formation constant for formation of dimers in $CDCl_3$ measured by Andrews and Buchanan (27), the concentration of dimers in a 0.2 M glutarimide/$CDCl_3$ solution (0.2 M being total glutarimide concentration), is 0.034 M. Thus, it can be reasonably assumed that the concentration of dimers present in a 0.2 M glutarimide/CH_3CN solution is less than 0.03 M since the N-H stretching bands are not detectable in such a solution. Then from Equation (3):

$$\frac{0.14}{0.03} = \frac{K_c}{K_d}\,\frac{10}{0.03}$$

$$K_d \geq 71\ K_c \qquad (4).$$

For this hypothetical case, the formation constant of the dimer would have to be 71 times as large as the formation constant of the solute-solvent complex. Experimental evidence is available (45) which indicates that the formation constants of these two complexes (dimer and solute-solvent interaction) would not differ by approximately two orders of magnitude. Thus, the G_2 concentration is expected to be well below 0.03 $\underline{M}$, and it is not surprising that the N-H stretching bands of the dimer are not detectable in glutarimide/CH_3CN solutions.

The strengths for the interactions encountered in this study are, in order of decreasing strength: A. glutarimide-glutarimide dimers, B. CH_3CN-glutarimide "complex", C. $CDCl_3$-glutarimide interactions. The order A-B is based on correlations between $\Delta\nu_s$ of the N-H group and various physical properties of hydrogen bonded systems (51), and the B-C order is based on the detection of dimers in solution.

SUGGESTIONS FOR FUTURE WORK

These studies could be extended to other members of the series, such as β-methyl and β-ethyl glutarimide, and all of the compounds listed in Table 1. It should also be noted that if the study is extended by normal coordinate analysis of these molecules, the observed frequencies could be obtained from matrix isolation spectra. This would avoid the problem of solvent absorption.

The concentration range could be extended in order to calculate self-association constants for the various glutarimides in the solvents used in this study as well as in other solvents.

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