Carbon-13 And Tellurium-125 NMR Studies Of Aryltellurium Halides And Proton Spin-Lattice Relaxation Rate Studies Of Some Simple Nitrogen Heterocyclic Compounds

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This Thesis

is

Dedicated

to

My Beloved Husband Deepal

My Parents

and

My Uncle

ABSTRACT

CARBON-13 AND TELLURIUM-125 NMR STUDIES OF ARYLTELLURIUM HALIDES AND PROTON SPIN-LATTICE RELAXATION RATE STUDIES OF SOME SIMPLE NITROGEN HETEROCYCLIC COMPOUNDS

Sriyawathie Peiris, Ph.D.
Concordia University, 1983

A series of three diaryltellurium dihalo compounds and three aryltellurium trihalides has been prepared by halogenation of the corresponding diaryltellurium or diaryl ditelluride, respectively. The ^{13}C and ^{125}Te NMR spectra of these compounds have been interpreted in terms of the electronegativities of halogens. The temperature dependence of ^{125}Te chemical shifts was investigated for one compound. The ^{13}C spectra of a series of parasubstituted diaryltellurium dichlorides have been interpreted in terms of resonance structures due to electron donor mesomeric contributions as well as electron acceptor properties of tellurium.

Proton spin-lattice relaxation rates of a series of 2-methyl and 2, 2-dimethyl substituted 4, 6-diamino-1-aryl-1-2-dihydro-s-triazines, 3-aryl-5, 5-dimethyl-2-thiohydantoins, their 5-monomethyl analogues, and 3-aryl-2, 3-dihydro-4(1H)-quinazolinones with different N-3 aryl ortho substituents, have been measured. Proton spin-lattice relaxation rates in these compounds have been measured in order to establish the relaxation rates of protons in different environments, and the factors influencing the rates. Evidence for anisotropic motion of the molecules, and inter-ring relaxation pathways has been considered.

The R_1 values of these compounds have been explained in terms of

free rotation of substituents (CH_3 groups), steric effects, preferred conformations, and inter-ring relaxation pathways. Inter-ring relaxation in triazines was confirmed by NOED experiments.

Proton spin-lattice relaxation rates of a series of simple nitrogen heterocyclic compounds, e.g. uracils, 2 pyrimidones, 4-pyrimidones, pyrimidine, and some similar types of bicyclic compounds have been measured. Unusually high relaxation rates for protons α-to sp^2-hybridized nitrogen atoms or protons which are adjacent to an sp^3-hybridized nitrogen atom which is influenced by proton exchange, have been observed. In certain cases, these higher relaxation rates were identified as being due to scalar coupling of the first kind. Selective pulse spin-lattice relaxation rate measurements were used to clarify the contribution of non-dipolar mechanisms.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SPECTRA

CHAPTER 1

13-CARBON NMR SPECTRA OF PHENYLTELLURIUM HALIDES

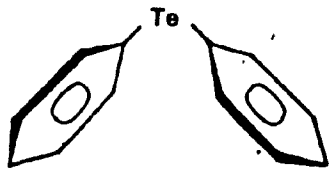
The application of ^{13}C NMR spectroscopy to organic and organometallic compounds[1-3] has been extensively reviewed. In general, ^{13}C spectra can provide information on substituent and steric effects, on the inductive and conjugative influences of substituents and on relaxation processes. Further, ^{13}C chemical shift measurements have been found to reflect the electron density at the carbon atom and, therefore, they have been particularly useful as probes for the study of organometallic compounds.

It is well known[4] that carbon atoms directly bonded to a heavy halogen (Br or I) exhibit an abnormally high ^{13}C shielding. The chemical shifts of these carbons do not, indeed, fit into the empirical linear correlations which have been established between ^{13}C chemical shift and electronegativity[5].

The chemical shift of the carbon atom which is attached to tellurium also exhibits an abnormally high ^{13}C shielding. This fact concerning the family of the chalcogens has received only slight attention in the literature. Sulfur and the heavier elements of group VI form compounds, called as a class chalcogens, in which the compound can be formulated as Ar-M-Ar where M= O, S, Se or Te. All that has been reported is a marked deviation in the resonance of the carbon atoms bearing the hetero atom in aromatic[6] and benzylic[7] ditellurides and derivatives. These results deviate significantly from additivity rules for the same carbons in phenyl vinyl selenides[3]. However, the available data on tellurium compounds are limited compared with those for sulfur

and selenium compounds[6,9-12]. A principal interest in this research has been to provide additional information on the ^{13}C spectra of tellurium compounds with the aim of gaining further insight into the factors which influence ^{13}C chemical shifts.

The unusual shielding effects which have previously been reported[7] may be due to the metallic nature of the tellurium atom[7]. Certain groups of workers, using dipole moment measurements[13], have suggested that diphenyltellurium, I, is not a planar compound. This inference may be supported by the unusual ^{13}C shielding effects noted for this compound.



I

If the molecule is planar, there is a possibility for overlapping of a lone pair electrons of tellurium with the 2p-Pi electrons of the aromatic ring. One therefore expects an upfield ^{13}C chemical shift, or shielding effect, for para carbons with respect to other ring carbon atoms. In fact, the chemical shifts of C-4 and C-4' i.e., the para carbons of the diphenyltellurium, are not much different (128.04 ppm) from the ^{13}C benzene chemical shift (128.5 ppm). This supports the idea that non-planarity of the molecule inhibits such electron overlap. If the compounds were planar one would expect significantly different chemical shifts for these two carbon atoms.

The study of the ^{13}C NMR spectra of the aromatic organotellurium

compounds reported in this thesis was undertaken in order to obtain information on the effects of tellurium on the chemical shifts of the carbon nuclei. Effects of aromatic substituents on the resonances of the skeletal carbon atoms were also investigated. It was expected that the information obtained would be valuable for structure determination purposes in future studies of compounds of similar type, and that insight into the use of ^{13}C spectroscopy for determining conformation would result. ^{13}C spectra, at 25.1 MHz, were measured for four diphenyltellurium dihalides, three phenyltellurium trihalides, three substituted diphenyltellurium dihalides, and four substituted phenyltellurium trichlorides, plus the reference compound diphenyltellurium.

EXPERIMENTAL

The pulse Fourier transform, ^{13}C NMR spectra of all of the compounds except a few were determined at a probe temperature of about 35°C using an extensively modified Varian HA-100 spectrometer operating at 25.1 MHz with a homonuclear (^{13}C) lock provided by the solvent. Broadband ^{1}H decoupling was employed. The spectrometer was interfaced to a Hewlett-Packard 2114A computer, using a 4K word data block and a block averaging technique to improve dynamic range. Spectral width was 5000 Hz (i.e. about 200 ppm) in all cases. Concentrations of 2 to 4% (weight/volume) in dimethylsulfoxide (DMSO) were employed, the proton decoupled solvent providing the lock signal.

^{13}C spectra of a few compounds were measured at approximately 28°C on a Bruker WH 400 spectrometer operating at 100 MHz, using DMSO-d_6 as solvent.

Some of the compounds were obtained from Dr Vijay Kumar, of this University, and were purified by recrystallization. Diphenyltellurium dihalo and phenyltellurium trihalo compounds were synthesized according already known procedures[14], as described later. Chemical shifts (ppm) are reported relative to tetramethylsilane (TMS), and were measured with respect to the DMSO signal (40.40 ppm). They are estimated to be accurate to 2.0 Hz (equivalent to about 0.05 ppm), unless otherwise indicated.

RESULTS AND DISCUSSION

As a general rule, the intensity of a slowly relaxing ^{13}C signal will be inversely related to its T_1 value, since insufficient time is usually allowed for complete relaxation. This information can be used indirectly as an aid to spectral assignment. In carbon atoms that have no directly bonded protons, dipolar relaxation is inefficient, leading to much longer relaxation times and smaller intensity of the observed ^{13}C signals. Quaternary carbon signals were identified by this method.

DIPHENYLTELLURIUM DIHALO COMPOUNDS

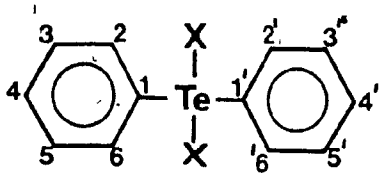
^{13}C chemical shifts for the diphenyltellurium dihalides are recorded in Table 1.1. Assignments of the aromatic signals were based on previous studies[6,15]. Examination of Table 1.1 reveals that the effect of changes in tellurium halo substituents is most strongly observed at C-1, to which the tellurium is directly attached, less so at C-2 (ortho) and C-4 (para) and least at C-3 (meta).

In all the diaryl dihalo compounds, the two meta and two ortho carbons are equivalent, because one signal is observed for each of the

two pairs of carbon atoms. The measured chemical shifts are, therefore, values averaged over a number of conformations arising from rotation about the phenyl-tellurium bond. The fact that the chemical shift of the para carbon of diphenyltellurium is not much different (128.04 ppm) from the ^{13}C benzene chemical shift supports the idea of non-planarity of the phenyl rings in this compound, leading to a less effective overlap of the p electrons of the tellurium atom with the Pi electrons of the phenyl ring. According to X-ray structure analysis of diphenyltellurium dibromide[16], diphenyltellurium dihalo compounds in the crystalline state are trigonal bipyramidal in structure, II, where the two halogens are in axial positions, the two phenyl nuclei and the lone pair of electrons from tellurium atom are in equatorial positions. The phenyl groups are equivalent, being related by a σ plane.

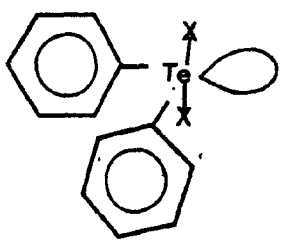
TABLE 1.1

13-CARBON CHEMICAL SHIFTS OF DIPHENYLTELLURIUM DIHALIDES



X	C 1, 1'	C2,2' 6,6'	C3,3' 5,5'	C 4, 4'
*	115.04	137.80	129.87	128.04
F	140.45	131.54	128.53	131.08
Cl	138.46	134.49	128.52	130.90
Br	135.19	135.91	129.38	130.93
I	130.71	136.48	129.12	142.24

* Diphehyltelluride



II

The chemical shift of the carbon which is attached to the tellurium dihalide group decreases (i.e. shielding increases) uniformly as the halogens vary from fluorine (140.45 ppm) to iodine (130.71 ppm). This effect arises from activation or deactivation (i.e. displacement of electrons to or from) of the directly bonded carbon of the phenyl group.

The tellurium-dihalide group can delocalise electrons primarily from the carbon which is attached to tellurium. Fluorine is the most electronegative halogen and is, therefore, expected to have the largest effect on carbon shielding. The deshielding of the ortho carbon atoms monotonically increases in the series F-Cl-Br-I, with an 5.06 ppm difference between the resonances in the difluoride and the diiodide. This could be due to the "ortho effect" in analogy with the similar effect in halobenzenes. The chemical shift of C-3 is somewhat dependent on the nature of the phenyl group substituents (see later). Within the group of four halo compounds the chemical shifts of C-2 and C-6 vary in the sequence I>Br>Cl>F. Plots of chemical shift versus the Pauling electronegativity (Figure 1-1) suggest a correlation but, rather surprisingly, the greater the electronegativity of the substituent at

the tellurium the greater the shielding of C-2 and C-6 (ortho carbons). There is no marked difference in chemical shift, with respect to benzene, of the meta carbons. In diphenyltelluride the para carbon (C-4) is slightly shielded with respect to benzene (0.8 ppm). The electron density of C-4, which determines its shielding must be influenced by coupling of a heteroatom electron pair with the Pi system of the benzene ring. C-4 is less shielded compared to chemical shifts of para carbons of derivatives of other heteroatoms in the same series[17]. The chemical shifts of the meta and para carbon atoms follow the same trend observed for the ortho carbon atoms, which is opposite to that found for the C-1 carbon atom.

PHENYLTELLURIUM TRIHALIDES

^{13}C chemical shifts for the phenyltellurium trihalides are recorded in Table 1.2. Examination of Table 1.2 shows that the effect of the halogen is most strongly observed at C-1, to which the tellurium trihalo group is attached, less so at C-2 (ortho) and C-4 (para), and hardly any at C-3 (meta).

Chlorine is more electro negative than bromine, hence should remove electron density, primarily from the carbon atoms to which the tellurium trihalide group is attached, and so the chemical shift at C-1 is displaced to lower field (Table 1.2). However, for the iodide substituent C-1 is deshielded compared to bromine. This can be attributed to the "heavy halogen effect". The chemical shifts of C-3 and C-5 (meta carbons) in all three halo compounds practically coincide (+/-0.4 ppm) with the ^{13}C benzene chemical shift. This indicates the lack of significant inductive effect from the tellurium trihalide group.

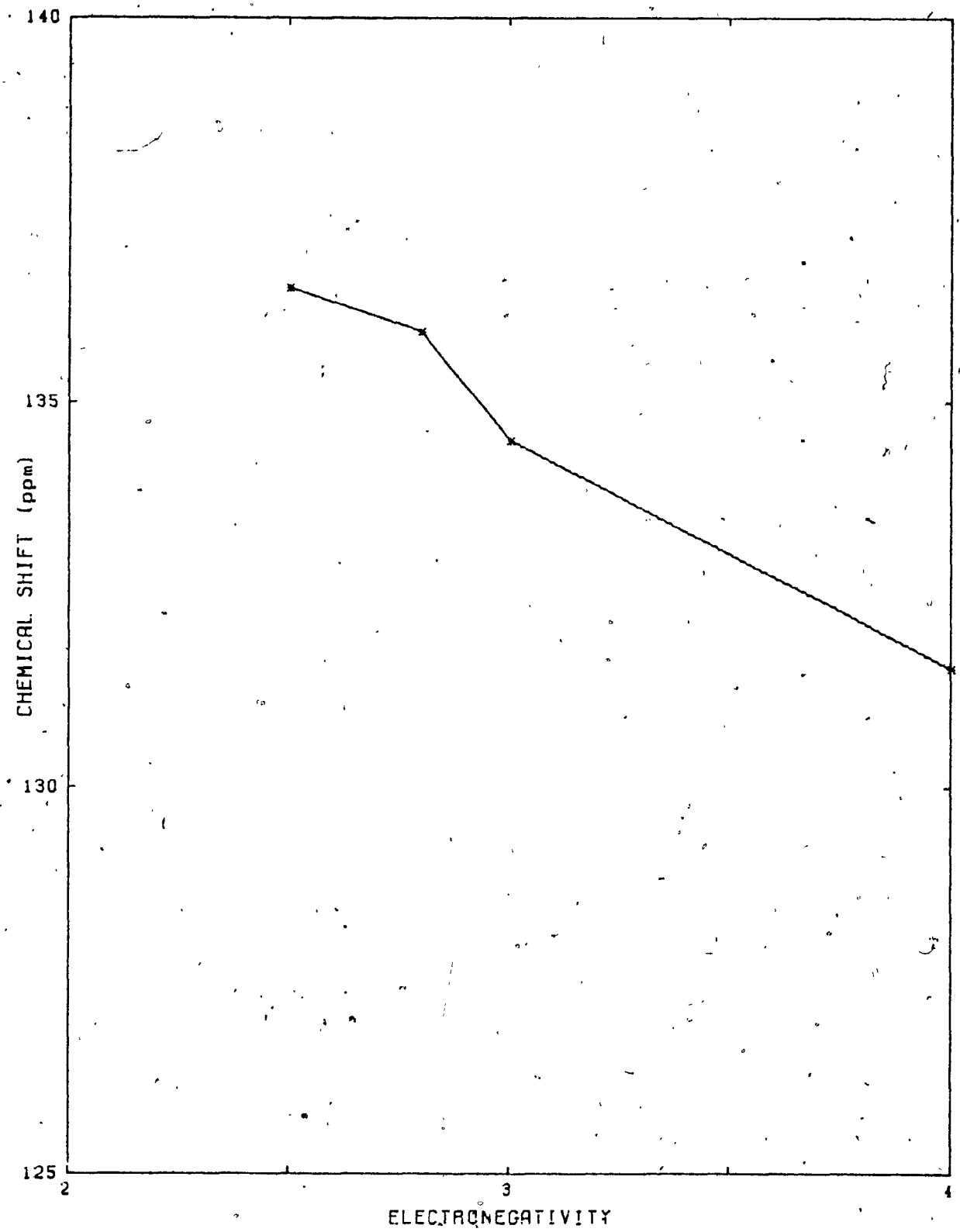
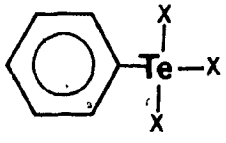


Figure-1.3. Plot of 13-C chemical shifts versus Pauling electronegativities of halo substituents.

The chemical shifts of(C-4) (para) are 1-3 ppm lower (i.e deshielded) than in benzene. This means that the substituents cause a decrease in the electron density at C-4. The low sensitivity to the nature of the halogen substituent group could be due to the greater length of the tellurium carbon bond compared to the carbon-oxygen, carbon-sulfur, carbon-selenium bond[15], leading to a decrease in the steric interaction. A longer bond implies that conditions are poorer for overlapping of the 5p orbitals of tellurium and the 2p orbitals of the benzene ring.

TABLE 1.2

13-CARBON CHEMICAL SHIFTS OF PHENYLTELLURIUM TRIHALIDES



X	C 1	C 2	C 3	C 4	C 5	C 6
Cl	153.28	132.70	128.52	130.51	128.52	132.70
Br	143.70	134.49	128.52	130.51	128.52	134.49
I	146.62	131.09	128.85	131.80	128.85	131.09

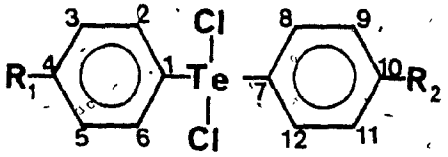
By comparing the data in Table 1.1 and Table 1.2, it is clear that for a given organic substituent, C-1 chemical shifts vary according to the number of chlorine atoms attached to tellurium, $PhTeCl_3$> $PhTeCl_2$> Ph_2Te. This trend can be explained by considering the polarity of the Te-C bond. On going from phenyltellurium trichloride to diphenyltellurium dichloride, there is a decreasing partial positive

charge on tellurium which corresponds to a decrease in the polarity of the Te-C bond. Magnetic anisotropic effects originating in the tellurium substituents are not expected to vary much in this closely related series, moreover, they are expected to be small[6]. Thus, the polarity of the Te-C bond appears to have the largest effect on the C-1 resonance. In contrast to C-1, for a particular substituent, chemical shift values of C-2 (ortho) change in the opposite direction, i.e., $PhTeCl_3 < PhTeCl_2 < Ph_2Te$. This can be due to the change of the conformation of the molecule with differing number of substituents on tellurium atom. Ortho effects are not well understood.

PARA SUBSTITUTED DIPHENYLTELLURIUM DICHLORIDES

TABLE 1.3

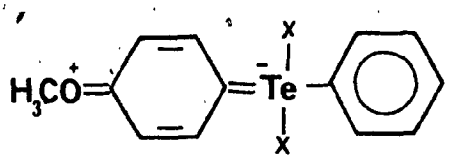
13-CARBON CHEMICAL SHIFTS OF PARASUBSTITUTED DIPHENYLTELLURIUM DICHLORIDES



R_1	R_2	C1	C2,C6	C3,5	C4	C7	C8,12	C9,11	C10
-	-	138.46	134.49	128.52	130.90	138.46	134.49	128.52	130.90
H_3CO	-	127.73	136.48	114.65	161.93	138.46	134.49	129.52	130.71
H_5C_2O	-	126.93	136.48	114.80	160.34	138.46	133.89	128.72	130.51
H_3CO	H_3CO	128.37	136.30	114.94	161.29	128.37	136.30	114.94	161.29

Table 1.3 shows the relationship between the C^{13} chemical shifts of the para carbon and the carbon which is attached to the tellurium

dichloride group. Apart from the small inductive effect of the tellurium compared to other elements in group VI, this element can act as an electron acceptor, presumably on account of its vacant 5-d orbitals. For example, when a powerful Pi donor group is present in the para position of the aryl nucleus some contribution is expected from the polar structure shown below.



III

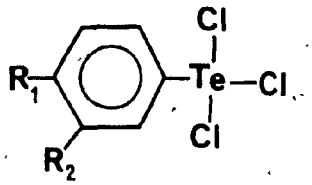
Thus an electron releasing group at the para position shields (10.73 ppm) the carbon (i.e. C-1) which is attached to the tellurium dichloride group. At the same time C-1 is deshielded compared to the para carbon of anisole by 8 ppm. This difference can be attributed to the tellurium dichloride group. As expected, C-3 and C-5 experience an upfield shift (13.91 ppm) due to the methoxy group at C-4. This clearly indicates the interaction of the lone pair of electrons of oxygen with benzene 2p-Pi electrons. On the basis of mesomeric effects, the methoxy group is an electron releasing group. The carbon which is attached to the tellurium dichloride group is more effectively shielded, compared to the corresponding carbon (i.e. C-7) of the phenyl ring which does not have a para substituent. The other important thing to note here is that the para substituent group does not have any effect on carbons of the other ring. These results show that ^{13}C chemical shifts reflect intramolecular electronic effects. Chemical shifts of the meta

carbons of the unsubstituted phenyl ring are not much different from the ^{13}C benzene value.

SUBSTITUTED PHENYLTELLURIUM TRIHALIDES

TABLE 1.4

13-CARBON CHEMICAL SHIFTS OF SUBSTITUTED PHENYLTELLURIUM TRICHLORIDES



R_1	R_2	C 1	C 2	C 3	C 4	C 5	C 6
-	-	153.28	132.70	128.52	130.51	128.52	132.70
H_3CO	-	142.44	134.49	113.61	160.73	113.61	134.49
H_5C_2O	-	142.34	134.49	113.81	160.34	113.81	134.49
H_3CO	H_3C	142.50	126.73	134.49	158.94	110.23	125.14
H_3CO	H_3CO	143.13	114.42	148.01	150.39	114.42	127.73

Table 1.4 shows the effect of substitution on the ^{13}C chemical shifts of phenyltellurium trihalides. As expected, from the data on substituted phenyltellurium dichlorides (Table 1.3) the carbon in the position para to the electron donor substituent, (i.e. C-1) is most sensitive to substitution. The chemical shift of C-1 has moved upfield by 10.84 ppm. The chemical shifts of ortho carbons (i.e. C-3 and C-5) follow the same trend (upfield shift) observed for the C-1 carbon. This can be explained via the changes in electron distribution, which changes by overlapping of the lone pair of electrons from oxygen with the 2p-Pi electrons from the benzene as shown before. The chemical shifts of meta

carbons (i.e. C-2 and C-6) move down field (1.4 ppm). When electron releasing groups are ortho to each other these effects are additive, so that, in compounds where there are methyl and methoxy groups ortho to each other, C-1 is more shielded than in the unsubstituted compound.

CONCLUSION

^{13}C chemical shift measurements on a series of phenyl and diphenyl tellurides were carried out . The shielding effect resulting from the presence of an atom from a higher row, as is already well known[4] for iodine, also exists for tellurium though to a lesser degree, but is much larger compared to other elements in the same series. This could probably be due to its metallic nature. Tellurium has electron donating mesomeric properties as well as electron acceptor properties because of the availability of vacant 5-d orbitals. This reflects in some ^{13}C chemical shifts of para substituted diphenyltellurium dichloro compounds. For example, in diphenyltellurium dichloride with relatively weak donor substituents, the tellurium atom interacts with the Pi system of the aromatic ring, mainly by an inductive mechanism, and shows a tendency to undergo polar conjugation.

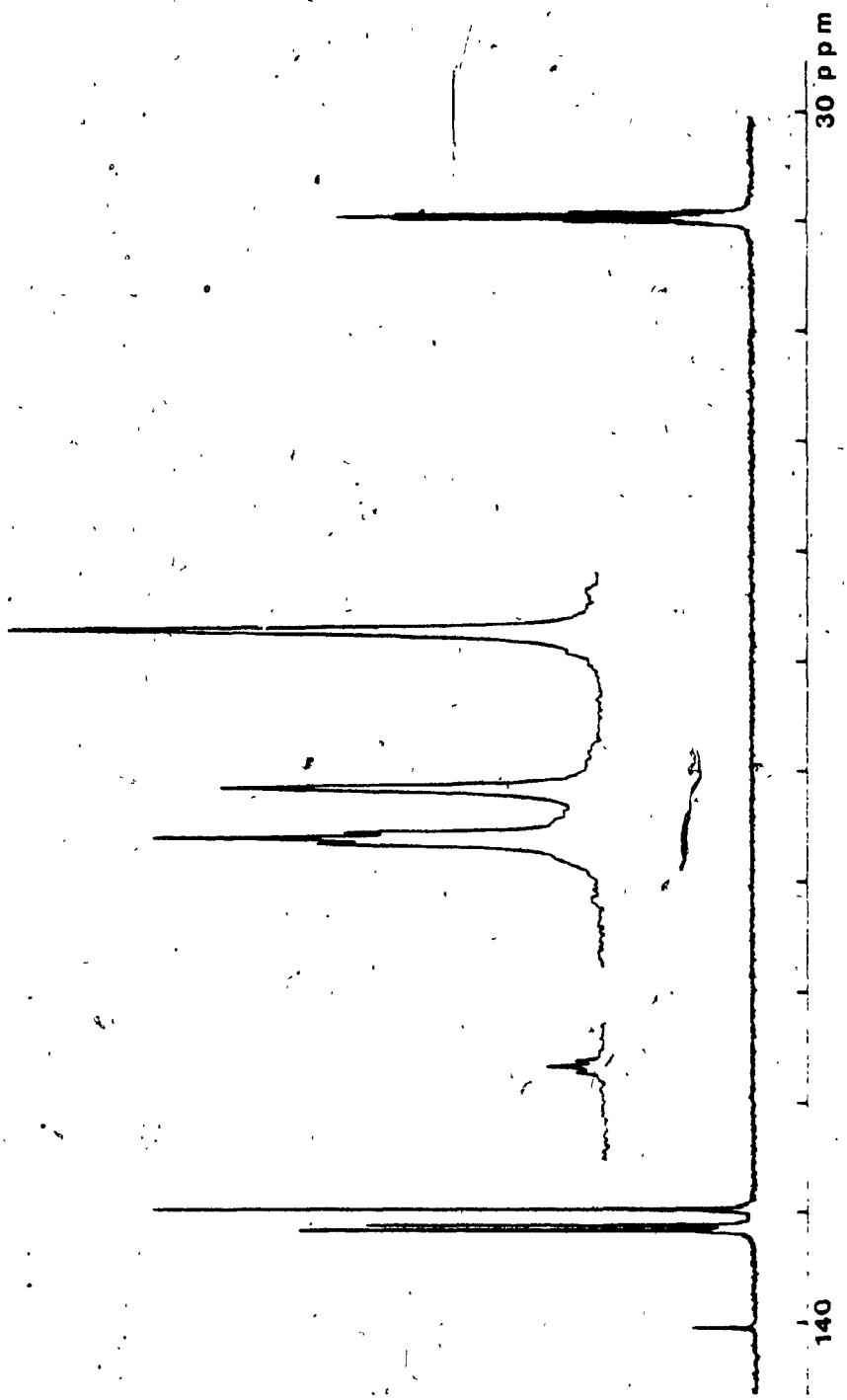


Figure 1.2 100 MHz Carbon-13 NMR spectrum of diphenyltellurium difluoride.

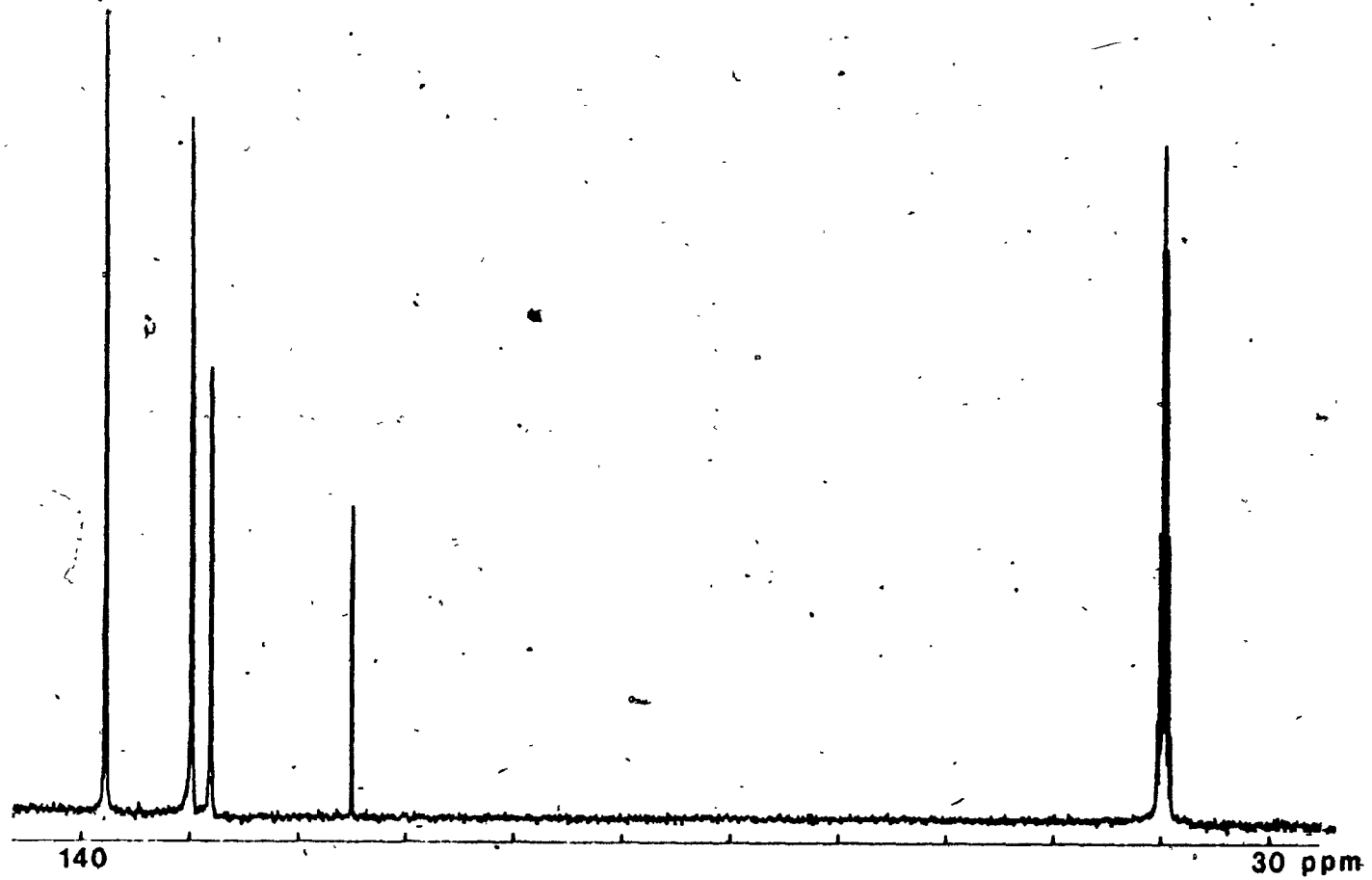


Figure 1.3 100 MHz Carbon-13 NMR spectrum of diphenyltellurium.

125-TELLURIUM NMR

The three naturally most abundant isotopes of tellurium (^{126}Te, ^{128}Te, ^{130}Te) have a nuclear spin quantum number of zero and are, therefore, unsuitable for investigation by NMR spectroscopy. Even though both ^{125}Te and ^{123}Te isotopes have spin 1/2, the very low natural abundance of ^{123}Te (0.89%) compared to ^{125}Te (7%) makes ^{125}Te more suitable for NMR studies. Difficulties associated with the low natural abundance of ^{125}Te and its low sensitivity to NMR detection (3.16% that of the proton at the same field strength) can be avoided by using the pulse Fourier transform method. This sensitivity is an order of magnitude larger than that of ^{77}Se. These factors appear to make ^{125}Te a favourable nuclide for NMR study. One problem, however, is that where nuclear Overhauser effects become important, the negative gyromagnetic ratio of the ^{125}Te nucleus may attenuate sensitivity.

Despite its favourable NMR properties, relatively few direct[18-20] or indirect[21-22] observations of ^{125}Te in organometallic compounds have been reported. In contrast to tellurium, a number of investigators have studied the ^{77}Se NMR spectra of a broad range of compounds in a variety of chemical environments. These studies have established the utility of ^{77}Se NMR in obtaining structural information, as a result of the wide range of chemical shifts observed (ca 1800 ppm).

Literature reports have documented ^{125}Te NMR shifts covering a range of 4000 ppm. Only a few reports[23-24] of ^{125}Te spin-lattice relaxation rate measurement have been found. No details of experimentally determined NOE effects have been reported.

In the current study, ^{125}Te chemical shifts of a series of phenyltellurium dihalides and trihalides have been measured. During

this work, the temperature effect on ^{125}Te chemical shifts has also been measured. The results show that the ^{125}Te chemical shifts of phenyltellurium halides are influenced to a measurable degree by variation of the directly bonded halogen substituent. In contrast, there appears to be no obvious correlation between changes in ^{125}Te chemical shift and change in substituent on the aromatic ring. The variation of the chemical shift of the diphenyltellurium dibromide with temperature is linear as shown in Figure 1-2.

RESULTS AND DISCUSSION

^{125}Te chemical shifts are recorded in Table 1.5 with reference to diphenyltellurium. The ^{125}Te chemical shift of the reference compound has been reported as 685 ppm with reference to dimethyl telluride[22]. Inspection of Table 1.5 shows that fluorine induces the largest downfield shift, whereas bromine induces the smallest. A correlation between halogen electronegativities and ^{125}Te chemical shifts is observed. This observation is analogous to the behaviour of the ^{13}C chemical shifts of these compounds. The large downfield shift (452 ppm) of diphenyltellurium difluoride is indicative of efficient electron withdrawal by the highly electronegative fluorine atom (inductive effect).

The same effect of halogens on ^{125}Te chemical shifts is seen (Table 1.5) in phenyltellurium trihalides, where the tellurium atom is deshielded to a much larger extent (390 ppm) in the trichloro compound than in the triiodo. ^{13}C chemical shifts of these compounds also show that C-1, which is attached to the tellurium trihalide group, is deshielded in the trichloro relative to the triiodo compound by 7 ppm.

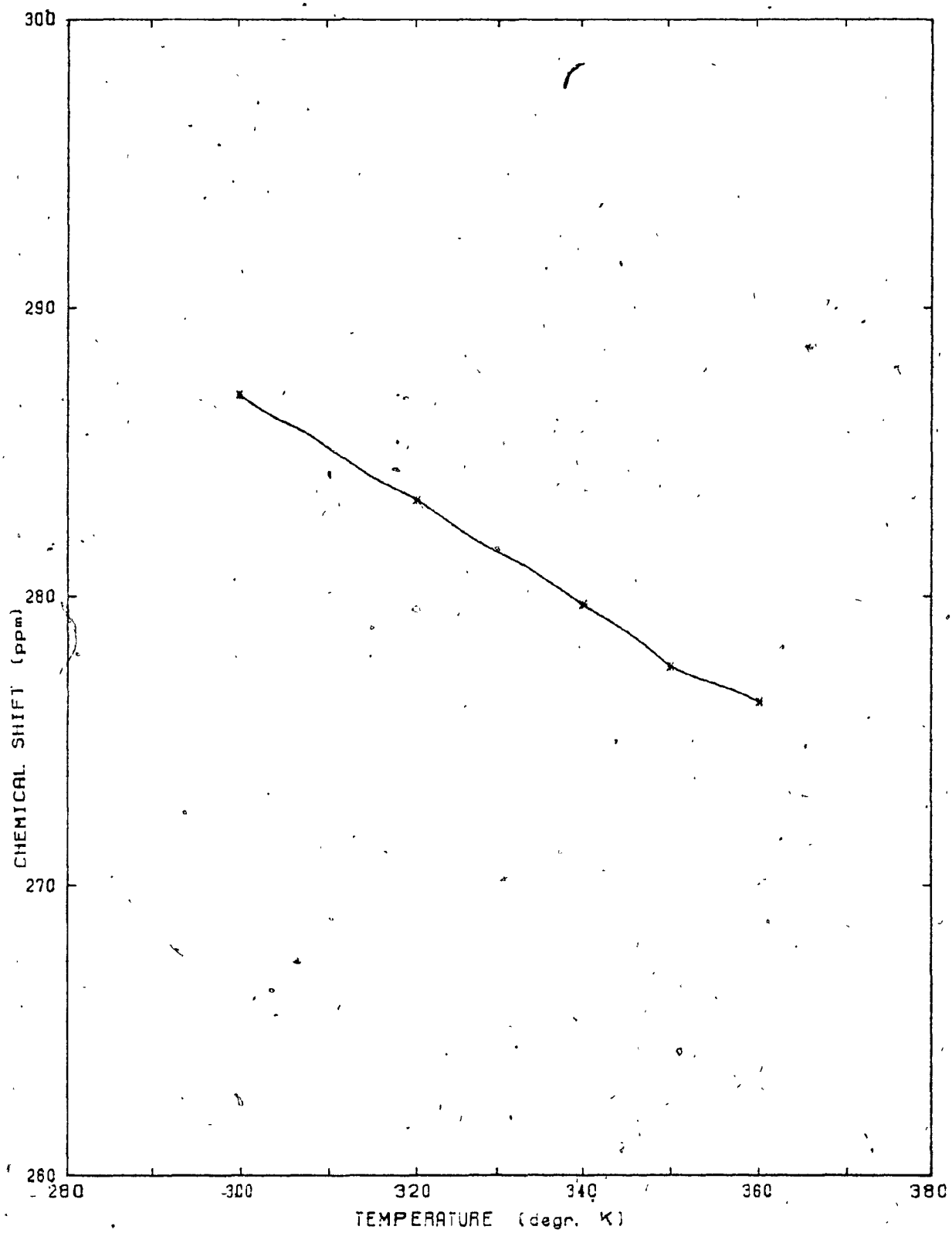


Figure-1.4.. Temperature dependence of 125-Te chemical shift of diphenyltellurium bromide.

Table 1.5

125-Te CHEMICAL SHIFTS OF PHENYLTELLURIUM HALIDES

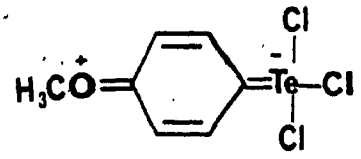
COMPOUND	*RESONANCE FREQUENCY OF Te^{125}, Hz	Te^{125}, PPM
Ph_2Te	38670	0
[1] Ph_2TeF_2	95727	451.85
Ph_2TeCl_2	77098	310.12
Ph_2TeBr_2	74781	286.36
$p-OCH_3PhTeCl_2Ph$	77187.5	305.13
$p-OC_2H_5PhTeCl_2Ph$	77484	306.25
$(p-OCH_3Ph)_2TeCl_2$	77613	308.50
$PhTeCl_3$	107318	543.90
$PhTeBr_3$	104220	519.06
[2] $PhTeI_3$	7167.04	153.12
$p-OC_2H_5PhTeBr_3$	105177.7	527.60
$p-OCH_3PhTeCl_3$	108552.73	553.73
$p-OC_2H_5PhTeCl_3$	108693.36	554.85
$p-OCH_33CH_3PhTeCl_3$	104158.8	518.92

*see text for an explanation of these numbers.

1) J_{Te-F} = 650 Hz. 2) measured using a 360 MHz spectrometer

It is clear that, in both the para substituted trichloro and tribromo compounds, the tellurium atom is more deshielded (10-8 ppm) than in the corresponding unsubstituted trihalo compounds. The opposite

effect was noted for the ^{13}C chemical shifts of the carbon atom which is attached to the tellurium trihalide group (i.e , C-1). For example, according to ^{13}C chemical shifts, the carbon which is attached to the tellurium trihalide group is more shielded (142.34ppm) in para-methoxy phenyltellurium trichloride than in phenyltellurium trichloride (153.28 ppm). As explained above for the ^{13}C chemical shifts, this could be due to the contribution of the polar resonance structure of the type as shown in, IV. It arises due to the conjugation of vacant 5d-orbitals on tellurium with the Pi orbitals of the benzene ring.



IV

This deshielding effect on ^{125}Te chemical shifts of para substituted phenyltellurium trihalides could be explained by considering the electronegativity of the halogens. Considering the polar resonance structure, electron density around the tellurium will be higher than in the para unsubstituted compound. However, delocalization of electron density away from the tellurium atom by the halogens will tend to reduce the influence of mesomeric electron donation. It is not clear why there is a net deshielding effect on tellurium under these circumstances.

Only a slight change in the ^{125}Te chemical shift was apparent upon an order of magnitude reduction in the concentration (Table 1.6). For example, a 0.5 M solution of diphenyltellurium dibromide in DMSO-d_5 has a chemical shift of 286.7 ppm and, on dilution, it has changed very

slightly to 287.2 ppm at 0.06 M solution concentration. The ^{125}Te chemical shift for the diphenyltellurium dibromide changes linearly with the temperature as seen in the Figure 1-7. An increase of temperature leads to an upfield shift of 0.18ppm/^{o}K for diphenyltellurium dibromide in the range 340– 360^{o}K (see Table 1.7).

The T_1 found for the diphenyltellurium dibromide is in the range 1-1.2 sec. This value is of the same order as the previously reported T_1 (i.e., 1.1 sec) for dimethyl telluride[24]. The spin-lattice relaxation time for tellurium has been found to be dominated by the spin rotation mechanism[24]. The only exceptions may be for the case where a tellurium atom is directly bound to atoms with a magnetic moment such as ^{1}H, ^{19}F and ^{31}P. In this situation the dipole-dipole mechanism may have a non-negligible influence. Observation of the ^{125}Te signal is facilitated by the convenient relaxation rate.

Experimental

^{125}Te NMR spectra were recorded with the broad band probe of the Bruker WH-400 spectrometer tuned to 68.46 MHz. The resonance position for diphenyl telluride was located by using a spectral width of 20,000Hz at 68.46 MHz, a pulse width of 30 micro seconds, and broad band proton decoupling . The ^{125}Te chemical shift values are referenced to diphenyl telluride. A 0.1M solution of diphenyl telluride in DMSO-d_6 was found to resonate at an offset frequency of 38630.9 Hz, and the ^{125}Te chemical shifts were subsequently calculated by frequency difference from this standard by using the relationship,

$$\delta_i \text{ (ppm)} = \frac{H_i - H_{ref}}{H_0} = \frac{\nu_i - \nu_{ref}}{\nu_0}$$

where

ν_i = resonance frequency of the ^{125}Te nucleus of the compound of interest

ν_{ref} = resonance frequency of the ^{125}Te nucleus of the reference compound.

ν_0 = spectrometer frequency

The offset frequency of the ^{125}Te nucleus for each compound is shown in Table 1.5. The ^{125}Te spin-lattice relaxation time for one compound (Ph_2TeBr_2) was measured by using the standard inversion-recovery pulse sequence, i.e., (180°-t- 90°-PD)n. The experiment employed a spectral width of 5000 Hz, a 90° pulse width of 20 micro sec, and a recycle time of $5T_1$ second.

The temperature dependence of the ^{125}Te chemical shift for one compound (ph_2TeBr_2) was measured, in $20^{\circ}K$ intervals. Temperature was measured with the thermocouple with a precision of $+/-0.5^{\circ}K$. The concentration dependence of the ^{125}Te chemical shift was also measured for the same compound in four different concentrations. DMSO-d_6 was used as the solvent for both experiments. Unless otherwise indicated, all experiments were performed at room temperature which was $293^{\circ}K$ ($20^{\circ}C$).

TABLE 1.6

EFFECT OF CONCENTRATION OF 125-TELLURIUM CHEMICAL SHIFTS OF DIPHENYLTELLURIUM DIBROMIDE

CONCENTRATION M	CHEMICAL SHIFT PPM
0.50	286.67
0.25	286.52
0.125	286.85
0.062	287.15

TABLE 1.7

TEMPERATURE DEPENDENCE OF 125-TELLURIUM CHEMICAL SHIFT OF DIPHENYLTELLURIUM DIBROMIDE

TEMPERATURE ^{o}K	CHEMICAL SHIFT PPM
300	286.98
320	283.33
340	279.71
350	277.56
360	276.35

CONCLUSION

It is clear that it is very important to give the temperature of the sample when precise measurements of chemical shifts of tellurium are made.

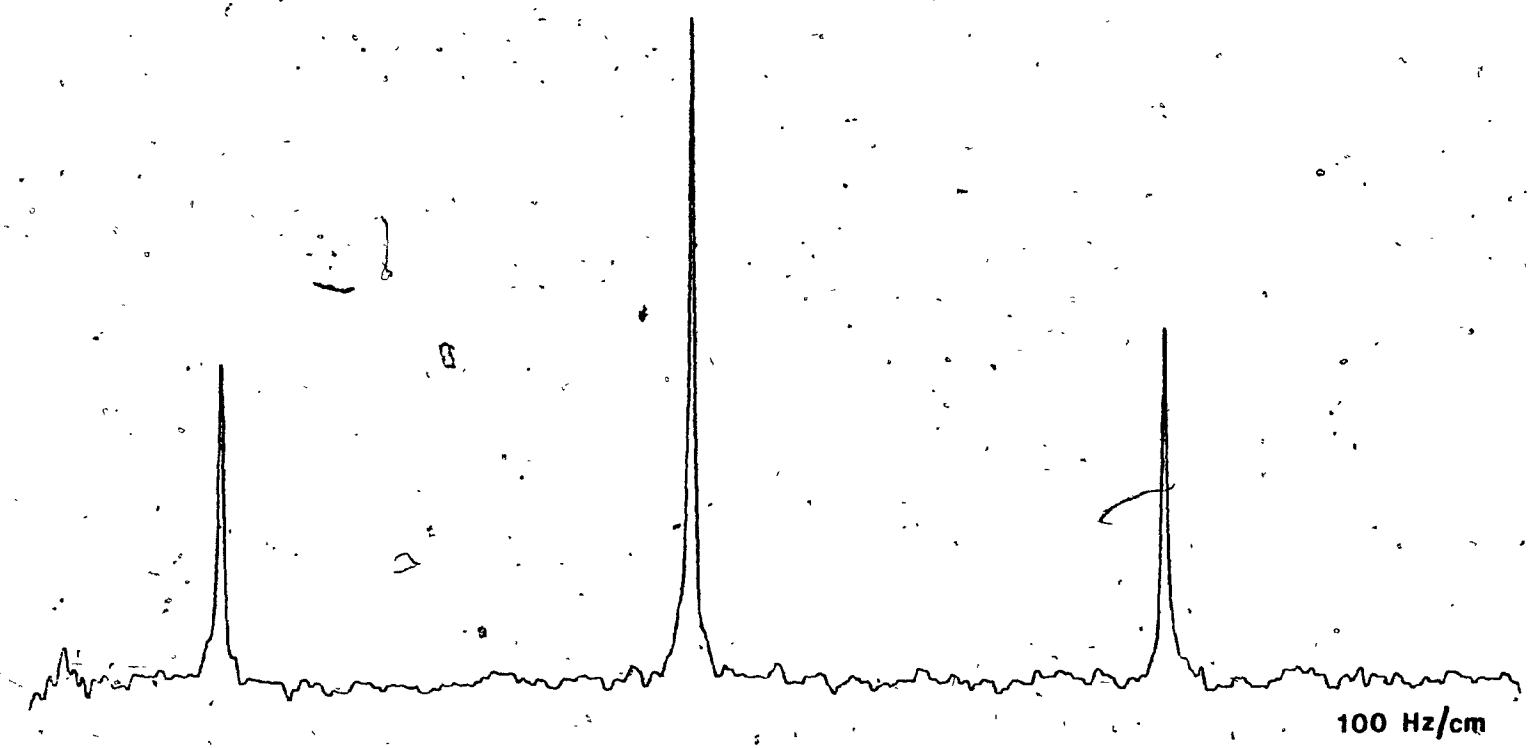


Figure 1.5 Tellurium-125 NMR spectrum of diphenyltellurium difluoride.

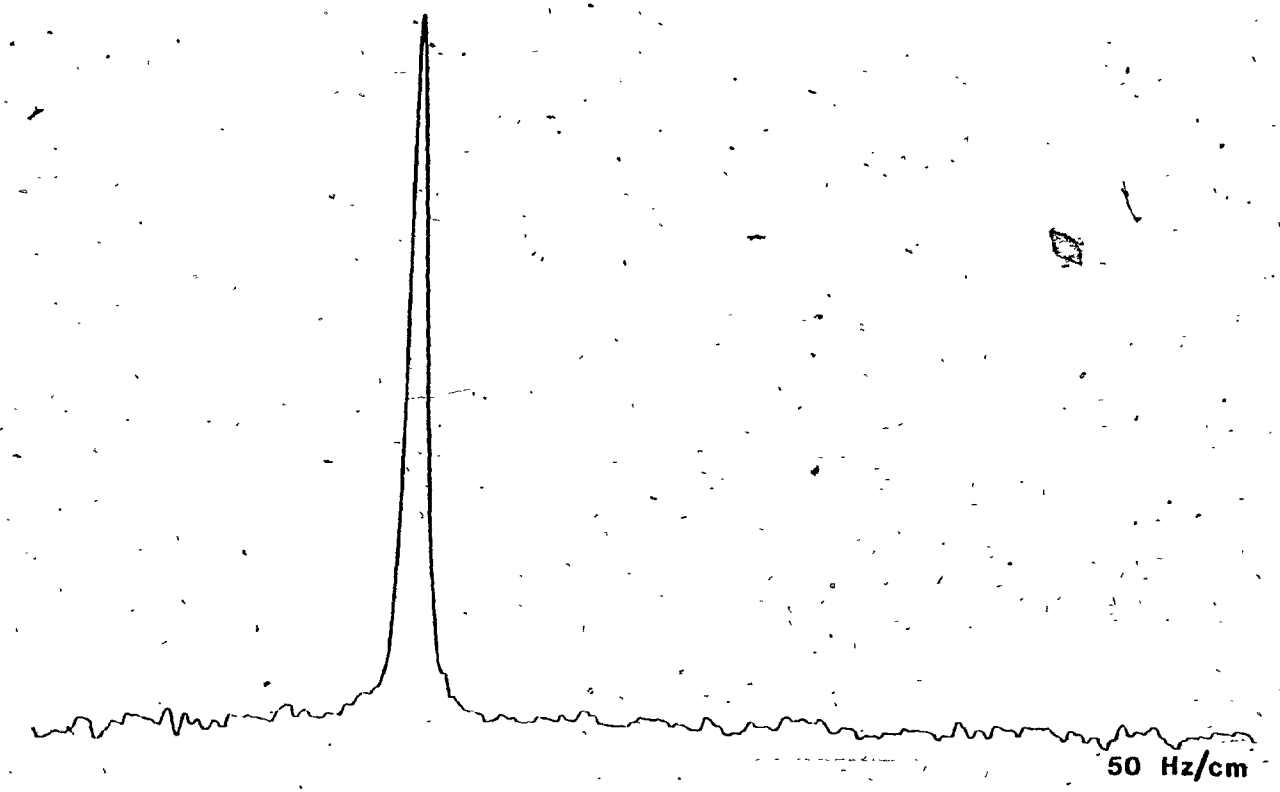


Figure 1.6 Tellurium-125 NMR spectrum of diphenyltellurium

SYNTHETIC PROCEDURES

Organotellurium compounds have been prepared by several methods[25-28] which either give poor yields or impure products. The preparation of phenyltellurium chloride from phenyl lead compounds has already been found to be very useful[29]. Organotellurium compounds for the current study were prepared from organotin compounds[30].

The organo-tellurium dihalides and trihalides required for this study were prepared by halogenation of the corresponding diphenyltellurium and diphenyl ditellurides, using established procedures, and were characterised by melting points, tellurium analyses, and ^{1}H NMR spectra.

The diphenyltellurium dihalides except diphenyltellurium fluoride, which was prepared according to Berry's method[30], were prepared according to Chand Paul's[14] method. However, the melting point found for the fluoro compound differs considerably from that reported in the literature[30]. The preparatory scheme of the diphenyltellurium dihalides (except for the fluoride) is shown in the Figure 1-3.

Tetraphenyl tin, tellurium tetrachloride, and dry toluene were employed as the precursors. Reaction was carried out under anhydrous conditions for three hours. Diphenyltellurium dihalides except the difluoride were recrystallized from absolute methanol, and identified by tellurium analyses and melting points. Tellurium analyses[31] were measured on an atomic absorption spectrometer by Mr P. Aysola in this University, and the melting points were measured on a Gallenkamp melting point apparatus.

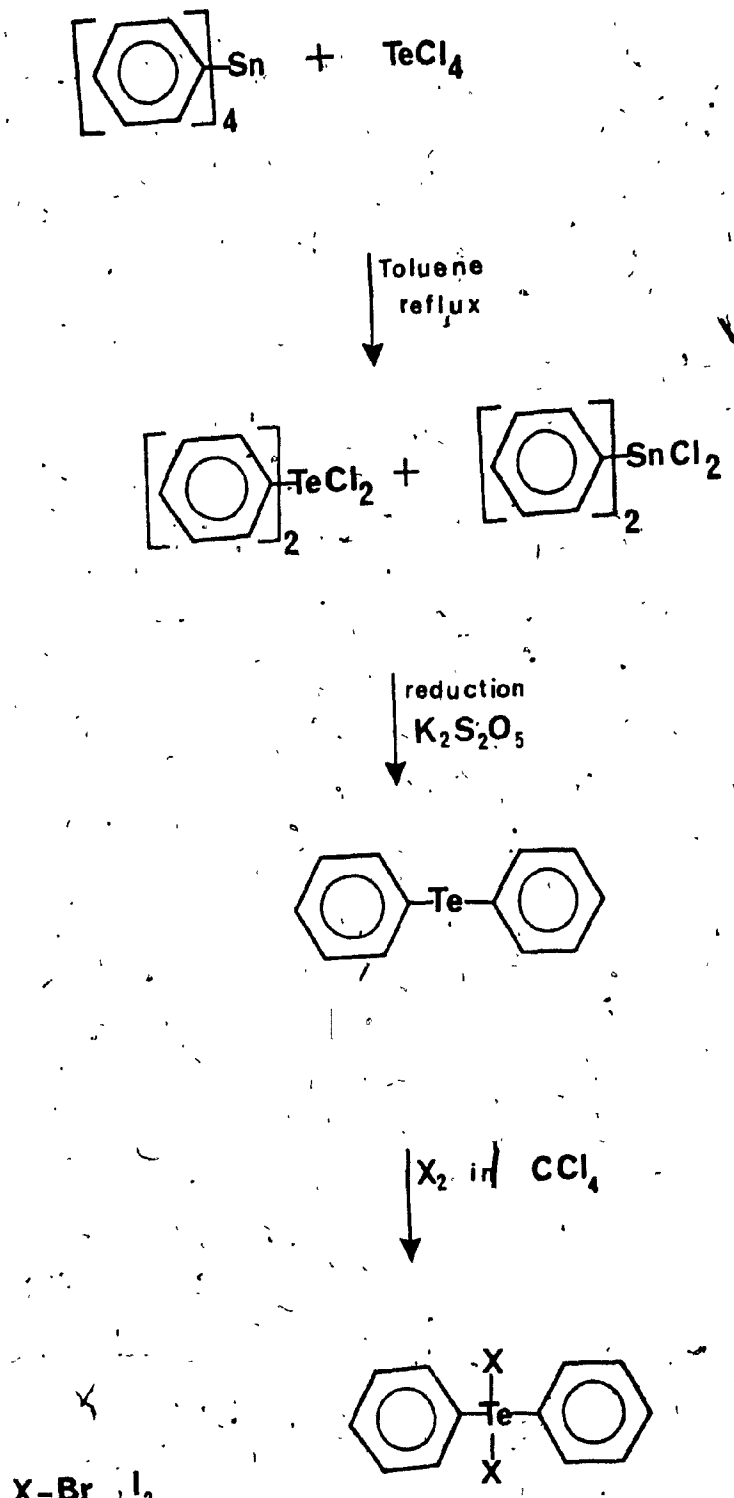

Sn
4
+ TeCl4
Toluene
reflux
TeCl2
2
+
SnCl2
2
reduction
K2S2O5
Te
X2 in CCl4
X
Te
X
X=Br2 , I2

Figure 1.3

PREPARATION OF DIPHENYLTELLURIUM DICHLORIDE

Tetraphenyltin (Pfaltz and Bauer) (25g, 0.586 mol) was dissolved in dry toluene (Aldrich) (25 ml, 0.235 mol), and was mixed with tellurium tetrachloride (BDH) (16g, 0.0593 mol) dissolved in dry toluene (20 ml, 0.19 mol) in a round bottom flask, fitted with a drying tube. The mixture was refluxed for three hours. After cooling, the solution was filtered to remove insoluble matter and was concentrated to 10 ml by distilling off excess solvent. Petroleum ether (40-60°C B. Pt.) was added until white needle-like crystals precipitated. The crude product was recrystallized twice from absolute methanol to yield 12.50g of pure white crystals that were then dried under vacuum.

Yield	=	12.5g (56.4%)
M.Pt.	=	158°C
	=	(Lit. 159°C)[30, 26]
	=	160°C[32]
Te % (calculated)	=	36.19%
(found)	=	35.85%

PREPARATION OF DIPHENYLTELLURIUM

Diphenyl tellurium was the precursor for diphenyltellurium diiodide and dibromide. Pure diphenyltellurium dichloride (7g, 0.0199 mol) was dissolved in a potassium metabisulfite (J.T.Baker) (12g, 0.054 mol) solution in 75 ml of cold water by stirring for 5 hours. The resulting yellowish green liquid was extracted three times with ether. The ether extract was dried over anhydrous potassium sulphate and was then evaporated to yield a dark yellow liquid (5.5 g) which was distilled by

using reduced pressure (about 7 mm. Hg). The product was collected at 170°C.

Yield		= 4.10 g (74.5%)
B.Pt.		= 170°C at 7 mm.
		= (Lit. 182°C at 16 mm)[33]
Te %	(calculated)	= 45.31
	(found)	= 44.68

GENERAL PROCEDURE FOR THE PREPARATION OF DIPHENYLTELLURIUM DIIODIDE AND DIBROMIDE

Diphenyltellurium (liquid) (2g, 0.0171 mol) was dissolved in anhydrous carbon tetrachloride (20 ml) (Aldrich) in a 200 ml three necked round bottom flask, fitted with a drying tube. A equimolar concentration solution of the halogen in carbon tetrachloride solution (20 ml) was slowly added to the magnetically stirred solution, using a separatory funnel. The solution was then stirred for 2-3 hours, after which a coloured precipitate was filtered and dried. The crude dihalo compound was recrystallized from absolute methanol. A brick red precipitate for the diiodo compound was obtained with a m.p. of 235°C (lit. 237-238°C)[32] while the dibromo compound was obtained as a light yellow powder having a m.p. of 197°C. (Lit. 198-201°C)[34]

Yield	(dibromo compound)	= 3.5g (37%)
M. Pt.		= 197°C
		= (Lit. 198-201°C)[34]
Te %	(calculated)	= 28.9

(found) = 29.2

Yield (diiodo compound) = 2.5g (52%)

M.Pt. = 235°C

= (Lit. 237-238°C)[32]

Te % (calculated) = 23.8

(found) = 22.4

PREPARATION OF DIPHENYLTELLURIUM DIFLUORIDE

Diphenyl tellurium dichloride (2.40g, 0 068 mol) was added in small quantities to a mixture of silver fluoride (82.04g, 0.014 mol) (Aldrich) in dry toluene (120 ml) which was boiled under reflux for one hour). The reaction mixture was filtered, and the filtrate was added to light petroleum ether (30-70°C). On standing in the refrigerator for several hours, this solution deposited light brown crystals which were filtered off and recrystallized from glacial acetic acid. Finally the material was recrystallized from petroleum ether (70-100°C). The melting point and tellurium analyses were as follows.

M.Pt. = 150°C

= (lit. 169-170°C)[35]

= 153°C[36]

yield = 1.25g (57%)

Te% (calculated) = 39.92

(found) = 39.54

The phenyltellurium trihalides were prepared by an adaptation of

the method of McWhinnie and Thavornyutikarn[37] via the diphenyl ditellurides by oxidation with either bromine or iodine[38]. Diphenyl ditelluride was prepared by reducing phenyl tellurium trichloride. It is possible to synthesize the phenyl tellurium trichloride by reaction of tellurium tetrachloride with the appropriate organotin compound[14]. Phenyltellurium trichloride prepared by this method was contaminated with a small amount of greyish material which was difficult to remove by recrystallization. It is convenient, therefore, to reduce the crude trichloride to the ditelluride and reoxidise the purified ditelluride with chlorine to pure phenyltellurium trichloride. The ditellurides were also required for the preparation of the bromide and iodide. The preparation scheme for phenyltellurium trihalides is given in Figure 1.4.

Crude phenyltellurium trichloride was prepared according to Chand Paul's method[14] using tetraphenyltin and tellurium tetrachloride. Tetraphenyltin (Pfaltz and Bauer) (40g, .094 mol) and tellurium tetrachloride (BDH) (25.24g, .094 mol) were stirred in dry toluene (Aldrich) (90 ml) for two hours at room temperature, in a round bottom flask fitted with a drying tube. A dull white precipitate separated and was filtered, washed with toluene, and dried. Recrystallization of this material once from glacial acetic acid yielded off-white crystals (about 15.6g, m.p. 210°C).

PREPARATION OF DIPHENYL DITELLURIDE

Crude phenyltellurium trichloride (15.6g, 0.050 mol) was dissolved in potassium metabisulfite ($K_2S_2O_5$) (J.T.Baker) (30g in 160 ml of water) solution by warming. The resulting dark greenish liquid was extracted

2-3 times with dry ether to yield a dark reddish solution. An ether extract was dried over anhydrous K_2SO_4, evaporated and the solid was recrystallized with distilled petroleum ether (60-70°C). Orange red crystals were obtained with a m.p. of 65°C.

Yield	= 8g (79%)
M.Pt.	= 65°C
	= (Lit. 66°C)[25]
Te% (calculated)	= 45.5
(found)	= 43.1

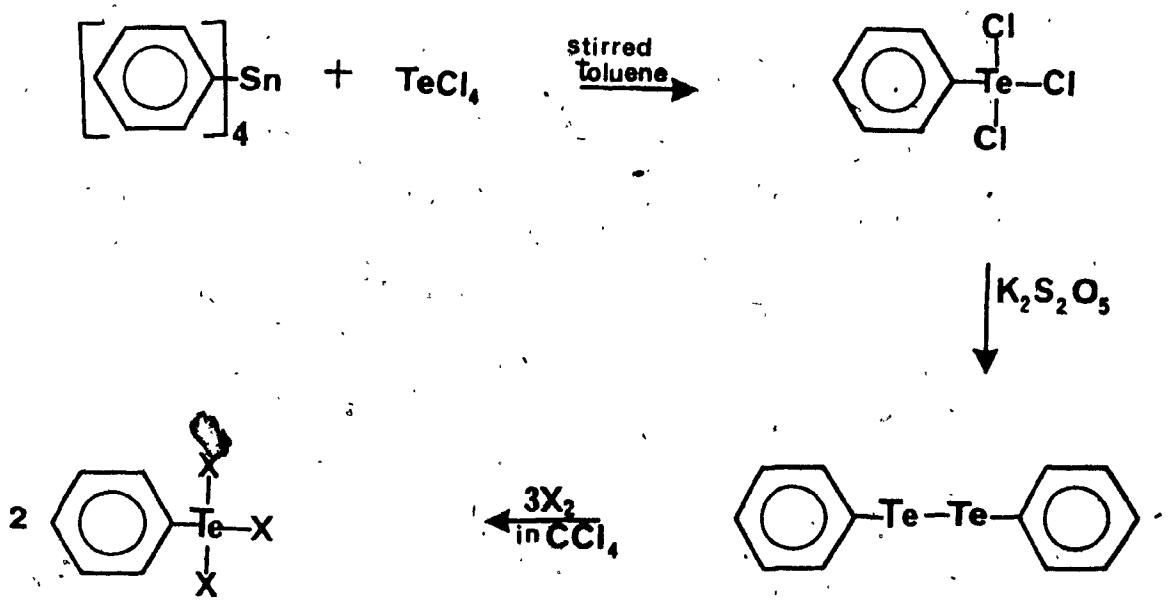


Figure 1.4

PREPARATION OF PHENYLTELLURIUM TRICHLORIDE

Diphenyl ditelluride (0.8364g, 0.002 mol) was dissolved in anhydrous carbon tetrachloride (Fisher) (35 ml) (distilled and dried over calcium chloride). Chlorine gas was dissolved in anhydrous carbon tetrachloride (Fisher) (35 ml) and was slowly added drop by drop to the diphenyl ditelluride solution in carbon tetrachloride, while maintaining the temperature at 10°C. Yellowish brown crystals were obtained, and the product was recrystallized from glacial acetic acid.

yield	= 0.69g (41.4%)
M.pt.	= 213-215°C
	= (Lit. 215-218°C)[37]
Te% (found)	= 40.2
(calculated)	= 41.0

PREPARATION OF PHENYLTELLURIUM TRIBROMIDE

Bromine (Fisher, 1.294g, 0.0081mol) in carbon tetrachloride was slowly added with stirring to a carbon tetrachloride solution of the diphenyl ditelluride (1.13g, 0.0027mol) at 10°C. The brown ditelluride became yellow, and yellow crystals were deposited. Addition of bromine was continued until an excess was present. The mixture was stirred for a further 30 minutes, after which the precipitate was filtered off and dried. The product was recrystallized from glacial acetic acid to afford yellow crystals of phenyl tellurium tribromide.

Yield	= 1.80g (67%)
M.pt.	= 227-229°C

= (Lit. 227-229°C).[37]

Te% (found) = 29.4

(calculated) = 28.7

PREPARATION OF PHENYLTELLURIUM TRIIODIDE

Diphenyl ditelluride (Ø.9633g, Ø.ØØ23mol) in anhydrous carbon tetrachloride (35 ml, Fisher) was maintained at 3-5°C whilst sublimed iodine (1.751g,Ø.ØØ69 mol) in anhydrous carbon tetrachloride (6Ø ml) was added slowly. The solution was then stirred for a further 3Ø miniutes, after which the red brown precipitate was collected and dried. The crude triiodide was recrystallized from benzene/light petroleum ether. It was noted that if iodine was added to diphenyl ditelluride at 1Ø-15°C a black benzene soluble material was obtained.

Yield = 1.8Øg (67%)

M.Pt = 18Ø-181°C

= (Lit. 18Ø-181°C)[37]

Te% (found) = 24.5

(calculated) = 21.8

CHAPTER II

INTRODUCTION

Routinely, high resolution nuclear magnetic resonance spectroscopy has been utilized for studying the structure and the stereochemistry of organic compounds. To the usual parameters measured from these spectra, namely the chemical shifts, the coupling constants and the integrated areas, further magnetic resonance information can be added. This includes the spin-lattice relaxation time (T_1) values and the spin-spin relaxation time (T_2) values

With the development of new instrumental techniques (especially Fourier transform (FT) spectroscopy), it has become possible to measure, on a routine basis, the T_1 value of any resonance that can be clearly resolved in a nuclear magnetic resonance spectrum, even in systems which are chemically complex. Spin-lattice relaxation times can be measured for protons, ^{13}C, ^{15}N, ^{19}F and many other nuclei.

There are numerous examples in the literature of investigations into the potential of proton spin-lattice relaxation times (T_1 values), or rates (R_1 values) for providing diagnostic information on the molecular structure of a variety of compounds such as carbohydrates[39] nucleoside[40] derivatives, alkaloids[41], natural products such as terpenoids[42] and steroids[43] and, recently, complex protein molecules[43].

Spin-lattice relaxation phenomena are associated with the way in which, and the rate at which, magnetic energy is transferred between the magnetic nuclei under study (the spins) and their surrounding environment (the lattice). The rate at which this transfer occurs is the relaxation rate (R_1 value, sec^{-1}), and the reciprocal of the rate is

the spin lattice relaxation time (T_1 value, sec.,).

Consider a sample containing nuclei with spin 1/2 placed in the magnetic field, H_0. The nuclei will precess around the direction of the field with a frequency known as the Larmor frequency ($W0$). The nuclei are either aligned with or opposed to the direction of H_0, as shown in Figure 2-1. Since, at equilibrium, there is a slight Boltzmann excess of nuclei aligned with the magnetic field, these will give rise to a resultant magnetization vector, M_0, which also lies in the same direction as H_0.

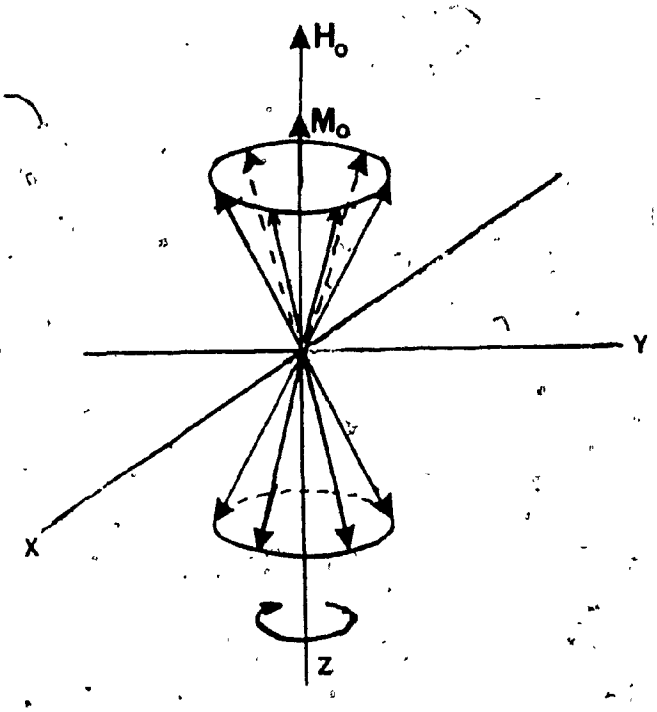


Figure 2.1 Motion of nuclei vectors in magnetic field.

This description of the nuclear motions is often referred to as the stationary or laboratory frame of reference. If, however, we were able to rotate the laboratory frame at the Larmor frequency, $W0$, then the nuclei would no longer appear to precess but would become stationary and

coincident with the magnetic field axis H_0, as shown in Figure 2.2. The magnetic behaviour is now completely described by a stationary bulk magnetization vector, M_0, acting along H_0. This system is referred to as a "rotating frame system" and its effect is to greatly simplify the description of the effects produced by the application of a radiofrequency pulse.

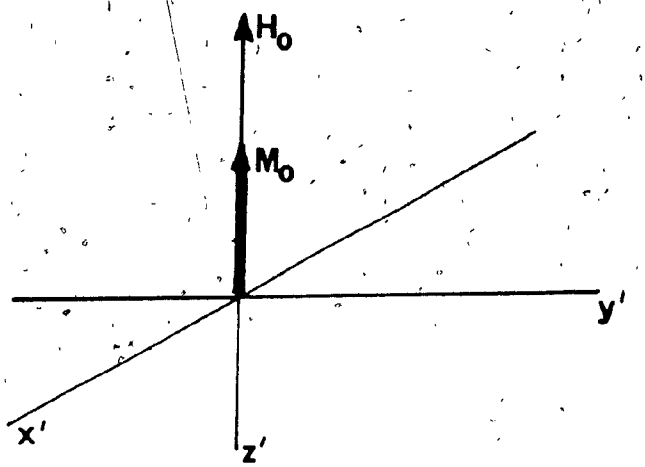


Figure 2.2 Orientation of bulk magnetization in a frame rotating at the Larmor frequency.

We can apply a pulse of radio frequency radiation for a time t also at the resonant frequency W0, along the x-axis to the frame (which is rotating at the same frequency, W0). This is equivalent to applying a static field H_1 along the x'-axis of the rotating frame. Consequently, as M_0 is stationary in the rotating frame, the effect of applying a constant field would be to cause M_0 to rotate, i.e. precess about the x' axis, as shown in Figure 2.3. The angle θ is known as the pulse, tip, or nutation angle.

It is important to point out (Figure 2.3.) that a bundle of spin vectors, with phase coherence, is aligned along the direction of M_0.

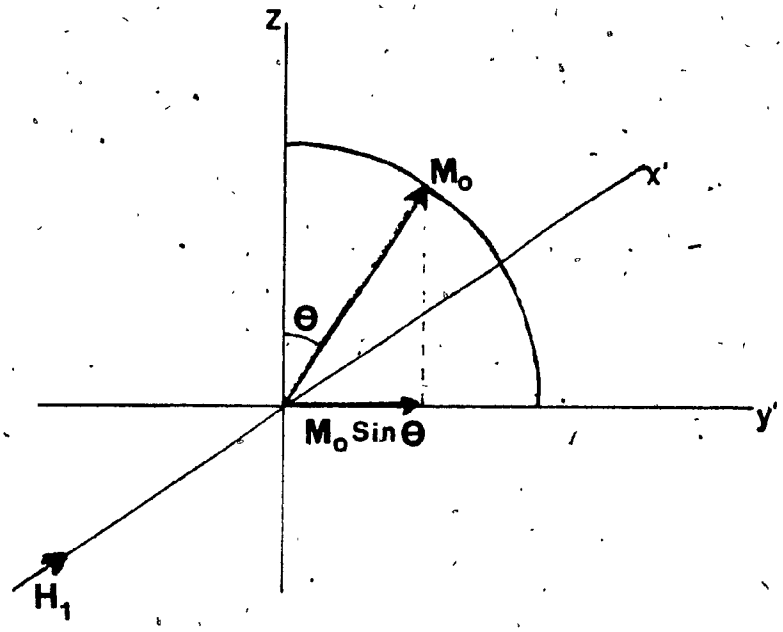


Figure 2.3 The behaviour of the bulk magnetization vector M after a pulse tipping it through an angle θ has been applied.

The net effect of the pulse is to "sweep up" the individual spin vectors, which were initially randomly distributed around the z' axis, so that they now have phase coherence.

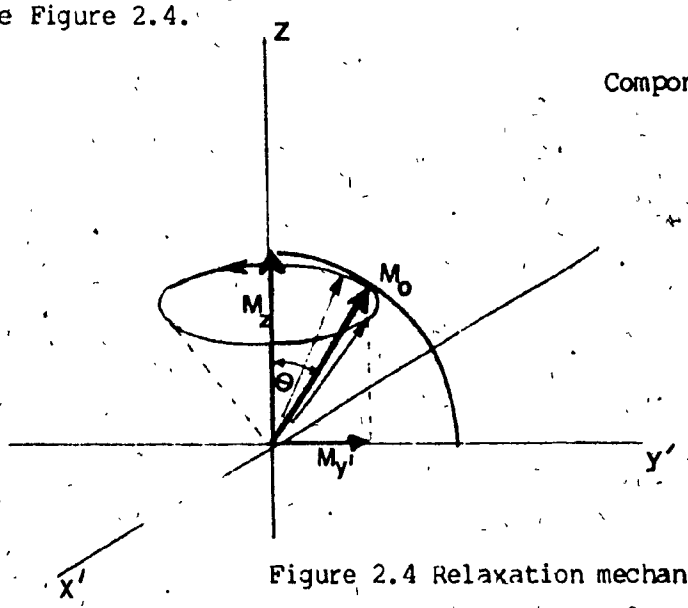
Once the radio-frequency pulse has been removed, the perturbed spin system will begin to relax back toward its equilibrium condition by means of two separate processes.

In the first of these, the component of the magnetization remaining along the z-axis returns to its original value, M_0, by an exponential decay process characterized by a relaxation time T_1. This process is known as spin-lattice relaxation[44], since relaxation occurs by the loss of energy from the excited nuclear spins to the surrounding molecular lattice.

In the second process, the nuclear spins interchange with one

another so that some spins now precess faster than M_0 while others precess more slowly, with the result the spins begin to lose phase coherence. This process is known as the spin-spin relaxation process.

In the spin-lattice relaxation process, if the initial magnetization along the Z axis is M_0, and the component at a time t sec. after a pulse has been applied is M_z, the M_z returns to M_o as shown in the Figure 2.4.



Component of M in x' y' plane

$M'_x = 0$

$M'_y = M_o \sin\theta$

$M_z = M_o \cos\theta$

Figure 2.4 Relaxation mechanisms

Mathematically, we can express this process as,

$$M_0 - M_z = M_0 (1-\cos\theta) \exp(t/T_1)$$

When M_z returns to M_0 along the y' axis, the component M_y' decays so that:

We have,

$$M_z = M_0$$

$$M_y' = 0$$

If after a pulse $M_y'(0)$ is the component of M[45]

$$M_y'(0) = M_0 \sin\theta \text{ and}$$

$$M_y'(t) = M_y'(0)\, e(-t/T_1)$$

SPIN-LATTICE RELAXATION

As mentioned before, spin-lattice relaxation involves a transfer of energy from the spins of the magnetic nuclei to their surrounding environment (the lattice). There are a number of distinct mechanisms that allow this transfer to occur, most of which involve the interaction of the spin with randomly fluctuating magnetic fields arising in the lattice. The most common of these, along with their associated relaxation times, are:

Dipole-dipole	T_1 DD
Spin rotation	T_1 SR
Quadrupolar	T_1 Q
Scalar	T_1 SC
Chemical shift anisotropy	T_1 CSA

Dipole-dipole relaxation can be of three types, namely:

a) intramolecular

b) intermolecular

c) paramagnetic

In principle and often in practice, several of these relaxation mechanisms operate simultaneously, and can contribute to the overall relaxation rate of a particular nucleus. In these circumstances, the spin-lattice relaxation time measured experimentally (T_1 experimental) is a composite value, and contains contributions from each of the several mechanisms. It can be described as follows:

$$1/T_1(\text{exp}) = 1/T_{1DD} + 1/T_{1SR} + 1/T_{1Q} + 1/T_{1SC} + 1/T_{1CSA}$$

For convenience, we consider the relaxation rates (R_1 in sec^{-1}) with the relation,

$$R_1 = 1/T_1$$

Hence,

$$R_1 \text{ (exp)} = R_{1DD} + R_{1SR} + R_{1Q} + R_{1SC} + R_{1CSA}$$

If this were always the case then it is quite probable that this entire phenomenon would have little or no relevance to organic chemists, since although it is a trivial matter to obtain an experimental value for a spin-lattice relaxation time, it is often a more difficult task to derive from that value the individual contributions from several different relaxation mechanisms.

Fortunately, we can conduct experiments in which one of these mechanisms, the intramolecular dipole-dipole mechanism, dominates the relaxation, and under optimum conditions is the only operative mechanism. In practice, the molecule studied must move more or less isotropically[46] in solution. To overcome the intermolecular effects, these molecules should be studied in dilute (0.1M) solutions in solvents which do not themselves provide relaxation. It is sufficient to use perdeuterated solvents for ^1H relaxation measurements, since the small magnetogyric ratio of deuterium makes this nucleus very inefficient for relaxation (the relaxation efficiency of deuterium is 6.3% that of an equivalent proton). In practice, using deuterated solvents to overcome intermolecular effects has the added convenience of providing a heteronuclear lock signal for the spectrometer. Dissolved oxygen in the solution is usually the most important source of paramagnetic (dipole-dipole) relaxation. If required, oxygen may be removed by standard techniques[46], but it has been shown[47] this is unnecessary for most qualitative studies. The rate constant for relaxation to oxygen is very similar for all protons in a molecule, so that all of the R_1 values

determined for protons in a molecule will be increased by an essentially constant amount.

DIPOLE-DIPOLE RELAXATION

In the system where the intramolecular dipole-dipole mechanism is predominant[48], the contribution can be expressed as,

$$R_1^R = 1/T_1^R \alpha \frac{\gamma_D^2 \gamma_R^2}{(r_{D,R})^6} Tc\ (D,R) \qquad (2.1)$$

This equation is valid provided that the molecule is tumbling rapidly enough that the extreme narrowing condition ($w_o^2 T_c^2 << 1$) is met. This is normally the case for small to medium sized molecules.

In this equation, D refers to the donor nucleus and R to the receptor nucleus. T_c is the rotational correlation time for the D,R vector, the γ's are the magnetogyric ratios, and r is the internuclear distance.

The efficiency with which any receptor nucleus, R, is relaxed by a donor nucleus, D, is proportional to the square of the magnetogyric ratio of each nucleus and to the correlation time of the motion of the vector D ----> R with respect to the field. It falls off as the inverse sixth power of the distance (r^6 D---> R) between the two nuclei. This means that contributions to the relaxation of a nucleus are attenuated very rapidly when the distance between the two nuclei increases. It follows that the R_1 value of a proton is largely dependent on the proximity of its immediate neighbours.

Since only protons have a high value of γ, intramolecular

relaxation will be dominated by interproton interactions, with the nearest protons making the largest contributions. Hence, proton relaxation times show pronounced configurational dependences. In most organic molecules, each individual proton will be relaxed by interactions with several other (D1, D2.....) in the same molecule, and hence its total relaxation rate will have the form given by the equation 2.2.

$$R_1^R = R_1^{D1} + R_1^{D2} + R_1^{D3} + \ldots\ldots\ldots \qquad (2.2)$$

The magnitude of each of these contributions will depend on the relative magnitude of the individual internuclear distances.

For several reasons, it is also important to note that the relaxation efficiency between the donor and the receptor is dependent on Tc. As a result, R_1 values can provide direct information concerning molecular motion, both the overall tumbling of the molecule and any additional degrees of motional freedom for pendant substituents. However, Tc values depend on the solvent, the solute concentration, temperature and on molecular weight and shape.

Since relaxation rates are dependent on rates of molecular tumbling (motional correlation time Tc), a change in the mass or geometry of a substituent in a molecule may affect the R_1 values of all of the nuclei, not only those in the immediate vicinity of the substitution site. Thus, if the R_1 values of molecules with different substituents, geometries or in different experiments are to be compared it is advisable to normalize the relaxation rates internally with respect to the rate of a nucleus remote from the site of substitution. For the molecules in this study, normalization is quite straightforward, because all of the molecules have a rigid planar structure, and interproton

distances will not vary much In general, a proton that is adjacent to two other protons will get about 95% of its intramolecular relaxation from these protons, and so this particular proton is the obvious choice for normalizing.

In summary, under suitable conditions, proton spin-lattice relaxation involves through space interactions between individual protons in the same molecule. Since the efficiency of these interactions decreases with distance, each proton receives most of its relaxation from its nearer neighbour protons. This feature can be used as a possible way to determine the conformation of the molecule.

SCALAR COUPLING RELAXATION

As seen before, any mechanism which gives rise to a fluctuating magnetic field at a nucleus is a possible candidate for a relaxation mechanism. In the case of spin-spin (scalar) coupling between the spins I and S (where I=1/2 and S>1/2), the quadrupolar nucleus S provides a relaxation mechanism for the I nucleus through scalar coupling. This is referred to as scalar coupling relaxation[49]. There are two kinds of scalar relaxation, namely, the first kind and the second kind of scalar relaxation.

SCALAR RELAXATION OF THE SECOND KIND

This arises when two nuclei are coupled and the second i.e. the S nucleus with spin>1/2 of these, has a relaxation time $T_1(s)$ (T_q) that is short compared to the inverse of the coupling constant 1/A (I, S). In this case the local field AS(t)/YI produced at nucleus I(H) by nucleus S(N) fluctuates with a correlation time $T_s = T_1(s)$. In this event, of

course, only the average value of the spin-coupling interaction is seen and one observes for nucleus I(H) not the expected multiplet, but a single line. In a manner similar to that shown above for the dipole-dipole interaction, it may then be shown that[50],

$$R_1^I = \frac{2A^2}{3} S(S+1) \frac{Ts}{1 + (W_I - W_S)^2 Ts^2} \qquad (2.3)$$

$$R_2^I = \frac{A^2}{3} S(S+1) \left\{ Ts + \frac{Ts}{1 + (W_I - W_S)^2 Ts^2} \right\} \qquad (2.4)$$

where A is the spin-spin coupling constant in radians/second and

Ts is the relaxation time of the quadrupolar nucleus (S).

This situation is provided in the case where S>1/2 e.g. ^{14}N, S is consequently relaxed primarily by the quadrupole interaction. In this case, which often is referred to as scalar relaxation of the second kind, $T_1^S = T_2^S = Ts$. Depending upon the strength of the coupling constant and the relaxation time of the quadrupolar nucleus a broadening of the spectrum of the spin 1/2 nucleus is usually observed. When the coupling is entirely washed out, the scalar coupling interaction is treated as a relaxation mechanism, and the nucleus of spin >1/2 treated as part of the lattice.

The broadening observed for the signals of the protons α to the nitrogen atom in the heterocycles is related to the presence of the nitrogen atom. There are two possible origins which can be considered for this broadening.

1) Shortening of the α proton relaxation time by interaction with the nitrogen nucleus.

2) Incomplete washing out of an N-H spin-spin coupling by N^{14} quadrupolar relaxation.

In the first case, two mechanisms might be operative. The nitrogen nucleus may contribute to the H-α relaxation through,

A) H-^{14}N nuclear magnetic dipole-dipole interaction modulated by the molecular movements in the liquid.

B) Scalar spin-spin interaction modulated by the ^{14}N quadrupolar relaxation[50]. One can examine cases A and B separately.

A) Contribution of H-^{14}N dipole-dipole interaction to H-α-relaxation

This is a case of relaxation by dipole-dipole interaction between unlike spins[50]. In the extreme narrowing approximation ($w_o^2 T_c^2 << 1$) the contributions T_{1D} and T_{2D} of the H-^{14}N dipole-dipole interaction to the H-α relaxation should be equal. The correlation time is very short in non-viscous solutions as in this study, with values from $10^{-10} \rightarrow 10^{-13}$ sec. Therefore, the extreme narrowing approximation is valid. T_{1D} should then be equal to T_{2D}. If the dipole-dipole relaxation mechanism is the dominating relaxation mechanism, T_1 should be equal to T_2. But Kintzinger[51] has shown that T_2 calculated from the line widths is smaller by a factor of 100 than the measured T_1's. Hence, it can be concluded that the H-^{14}N dipole-dipole interaction mechanism is not the cause of observed line broadening. Because of the small magnetic moment of the ^{14}N nucleus, the contribution of T_{1D} and T_{2D} is expected to be small in the case of H-^{14}N as compared to H-H nuclei. One may easily show that[50],

$$(1/T_{1D}(H\text{-}H))/(1/T_{1D}(H\text{-}N)) = \frac{3}{2}\ (\gamma H/\gamma N)^2\ \frac{I_H(I_H+1)}{I_N(I_N+1)} = 108$$

γ = magnetogyric ratio

T_{1D} = spin-lattice relaxation due to dipole-dipole relaxation

I = spin quantum number

Therefore, at the same internuclear distance, spin-lattice relaxation is more efficient by a factor of 108 in the case of H-H nuclei than in the case of H-^{14}N nuclei. Hence, this mechanism is seen to be negligible.

B) Contribution of H-^{14}N scalar interaction to H-α relaxation

When the quadrupolar relaxation time T_q is long, the proton signal is split into a triplet corresponding to the three spin states +1, 0, −1 of the ^{14}N nucleus. As T_q decreases, the lifetimes of the ^{14}N spin states decreases and the lines of the proton triplet become broad. As T_q continues to decrease, the proton spectrum coalesces into a single line which then narrows (intermediate case). Finally, when T_q is very short, so that it becomes comparable to the proton Larmor period, the nitrogen quadrupolar relaxation acts as a relaxation mechanism of the proton via the scalar H-^{14}N coupling. The contributions of this mechanism to T_1 and T_2 are different and may render T_2 appreciably shorter than T_1[50]. In this last case the proton is treated as seeing an average field from the quadrupolar nucleus, and T_q, the time constant of the fluctuations of this field, is considered to be much smaller than $(2\pi A)^{-1}$ where A is the H-N coupling constant.

SCALAR RELAXATION OF THE FIRST KIND

Scalar relaxation can also occur when coupling constant (A) becomes a function of time. This situation is often referred to as scalar relaxation of the first kind and arises when chemical exchange takes place. In this case, the local field at I is AS/γI when I and S are covalently bound in the same molecule and zero otherwise. In the case of chemical exchange that causes bond breaking, the magnetic field at I fluctuates because the coupling constant (A) is modulated from its normal value to zero.

If the chemical exchange rate is much larger than either the coupling constant (A), or 1/T for either I or S, and if the time the nuclei are uncoupled is short compared with the time they are coupled, only a single line is observed for the α proton. This is similar to scalar relaxation of the second kind and Ts becomes Te, the exchange time. If Ts or Te is not short enough to cause the multiplet to collapse completely to a single narrow line (a few Hz or less) a more detailed analysis is needed to obtain useful chemical informations[52].

The fact that equations 2.3 and 2.4 are identical for the case Te= Ts is quite reasonable, for all nucleus I experiences is a local field of magnitude AS/γI which is fluctuating in a characteristic time t. It is immaterial to nucleus I whether this fluctuation arises from a chemical exchange process or from a fast relaxation process of nucleus S. This is frequently the case when one of the nuclei has nuclear spin >1/2 since such nuclei possess an electric quadrupole. As this quadrupolar nucleus moves in solution, the quadrupolar coupling tensor becomes a function of time and provides a relaxation mechanism which for

this type of nucleus is generally dominant.

One might think whether this scalar interaction should be expected to be an effective relaxation process since the scalar coupling interaction is usually small ($\mathcal{H}s=10^4$Hz) compared to the dipole-dipole interaction ($\mathcal{H}d=10^8$Hz). It can be very effective under the proper conditions. Although $\mathcal{H}d$ is generally much larger than $\mathcal{H}s$, the molecular correlation time Tc is, for most liquids, rather small ($Tc=10^{-11}$ sec). On the other hand, Ts and Te can be, and often are, in the range where $(w_i - w_s)t=1$. In this case, the scalar relaxation interaction is greatly enhanced and is sometimes the dominant relaxation mechanism.

TEMPERATURE EFFECTS

The quadrupolar relaxation time of the ^{14}N nucleus is given by[53],

$$T_q^{-1} = \frac{3}{8}\left(\frac{e^2qQ}{\hbar}\right)^2 t_q \qquad (2.5)$$

where $e^2qQ/\hbar$ is the quadrupolar coupling constant and t_q is the correlation time.

In the simplified case of the rotation of a sphere of radius a in a medium of viscosity η one has,

$$t_q = \frac{4\pi\eta a^3}{3KT} \qquad (2.6)$$

where

K = Boltzmann's constant

and

T = absolute temperature.

When the temperature is lowered, t_q increases (as also does the

viscosity) and hence, T_q decreases i.e. the quadrupolar relaxation becomes more efficient. As a consequence the N-H coupling is also more efficiently washed out and the H-α signals sharpen up. Therefore, α-protons relax faster than the others.

EFFECT OF THE VISCOSITY OF THE SOLUTION

From equation 2.5 and 2.6, it is clear that when viscosity increases, tq increases and T_q decreases. As a result quadrupolar relaxation becomes more effective, the ^{14}N linewidths increase and the H-α signals sharpen up[51]. The H-α signals of the neat liquids or of solutions in low viscosity solvents should be broadened. Whilst in the viscous solutions a strong broadening of the ^{14}N signals and a sharpening of the α-proton signals can be expected.

SPIN-LATTICE RELAXATION EFFECTS OF NON-SELECTIVE PULSES

In general terms a spin-lattice relaxation experiments consists of exciting the spin system to a non-equilibrium state and then monitoring the level populations of the spin system as they return to the equilibrium state. A homonuclear spin system may be excited with rf pulse that are so intense compared with the frequency width of the spectrum that all the resonances are essentially uniformly excited to the nonequilibrium state. This is a non selective pulse experiment.

For a non selective 180° perturbing pulse the initial conditions of the experiment are;

$$M_i(0) = -M_i(\infty) \qquad (2.7)$$

for i=A, M, and X.

The non selective relaxation rate, $R_{1(ns)_i}$, so derived for spin i=A, M, X, has a simple relationship with the more fundamental rate values ρ_{ij} and σ_{ij} according to,

$$R_{1(ns)_i} = \sum_{j \neq i} (\rho_{ij} + \sigma_{ij}) + \rho_i^* \qquad (2.8)$$

where,

ρ_{ij} = intramolecular dipolar term

ρ_i^* = relaxation contribution from other mechanisms

σ_{ij} = cross relaxation term

$*$ = homo nuclear or "like" spins.

The extreme narrowing limit values of ρ_{ij} and σ_{ij} are given by equation (2.9 and 2.10).

$$\rho_{ij} = \frac{\gamma_i^2 \gamma_j^2 \hbar^2}{r_{ij}^6} \tau_{ij} \qquad (2.9)$$

$$\sigma_{ij} = 1/2 \ \rho_{ij} \qquad (2.10)$$

Cross relaxation is caused by a "transfer" of magnetization from any neighbouring non equilibrium spin. By definition, cross relaxation exists between any two nuclear spins and for dipolar interactions it depends on the inverse sixth power of the internuclear distance between the two spins.

The effect of a non-selective pulse may be regarded as "switching on" all the cross relaxation paths of the spin states, thereby increasing the observed relaxation rates by term (σij's), which contain only dipolar contributions.

SPIN-LATTICE RELAXATION EFFECTS OF SINGLE-SELECTIVE PULSES

In the NMR spectrum where the chemical shift differences between individual resonances are sufficiently large, as in the AMX spin system, the magnetization of a nuclear spin can often be excited with a selective rf pulse without perturbing the other nuclear spins. For example, each of the four components of the resonance of spin A in the AMX system can be exited equally with a single selective 180^{o} pulse without perturbing any of the transitions in the M and X resonances. For such a selective pulse, the boundary conditions for the motions of the spins can be described by equations (2.11) as given below:

$$M_A\ (0) = -M_A\ (\infty) \qquad (2.11a)$$

$$M_M\ (0) = +M_M\ (\infty) \qquad (2.11b)$$

$$M_X\ (0) = +M_X\ (\infty) \qquad (2.11c)$$

The resulting single selective relaxation rate for spin A, $R_1^A\ (A')$ can be obtained from the initial slope plot of $\ln \{M_A(\infty)-M_A(t)\}$ versus t is given by,

$$R_{1A}\ (A') = \rho_{AM}+\rho_{AX}+\rho_A^* \qquad (2.12)$$

where the tilde (') is introduced to designate that only the nuclear magnetization of spin A has been perturbed.

ρ = cross correlation effects.

* = homo nuclear or " like" spins.

Qualitatively one may imagine that the single selective pulse prepares the spin population in a way as to "switch off" the cross relaxation paths of the perturbed spin by not allowing it to "sample" the magnetization of the other unperturbed spins. However, the unperturbed spins will sample the magnetization of the perturbed spin

because the motions of the unperturbed spins are "coupled" via the cross relaxation paths to that of the perturbed spin. Thus, the initial motion of the perturbed spin is independent of cross relaxation while the initial motion of any unperturbed spin depends only on its cross relaxation with the perturbed spin.

In general, the single selective relaxation rate of spin i which is part of the pseudo first order multispin system may be defined by,

$$R_1(i')_s = \sum_{j \neq i} \rho_{ij} + \rho_i^* \qquad (2.13)$$

This leads to an extremely important conclusion and provides the fundamental quality control for the dipole-dipole mechanism. If it is correct to assume that there is 100% dipolar interaction, i.e. $\rho_i^* = 0$,

$$R_{1i}(i')_s = \sum_{j \neq i} \rho_{ij} \qquad (2.14)$$

Then combining of equations (2.14, 2.7, 2.8) and (2.12) results in the following ratio[48,54] for a pseudo first order spin system.

$$\frac{R_1^i(i)\ ns}{R_1^i(i')} = \frac{\sum_{j \neq i} (\rho_{ij} + \sigma_{ij})}{\sum_{j \neq i} \rho_{ij} + \rho_i^*} + \rho_i^* \qquad (2.15)$$

$$\frac{R_1^i(ns)}{R_1^i(i')} = 1.5 \qquad (2.16)$$

Equation (2.16) then contains the criterion used to define the extent to which a particular proton relaxes via the dipole-dipole mechanism. It is this quality control experiment which confers a major advantage to the relaxation method over the nuclear Overhauser method.

The equivalent quality control for the latter would require all but the receptor resonance to be saturated.

MEASUREMENT OF PROTON SPIN-LATTICE RELAXATION TIMES

In recent years, several semi-automated systems have become available for routinely determining spin-lattice relaxation times. Such measurements impose very high demands on the spectrometer, especially upon its ability to provide a sequence of accurately timed pulses of extremely short duration. As we have seen, the magnetization vector normally lies along the z' direction at equilibrium, while the spectrometer detects signals in the x'y' plane (Figure 2.1 and 2.2). Thus, to assay the amount of magnetization it is necessary to tip the magnetization vector through 90° into the x'y' plane. This can be done by applying a suitable amount of radio frequency in the form of short pulse which is able to tip the magnetization through 90° from the z to the y' axis. This is known as a 90° or (Pi/2) pulse, and the time for which the pulse is applied as the 90° pulse time. The time for which the pulse is applied must be short when compared to the rate of change of magnetization along the z' axis, so an intense pulse is required. The tip angle, θ, is given by,

$$\theta = \gamma H_1 t_p$$

where tp is the duration of the pulse (sec) and H_1 is the magnitude of the field.

If twice that amount of power is applied by doubling the length of the pulse, then the original magnetization will be tipped through 180° and will be along the -z' axis (Figure 2.5). This pulse is known as a

180^{o} or (Pi) pulse.

There are two common methods for determining spin-lattice relaxation times. The relaxation rates of the aromatic heterocyclic compounds were determined by using the conventional " inversion recovery " two pulse sequence. In this method, a 180^{o} pulse is applied to invert the magnetization to the -z'axis (Figure2.5). Hence, immediately after the pulse, the magnetization vector M_z equals $-M0_z$, and will now begin to relax back along the z' axis towards its equilibrium value, M_z, via the spin-lattice relaxation process, as shown in the Figures 2.5 and 2.6.

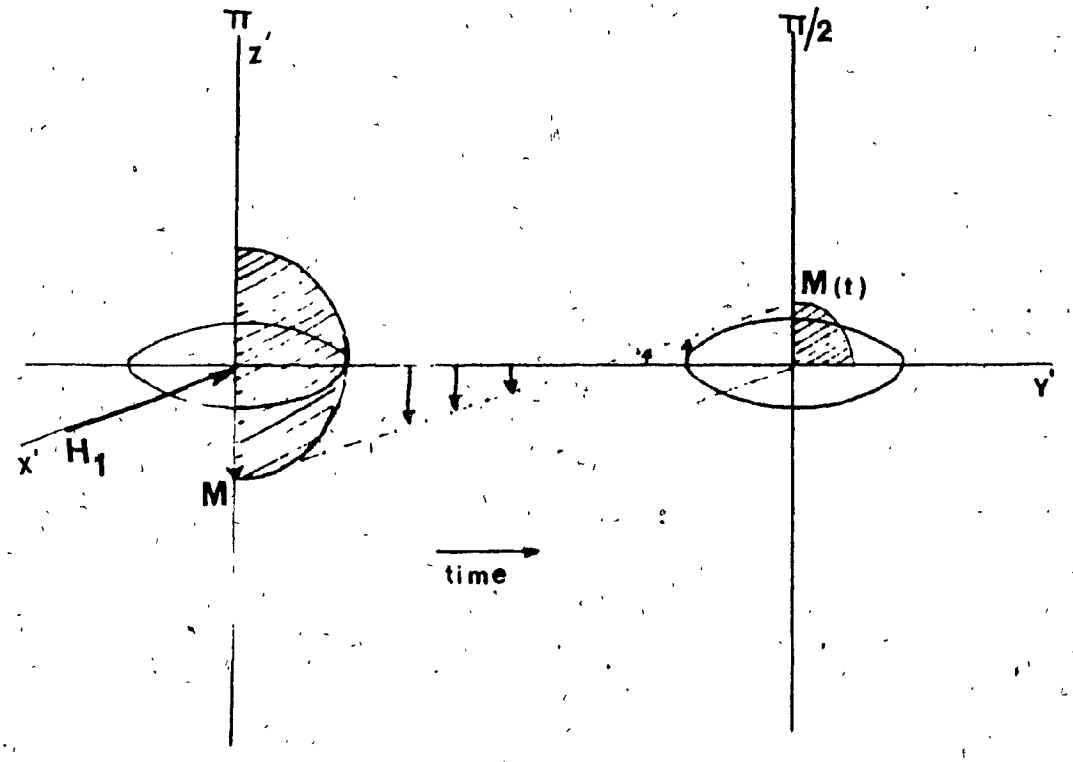


Figure 2.5 Diagrams illustrating the principal of the inversion recovery experiment.

This can be expressed mathematically as:

$$M_z = M0_z \{1-2\exp(-t/T_1)\}$$

Where M_z is the component of M along the -z axis, t sec after the application of the 180° pulse. $M0_z$ is its equilibrium value, and T_1 is the spin-lattice relaxation time. Hence, at one point M_z will actually pass through zero, i.e., $M_z = 0$.

Therefore,

$$0 = M0_z \{1-2 \exp(-t_o/T_1)\}$$

where t_o is the time at which $M_z = 0$

We have now,

$$0 = 2 \exp(-t_o/T_1)$$

$$T_1 = t_o / \ln 2$$

$$T_1 = t_o / 0.693$$

or

$$R_1 = 0.693 / t_o$$

This provides one method of determining T_1 or R_1 values, providing that spectrometers could detect signals along the -z-axis. However, most spectrometers cannot detect signals along the z axis, but are designed to detect signals in the x'y' plane. Therefore, after a delay time of t sec, a 90° pulse is applied which tips the magnetization on to the y' axis, where it can be detected. The full pulse sequence of 180° pulse-delay t- 90° pulse is shown in the Figure 2.6. The signal which has been inverted along the z axis gradually recovers its normal upright intensity, passing through the zero (also called the "null point").

However, at the end of the cycle, the magnetization lies along the y' axis, and so before a second 180° pulse can be applied, it is

necessary to wait a period of about $5*T_1$ to allow the magnetization vector to relax back to $M0_z$.

After $5T_1$,

$$M_z = 0.993\ M0_z.$$

Hence, a pulse delay (PD) equal to $5T_1$ must be inserted between cycles, giving the overall structure:

$$[180^\circ \text{ pulse} - t \text{ sec delay} - 90^\circ \text{ pulse} - PD\ ]n$$

where n is the number of times the cycle is repeated. The timing of the pulse and the delay is normally performed automatically by the computer. In practice, a series of cycles with different values of t are carried out. The spectra obtained as a function of t may be displayed in the form of a stack plot (Figure 2. 7).

The relaxation rates of individual nuclei may also be obtained by fitting the theoretical expression for the exponential recovery of magnetization to the measured signal intensities as a function of the time delay:

$$M_z - M0_z = -2Mz_o \exp(t_o / T_1)$$

Hence, taking logs,

$$\ln(M_z - M0_z) = \ln 2M0_z\ (t_o/T_1)$$

Hence, a plot of $\ln(M_z - M0_z)$ against t will give a straight line with a gradient of $-1/T_1$. In practice, at the end of the experiment, the accumulated free induction decay is Fourier transformed and the intensity of the signal is determined. Then the intensities or ln of the intensities of the signal are plotted as a function of t, and the T_1 values are determined. The fitting process can be carried out using

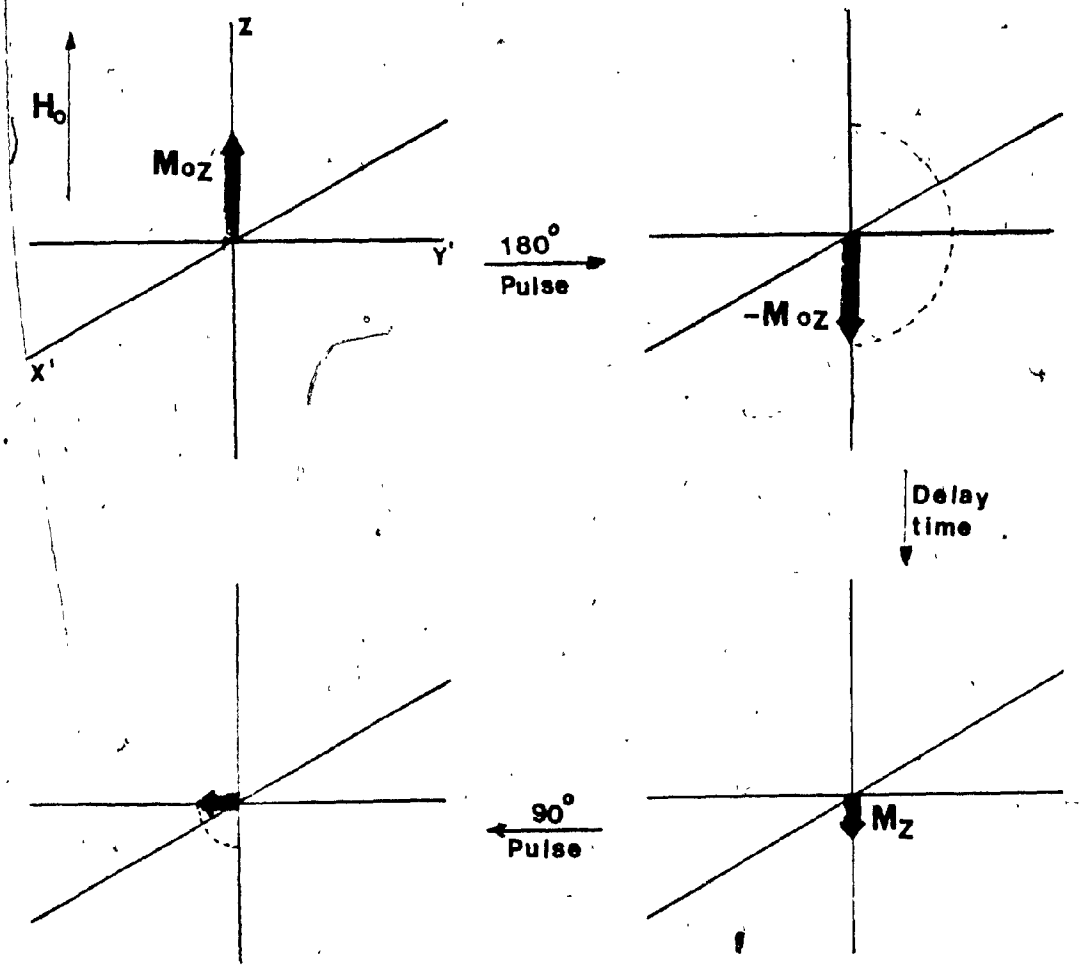


Figure 2.6 The rotating reference frame model for the measurement of spin-lattice relaxation

linear (semi log) regression, or graphically, or by non-linear regression, as in this study. However, it is possible with considerable saving of time, to calculate the T_1 (R_1) value using the " Null point " method on the stack plots, considering the relationship between the " Null point " and the relaxation time.

$$R_1 = 1/T_1 = 0.693/t_o$$

By comparing the R_1 values determined by the " Null point " and the regression method, it has been demonstrated[47] that the null point method provides sufficient accuracy for qualitative studies. The R_1 values

reported in this thesis were measured by the two parameter non-linear regression computational method, but some values were also determined by the " Null point " method.

The relative values of R_1 for the protons reported here were calculated using a program which assumes isotropic motion and compares the relative inter proton distances (see below) as measured in Dreiding molecular models.

As explained before, in dilute solution in a non viscous deuterated solvent, the spin-lattice relaxation is dominated by dipole-dipole interactions with the other protons in the same molecule. The rate equation for dipolar relaxation of a proton j is given by:

$$R_{1j} = K_i * \Sigma (1/r_{ij})^6 * Tc_{ij} \qquad (2.17) \quad i=/j$$

where r_{ij} is the distance between protons i and j, and Tc is the correlation time for motion of the i,j vector. Since the ^1H spin-lattice relaxation rates are governed by the inverse sixth power of inter-nuclear distance, only relaxation due to near neighbours will be significant.

For a rigid isotropically tumbling molecule, all of the Tc_{ij} values will be equivalent, and the rate equation (equation 2.17) can written as:

$$R_{1j} = K_j * \Sigma (1/r_{ij})^6 \qquad (2.18) \quad i/=j$$

The ratio of R_1 values of any two protons in the same molecule will, therefore, depend on inter proton distances

$$\frac{R_{1i}}{R_{1j}} = \frac{K'_i \Sigma (1/r_{ij})^6}{K'_j \Sigma (1/r_{ij})^6} \qquad (2.19)$$

Relaxation rates can be calculated semi quantitatively using

inter-nuclear distances measured from Dreiding molecular models.

The measured R_1 values in different experiments may be different because of changes in motional correlation time. Motional correlation times (Tc) depend on the solvent, the solute concentration, temperature molecular weight and shape. It is possible to eliminate the above experimental variations by using the R_1 value of a selected proton to normalize the R_1 values of the remaining protons (see page 65).

EXPERIMENTAL

Spectra were acquired using the Bruker WH-400 spectrometer at the Montreal Regional High Field NMR Centre. Measurements were made on 0.1M solutions in deuterated dimethyl sulfoxide with only occasional degassing to check the constancy of the relaxation from dissolved oxygen, and for selective pulse experiments. All relaxation rates were determined using the standard inversion-recovery pulse sequence[55] (180°- t-90°), at ambient temperature and with the averaging of 8 free induction decays into a data block of 16 or 32K.

The delay between sequences was at least five times the estimated value of the longest T_1. Before each run, the 180° pulse length was optimized by finding the length which produced a null in the amplitude of the free induction decay. Typically, data for about fifteen values of t, the maximum which could be accommodated, were averaged, Fourier transformed, phase corrected, and stored automatically on the disk for later processing, the appropriate range of t values having been selected in a preliminary experiment. The longest value of t was chosen so that all peaks had relaxed through their null points.

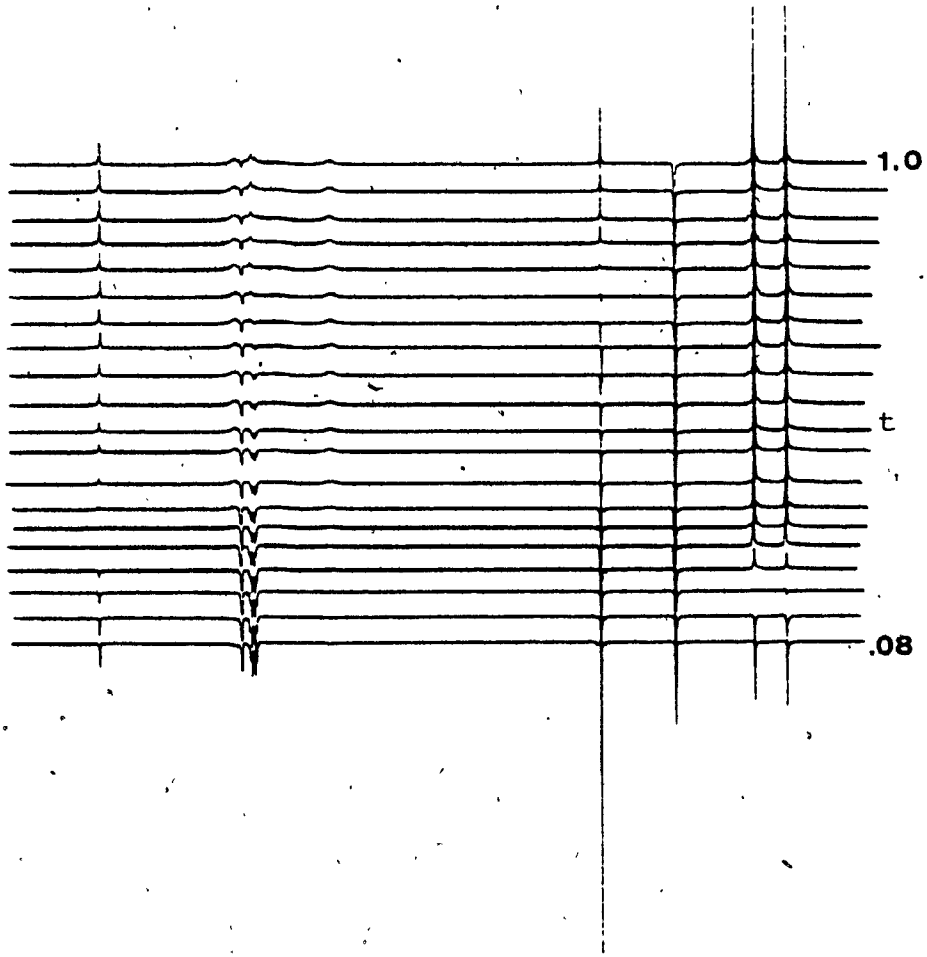


Figure 2.7 Stack plot displaying a selected series of partially relaxed spectra of 1-(2'-chlorophenyl)-4-6-diamino 2,2-dimethyl-s-triazine.

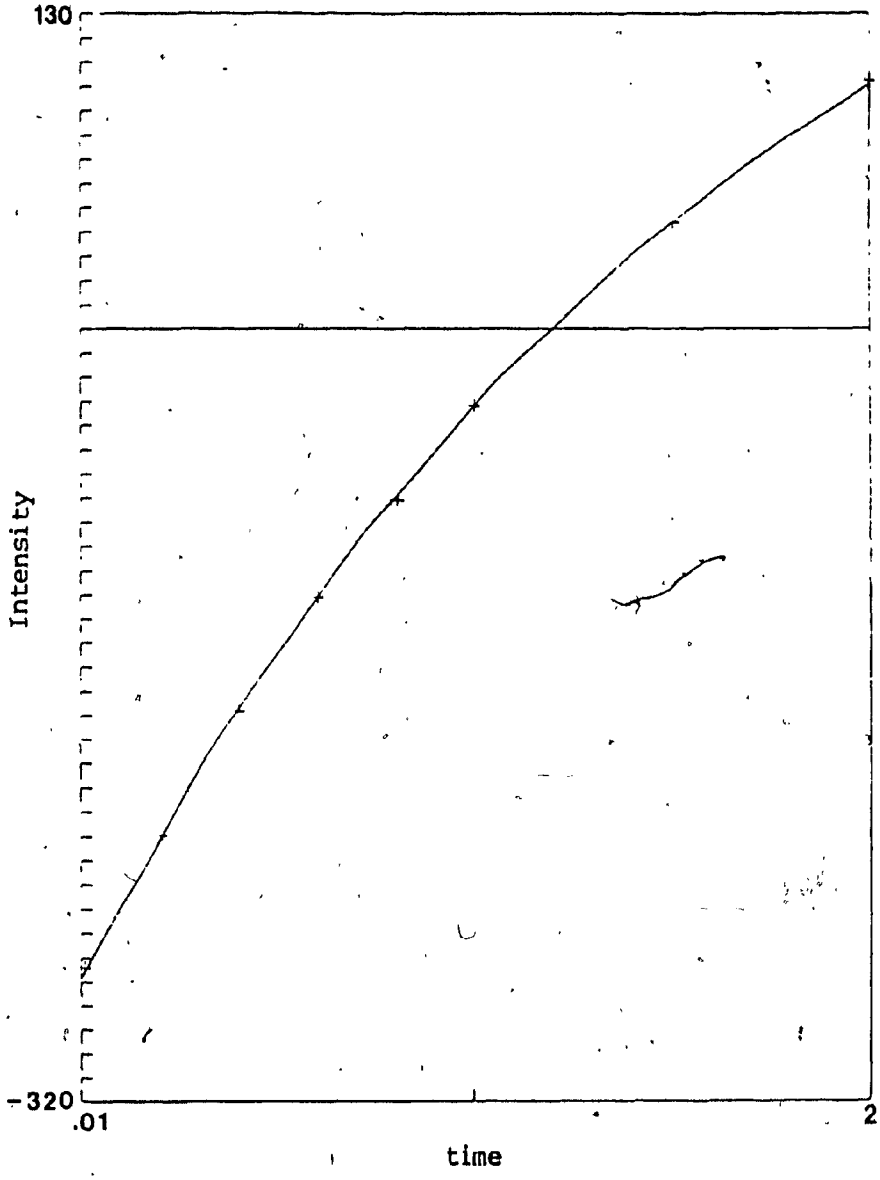


Figure 2.9 Plot of spin-lattice relaxation data (Intensity vs time for 8.2 ppm 6-H doublet of 1-ethyl-2-pyrimidone following the inversion recovery pulse sequence. The best fit non-linear regression curve is shown.

```
NLNT1
FIT AFTER   3 ITERATIONS

1 ETHYL PYRIMIDONE 6-H 8.24PPM INITIAL SLOPE

PARAMETERS: B(1) =   268.82 (EQUILIBRIUM INTENSITY)
            B(2) =     .581 (RELAXATION RATE, R1, /SEC.)
              T1 =    1.722 (RELAXATION TIME, T1,  SEC.)

PARAMETER CORRELATION MATRIX
 1    1.000    .205
 2     .205   1.000

          STD          ONE-PARAMETER          SUPPORT PLANE
        ERROR         LOWER         UPPER       LOWER         UPPER
 1   .9393E+00    .2669E+03    .2707E+03    .2662E+03    .2715E+03
 2   .2068E-02    .5765E+00    .5847E+00    .5748E+00    .5865E+00

 NONLINEAR CONFIDENCE LIMITS

 PHI CRITICAL =    .27416523E+02

 PARA    LOWER B         LOWER PHI       UPPER B         UPPER PHI
  1    .266250E+03    .273125E+02    .271411E+03    .274162E+02
  2    .574829E+00    .276765E+02    .586281E+00    .274232E+02

 #    TIME      INTENSITY      REGRESSION DATA
       SEC                       FIT        DIFF
 1    .010        -264.10       -265.67       1.57
 2    .200        -209.40       -209.33       -.07
 3    .400        -158.40       -156.43      -1.97
 4    .600        -111.00       -109.38      -1.62
 5    .800         -71.00        -67.53      -3.47
 6   1.000         -32.00        -30.32      -1.68
 7   1.500          43.80         45.69      -1.89
 8   2.000         102.50        102.38        .12


PLOTTING PARAMETERS:
     TIME AXIS:  LENGTH =   6.0 INCHES
                 TIME =     .0 TO    2.0 SEC.,  TICK =  1.0
INTENSITY AXIS:  LENGTH =   8.0 INCHES
                 INTENSITY =   -320.0 TO   130.0,  TICK =   10.0
```

R_1 values were determined by the null point method[47] using interpolation between data sets straddling the null point, and also in a number of cases by computer fitting the peak intensities by the exponential recovery curve using an iterative nonlinear regression program run on a Hewlett-Packard 1000 computer.

This program can sum the intensities of the components of a multiplet. Intensities were obtained from the computer print-outs. In every instance, attempts were made to ensure that only the data from the initial slope region were used.

Selective relaxation rates were determined by using a highly selective 180° pulse for the particular proton of interest, and then monitoring the recovery rate of that proton by using the usual non-selective 90° pulse. For the selective pulse experiment, the decoupler offset frequency (O2) was set at the mid point of the singlet by using the cursor. For a multiplet, the frequency at the middle was chosen to be the correct offset frequency. The frequency band width in Hz of such weak selective pulses is approximately given by $1/(\tau 180)$ where $\tau 180$ is the duration of the selective 180° pulse in seconds. It was found that, for a satisfactory inversion of a complete proton multiplet, an effective band width of $1/(2\tau 180)$ Hz is generally required. Note that the band width at half height, $\Delta\nu 1/2$ is given by,

$$\Delta\nu_{1/2} = \gamma H_1/2\pi = 1/2\tau 180 \qquad (2.20)$$

Equation (2.20) was used as the basis for the choice of values of $\tau 180$ in the selective pulse experiments. Thus, the duration of 14 msec for the perturbation pulse of 35Hz bandwith, was chosen as being a good

compromise for the bandwidth required to invert a multiplet resonance, without generating excessive off resonance fields at neighbouring resonances. The selective pulse must be strong enough to invert all the transition lines within the multiplet with equal intensity.

By using a estimated value for the pulse length i.e. D2, the optimum power (DP) which was needed to invert a particular signal was determined. The required experimental conditions for the selective pulse experiment can be optimized by changing the decoupler offset frequency, decoupler power, and the pulse length alternately. The plotted spectra under different conditions were used to find out the optimum conditions.

R_1 values were obtained using an HP-1000 computer by a two parameter non-linear regressional analysis of the peak intensities. The relative values of R_1 for the protons in all molecules were also calculated, using a program which assumes isotropic motion and compares the relative inter-proton distances as measured in Dreiding molecular models (see page 60).

Normalization

When R_1 values of corresponding protons measured in different experiments are to be compared, changes in operating conditions and differences in molecular size and shape will affect the motional correlation time, and therefore, the measured R_1 value. This problem is overcome by normalizing the observed rate internally, to that of a proton that is remote from the site of structural variation. For the molecules studied in this thesis, normalization is quite straight forward, because all the molecules have a rigid planar structure, and

inter-proton distances will not vary by much. In general, a proton that is adjacent to two other protons will get about 95% of its intra-molecular relaxation from these adjacent protons and so this particular proton is the obvious choice for normalizing.

Since the interpretation of the proton spin-lattice relaxation data requires an accurate assignment of the multiplets in quinoline and isoquinoline, computer analysis of the spectra was required. The final analysis was based to some extent on the "best fit" criteria returned by the computer, but mainly on comparison of computed intensities of lines within the multiplets with the experimental spectra.

The spectra were analysed using the iterative program LAOCN 3[56]. This program requires that an initial spectrum be calculated using a first guess as to the values of the chemical shifts and the coupling constants. The chemical shifts were estimated from the centers of the multiplets, allowing for some second order skewing. These assignments were confirmed by NOE and proton decoupling experiments. Initial estimates of coupling constants were obtained by measuring the line separations from the expanded spectra.

All coupling constants were assumed to be positive[57]. As an initial check on the accuracy of the spectral assignments, theoretical spectra were calculated using a Hewlett-Packard 1000 computer, and plotted (using an X-Y recorder) on a scale suitable for visual comparison with the experimental spectra. Reasonable agreement i.e. close visual correspondence in line position and intensity was obtained in both cases.

The program LAOCN 3 was then used to fit a theoretical spectrum to the experimental line positions (using a CDC Cyber 172 computer). This requires an initial assignment of theoretical transition numbers to lines in the actual spectrum; these were obtained from the print-out of the initial calculation. The iterative fitting procedure converged rapidly in both cases. Use of LAOCN 3 requires that any obvious discrepancies in transition assignments be rectified at this stage, and the fitting process be repeated. Some minor adjustments were made in both cases, eventually it was clear that the transitions were correctly assigned.

Fairly good fits to the experimental line positions were obtained in both cases, though the error analysis revealed significant differences. It should be noted that LAOCN 3 fits only to line positions, not to line intensities.

The best fit spectra of each pair were resimulated (as plots on the X-Y recorder) and compared with the experimental spectra. Differences in the spectral intensities were sufficient to enable an unambiguous assignment of the chemical shifts in both cases. Experimental and best fit simulated spectra of Quinoline and Isoquinoline are shown in Figure 2.9 and 2.10.

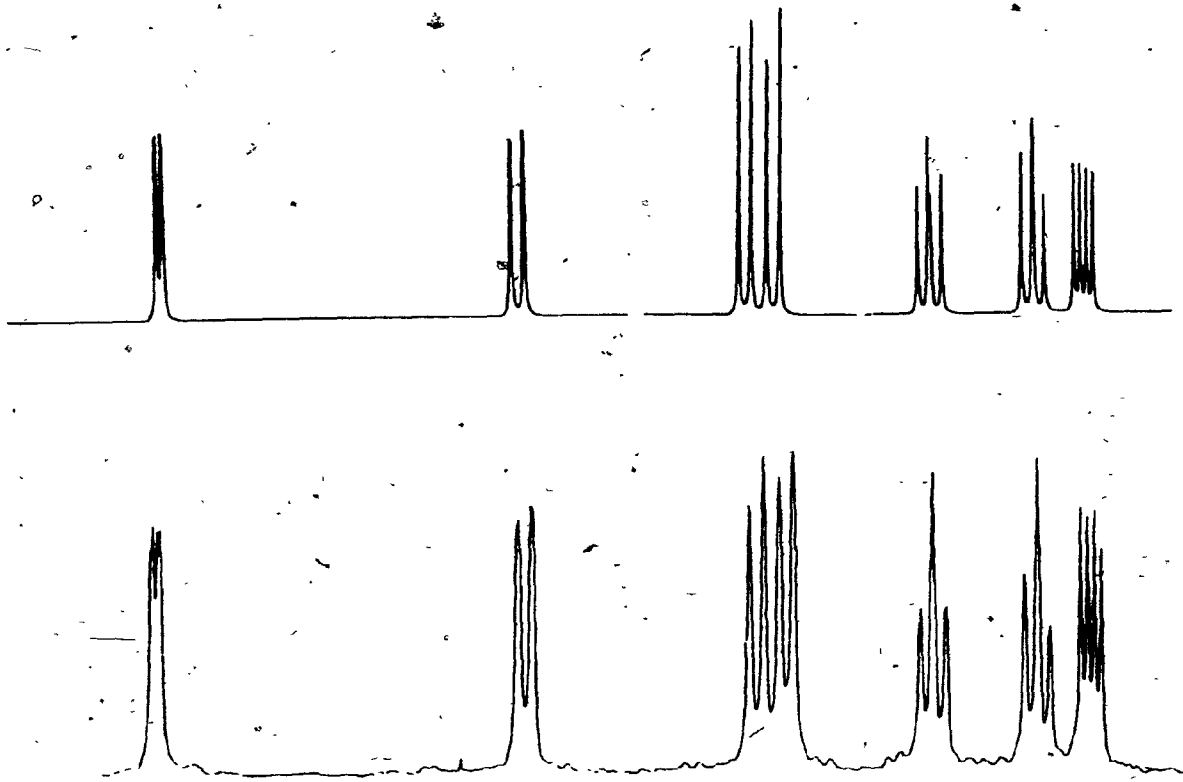


Figure 2.10 Experimental (lower curve) and calculated (upper curve) spectra of the ring protons of quinoline.

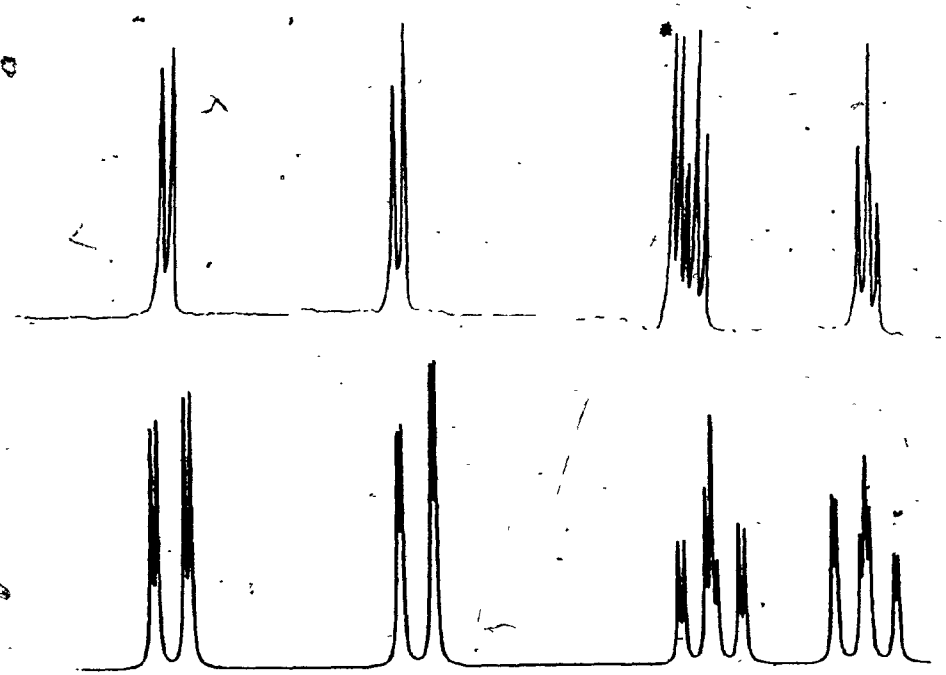
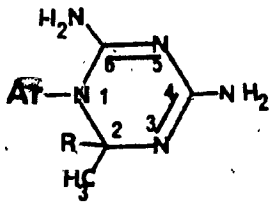


Figure 2.11 Experimental (upper curve) and calculated (lower curve) spectra of the carbocyclic proton region of isoquinoline. The simulated spectrum is plotted under higher resolution, on a different scale from the experimental spectrum. *Multiplet from a proton on the heteroring.

CHAPTER III

INTRODUCTION

The stereochemistry of 1-aryl 4,6-diamino-s-triazines, (I), has



I

been of interest because of an apparent relationship between molecular configuration and biological activity.[1] For example, the ability of these compounds to interfere with bacterial and mammalian cell growth depends markedly upon the location of substituents in the aryl moiety[58]. In antibacterial and mammalian cell culture assays, compounds containing an ortho-substituted phenyl ring exhibit much lower activity than the meta- or para-substituted isomers, regardless of the nature of the aryl group substituent. This finding has led to the hypothesis that non-bonded interactions between bulky ortho substituents and groups at position 2 and 6 of the triazine ring hinder the attainment of a planar configuration when the inhibitor molecule is bound to the enzyme dihydrofolate reductase, apparently a requisite for maximum activity in bacteria and mammalian systems[59]. It has been previously reported[60] from a ^1H NMR study of these compounds that, when R=H or CH_3, and the aryl group is ortho substituted, the barrier to internal rotation about the aryl C-N bond is high. In fact, in most of the 2,2 dimethyl compounds, the rotational barriers were found to be too high to be measured by the ^1H NMR line shape method. When the blocking groups on

the aryl moeities are large, it has proved feasible to isolate one of the diastereomeric rotational isomers of some 2-methyl compounds by crystallization, and to measure the barriers to rotation by measuring the rate of equilibration. When the blocking groups of the 2-methyl compounds were sufficiently small, rate constants for rotation could be measured by ^{1}H NMR line shape analysis. Mean conformational lifetimes at normal temperatures may be estimated from these data.

^{1}H spin-lattice relaxation measurements (^{1}H-R_1 values), and selected Nuclear Overhauser Effect Difference (NOED) experiments were carried out for a number of triazine compounds. The R_1 values for the present series of compounds were determined with the aim of establishing the influence of structural and stereochemical features on the ^{1}H-R_1 values. Of particular interest was the possibility of using R_1 values and Nuclear Overhauser Effect Difference experiments to correlate chemical shifts, and to identify diastereomeric rotational isomers in a direct manner.

Positive identification of rotational isomers is normally difficult, although reasonable inferences may be based on ^{1}H NMR chemical shifts in association with estimates of probable conformations[60]. However, there is reason to believe that preferential solvation effects may have a dominating influence on conformational preferences in certain cases[61]. In one instance, the identity of an isolated diastereomeric rotational isomer has been established by X-ray crystallography[61], but this method is of limited applicability. A method which permitted the direct identification of diastereomeric rotational isomers in solution, without separation, would be desirable.

The potential usefulness of ^{1}H-R_1 values for the determination of

molecular structure and stereochemistry follows from the observation that, under normal experimental conditions, i.e. dilute solution (<= 0.1 M) in a deuterated solvent, the dominant relaxation pathway is via the intra-molecular dipole-dipole mechanism[62], which has a very strong dependence on inter-proton distance. Provided that the molecule is tumbling sufficiently rapidly that the extreme narrowing condition ($w_o^2 \tau_c^2 << 1$) is met (normally the case for small or medium sized molecules), the relaxation rate shows the following dependence on molecular parameters:

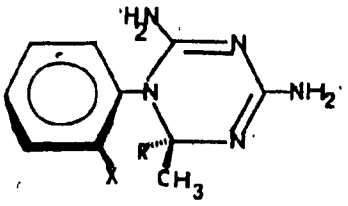
$$R_{1j} = 1/T_{1j} = K_i (1/r_{ij})^6 \, T_{cij}$$

where j refers to the donor molecule and i to the receptor nucleus, Tc_{ij} is the motional correlation time for the i,j vector, and r_{ij} is the inter- nuclear distance. Nuclear Overhauser effect enhancements may be formulated by evaluating the contribution of each ($1/r^6$) term to the overall sum. The dependence of the relaxation rate on the inverse sixth power of the internuclear distance ensures that contributions to the relaxation of a nucleus attenuate very rapidly with increasing distance, so that the R_1 value of a proton is largely dependent on the number and proximity of its immediate neighbours.

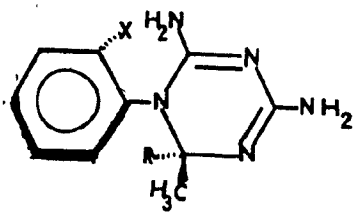
The Tc term may contain contributions from local motion of groups which have some freedom of movement within the molecule, as well as from tumbling of the molecule as a whole. In the triazines, rotation of methyl groups about their three fold axes is expected to reduce their dipolar relaxation rates. These groups may also experience a minor relaxation contribution from the spin rotation mechanism.

Previous studies[60, 63, 64] of these compounds have indicated that steric interference between the ortho substituents of the 1-aryl group

and the groups in the 2- and the 6-positions of the hetero-ring prevents co-planarity of the two rings in the conformational ground state. Those compounds with unsymmetrically substituted aryl groups may, therefore, be classified into two stereochemical groupings, depending on the nature of the 2-substituent of the hetero-ring (Table 3.1).



II ($R=CH_3$)



III ($R=CH_3$)

IV ($R=H$)

V ($R=H$)

When the aryl group in the triazines is unsymmetrically substituted and $R=CH_3$ (compounds 1-3), the stereoisomers, II and III, resulting from restricted internal rotation about the C-N pivot bond between the aryl and the heterocyclic moeities are enantiomers which have indistinguishable NMR spectra in achiral media. However, the geminal 2,2-dimethyl groups are diastereotopic and are expected to give rise to two ^1H singlets provided that rotation about the C-N bond is slow on the NMR time scale and that the chemical shift difference between the methyl groups is adequate. If rotation about the C-N bond were fast on the NMR scale the two signals would collapse to a one signal. If the mean life times of the rotamers were sufficiently long, the diastereomeric methyl groups should, in principle, have different R_1 values.

When R=H (4 and 5) the rotational isomers, IV and V, are diastereomers, and should have distinguishable spectra, of unequal intensity, at conformational equilibrium, provided that the conditions for slow rotation and chemical shift differences are met. Each diastereomeric rotational isomer can exist as an enantiomeric pair (corresponding to inversion of configuration at C-2), the members of which are indistinguishable by NMR using achiral media. If the mean rotational lifetimes were sufficiently long , all protons in one rotamer should have R_1 values different from those in the other rotamer. Each diastereomeric rotamer should give rise to a 2-methyl doublet and a 2-methine quartet resulting from proton spin coupling. Under conditions of fast rotation the time averaged spectrum should be obtained, so that the pair of 2-methyl doublets and the pair of 2-methine quartets should collapse to a single doublet and a single quartet, respectively.

RESULTS AND DISCUSSION

Steady-state NOE difference spectra were obtained by the method of Hall and Sanders[65] using irradiation times of $5*T_1$, followed by subtraction of a reference free induction decay from the decay containing the NOE information. Both data sets were subjected to exponential multiplication corresponding to line broadening of 0.8-1.5 Hz, before Fourier transformation. Substantial line broadening optimized the quality of the difference spectra, particularly for tall narrow lines. The resultant nulling of enhanced signals was very satisfactory, as had been reported previously by Hall and Sanders[65]. By correlating the enhanced peaks to irradiated peak specific relaxation pathways could be determined, and hence different rotamers could be

identified.

At 400 MHz, all of the compounds with enantiomeric rotational isomers (1-3), showed two sharp signals (Table 3.1) arising from the 2,2-dimethyl groups, indicating that these groups are diastereotopic and that internal rotation is slow under the conditions of the experiments. The methyl group R_1 values are greater for the 1'- and 2'-naphthyl compounds, 2 and 3, than for the 2'-chlorophenyl compound, 1, reflecting the slower tumbling rates of the larger molecules. With the exception of the 2'-naphthyl compound, 3, the 2,2-dimethyl groups have different ^1H-R_1 values. Since it lacks a bulky ortho substituent, this compound almost certainly has the lowest rotational barrier ($\Delta G^{\#}$ = 23.1 kcal/mol at 141°C in perfluorobutyric acid solution)[60] of the series.

The remaining compounds, 1 and 2, which have mean conformational lifetimes at normal temperatures of many hours (in perfluoro carboxylic acid solvent)[60], have different relaxation rates for their 2,2-dimethyl groups (8 and 14%, respectively). In each case it is the lower field methyl group which has the faster relaxation rate.

Direct positive identification of the chemical shifts of the 2,2-dimethyl groups in 1 has been obtained using nuclear Overhauser effect difference[66, 67] experiments. Irradiation of the low field (1.28 ppm) methyl transitions produced an enhancement of an aromatic proton multiplet at about 7.54 ppm, attributed to the 6'-protons. However, irradiation of the high field (0.91 ppm) methyl signal under the same conditions failed to produce a significant enhancement in the aromatic proton region (Table 3.2). This experiment establishes the existence of an inter-ring relaxation pathway between the 6' aromatic proton and a 2-methyl group, and definitively correlates the low field (1.28 ppm)

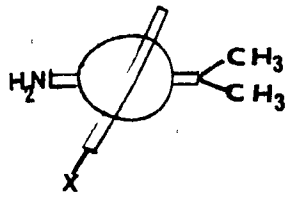
2-methyl signal with the methyl group transoid to the 2'-chloro substituent in 1.

In each NOED experiment, irradiation of a 2-methyl group was accompanied by an enhancement of the other 2-methyl signal, indicating the presence of a dipolar relaxation pathway between the methyl groups of the geminal system. Small enhancements of the $-NH_2$ signals were also observed.

Since protons within methyl groups relax each other efficiently because of their close proximity, relaxation contributions from protons external to the 2,2-dimethyl group are of minor importance, so that the major factor which influences methyl group relaxation is the rate of internal rotation about the three fold axis (i.e. a Tc effect). The difference between methyl group R_1 values within each geminal pair is, therefore, attributed to steric influences on the barriers to internal rotation of the methyl groups.

On the assumption that the conformational preferences of these molecules are influenced by internal steric interactions, and that possible effects of preferential solvation are unimportant, a model relating 2,2-dimethyl group relaxation rates and the preferred conformation may be proposed. The most probable conformation, VI, of a dimethyl compound which minimizes steric interaction between the ortho substituent, X, and the groups in the 2- and 6-positions of the hetero ring may be estimated with the aid of models.

In the most probable conformation, VI, the ortho substituent is displaced towards the $-NH_2$ group in the 6-position in order to minimize steric interactions with the nearby 2-methyl group. Consideration of the effects of aromatic ring currents leads to the conclusion that the



VI

2-methyl group cisoid to the ortho substituent should be more shielded than the transoid 2-methyl group, in accord with the assignments established by the NOED experiments.

Since the methyl group R_1 value is reduced by steric interference from the ortho substituent, its rate of rotation must have increased, through raising of the energy of its conformational ground states with a consequent net reduction in the barrier to rotation. Examples of this type of influence on ^1H and ^{13}C relaxation rates of methyl groups have been reported[68]. This prediction is consistent with the experimental data.

At 400 MHz, the monomethyl compounds, 4 and 5, exhibit well separated 2-methyl doublets and 2-methine quartets (Table 3.1) for the two diastereomeric rotational isomers. The aryl proton signals are only partially resolved. At equilibrium, the conformers of 4 and 5 are present in concentration ratios of 1:1.4 and 1:1.2, respectively.

The spectra of the two rotational isomers of 4 and 5 have been directly correlated with the structures using NOED experiments, resulting in verification of the previously proposed stereochemistry[60]. Since the 2'-methyl signals of the two diastereomeric rotamers of the 2'-tolyl compound, 5, are not resolved, irradiation of the 2'-methyl

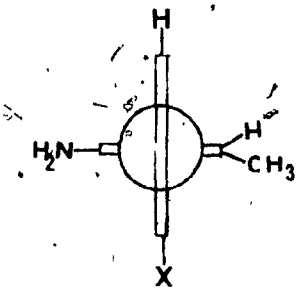
transitions (2.23 ppm) permits simultaneous observation of nuclear Overhauser effects on both rotamers. In addition to the expected enhancement of the signals of the nearby aromatic protons, enhancement of the high field (4.91 ppm, major isomer) 2-methine signal. and the low field (5.24 ppm minor isomer) 2-methyl signal is observed. This experiment definitively establishes that the 2'-methyl group and the 2-methine protons are in close proximity in the major isomer, so that it has the transoid structure, V, X=CH_3.

Irradiation of the low field (1.28 ppm, major isomer) 2-methyl transitions of the 2'-chloro compound, 4, produced the expected enhancement of the high field (4.98 ppm) 2-methine signal of the same (major) isomer. In addition, a significant enhancement of an aromatic proton multiplet near 7.56 ppm was observed, indicating that the 2-methyl group was in close proximity (i.e. cisoid) to an aromatic proton. This experiment establishes the structure of the major isomer of 4 as V, X= Cl. When the high field (1.07 ppm, minor isomer) 2-methyl transitions were irradiated under the same conditions, the expected enhancement of the low field (5.25 ppm) 2-methine signal of the same isomer was observed, accompanied by only a very small enhancement of signals in the aromatic region.

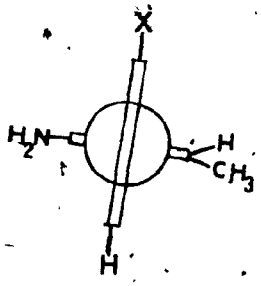
Since the 2-methyl and 2-methine signals of the two rotamers are distinct, R_1 values may be measured for each isomer. The R_1 values of the rotamers show significant differences. The methyl group protons of the major rotamers of 4 and 5 relax 9% and 16%, respectively, more slowly than the corresponding protons of the minor isomer.

Although the aromatic proton signals of 4 and 5 partly overlapped, so that it is not possible to measure relaxation rates for the

individual rotamers, it is clear that the fastest relaxing aromatic protons in 5 are the 6'. If the four aromatic protons in 4 formed an isolated system, tumbling isotropically, calculations based on inter proton distances show that the 3' and 6' protons should relax at 52% of the rate of the 4' and 5' protons. The observed enhanced relaxation rate of the 6' proton is evidence for an additional relaxation pathway, namely to protons on substituents on the 2- and 6-positions of the heterocyclic moiety. The existence of an inter-ring relaxation pathway between the 2-methyl group and an aromatic proton has been established by NOED experiments.



VII



VIII

In comparing the relaxation rates of protons in different compounds (or different isomers), it is desirable to minimize the possible effects of different tumbling rates resulting from differing mass or geometry, by normalizing the rates to the rate of a remote proton, common to both species[69]. This approach is not feasible here, since there is no suitable resolved signal of a proton which is not affected by the conformational change. However, it is clear that the tumbling rates of the rotamers of 4 and 5 cannot be very different. If one isomer was tumbling appreciably faster than the other, all of its R_1 values would be smaller, but this is not the case. In both 4 and 5, one type of

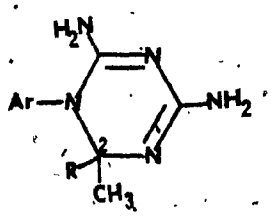
proton relaxes faster, and one slower, in one isomer than in the other. The difference in the R_1 values of the 2-methyl and the 2-methine protons must, therefore, result from differences in the interactions with the aryl group.

Assuming, therefore, that the rotamers have similar tumbling rates (i.e. similar Tc values), the differences in the R_1 values of the 2-methyl and the 2-methine protons must result from differences in the interactions with the aryl group. Interpretation of the R_1 data is simpler for 4 than for 5, since the ortho substituent, X= Cl, in 4 cannot contribute to the relaxation of the 2-methine and 2-methyl protons. In VII, the 2-methine proton has an effective relaxation pathway to the ortho proton in the 6'-position. This pathway is absent for VIII. Hence the 2-methine proton would be expected to relax faster in VII than in VIII. Application of the model used to predict relative relaxation rates of the 2,2-dimethyl protons (see above) results in prediction of a higher relaxation rate for the 2-methyl group in VIII than in VII. Thus the models correctly predict the relative relaxation rates of the 2-methyl and 2-methine protons in the rotamers, VII and VIII, of 4.

Interpretation of the R_1 values of 5 is more complicated since the ortho methyl substituent is a source of relaxation of the 2-methine and 2-methyl protons. However, the R_1 values follow the same pattern in 5 as in 4, indicating that the relaxation pathway from the 2-methine proton to the 6'-proton in VII is more important than the pathway to the 2'-methyl group in VIII.

TABLE 3.1

PROTON CHEMICAL SHIFTS[a] AND SPIN-LATTICE RELAXATION RATES ($R1, s^{-1}$)[b] of 4,6-DIAMINO-1-ARYL-1,2-DIHYDRO-2-METHYL- AND 2,2-DIMETHYL-S-TRIAZINES



				Chemical shifts		R_1 values	
	Ar	R	Isomer	2-CH_3	R	2-CH_3	R
1	2'-Chlorophenyl	CH_3		0.91	1.28	3.14	3.40
2	1'-Naphthyl	CH_3		1.07	1.65	3.40	4.76
3	2'-Naphthyl	CH_3		1.37	1.40	3.94	3.94
4	2'-Chlorophenyl	H	Major	1.28	4.98	3.14	0.92
			Minor	1.04	5.25	2.94	1.01
5	2'-Tolyl	H	Major	1.29	4.91	3.14	1.08
			Minor	1.07	5.24	3.00	1.28

a) Ppm from TMS, determined at 400 MHz, 0.1 M solutions in DMSO-d_6.

b) R_1 values were determined by the null point method, using the inversion recovery pulse sequence.

TABLE 3.2

SUMMARY OF NUCLEAR OVERHAUSER EFFECT ENHANCEMENT OBSERVATIONS

Compound	Isomer	Group irradiated		Observed enhancement				
			Aryl	2-methine		2-methyl		NH_2
				High	Low	High	Low	
1		0.91 ppm 2-methyl	a			b		
		1.28 ppm 2-methyl	b				b	a
4	Major	2-methyl (1.28 ppm)	b	a				
	Minor	2-methyl (1.04 ppm)	a		a			
5	Major	2'-methyl	b	a				
	Minor	2'-methyl	b				a	

a) Small enhancement

b) Large enhancement

CONCLUSIONS

This study has demonstrated that NOED measurements may be used in a straightforward an unambiguous manner to identify the diastereomeric rotational isomers of suitably substituted compounds which undergo biphenyl-like isomerism. The technique is also useful in correlating chemical shifts with structure and stereochemistry. Diastereotopically related protons, and the corresponding protons on diastereomeric rotational isomers may have different spin-lattice relaxation rates which may be used to obtain stereochemical information. Under favourable circumstances, ^1H-R_1 values may be used to identify diastereomeric rotational isomers.

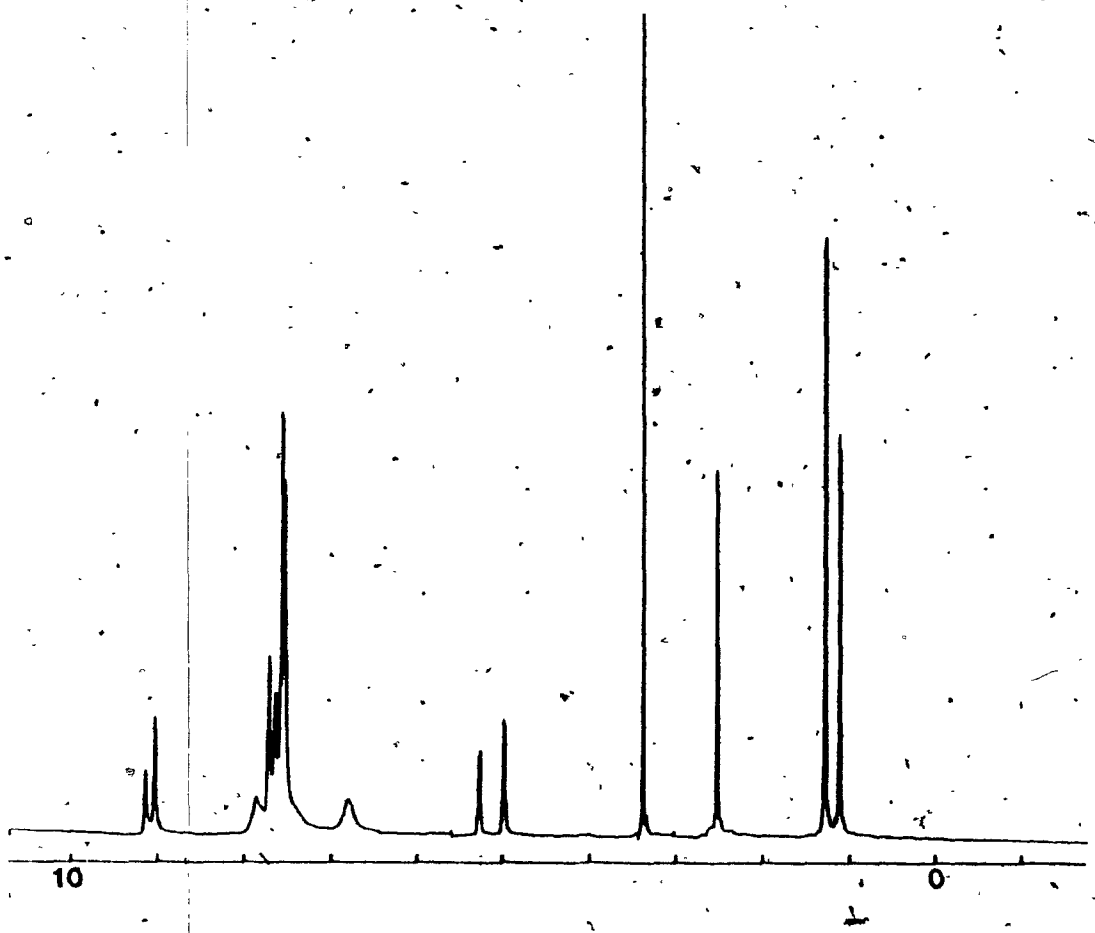


Figure 3.1 400 MHz proton NMR spectrum of 1-(2'-chlorophenyl) -4-6-diamino-2-methyl-s-triazine, 4.

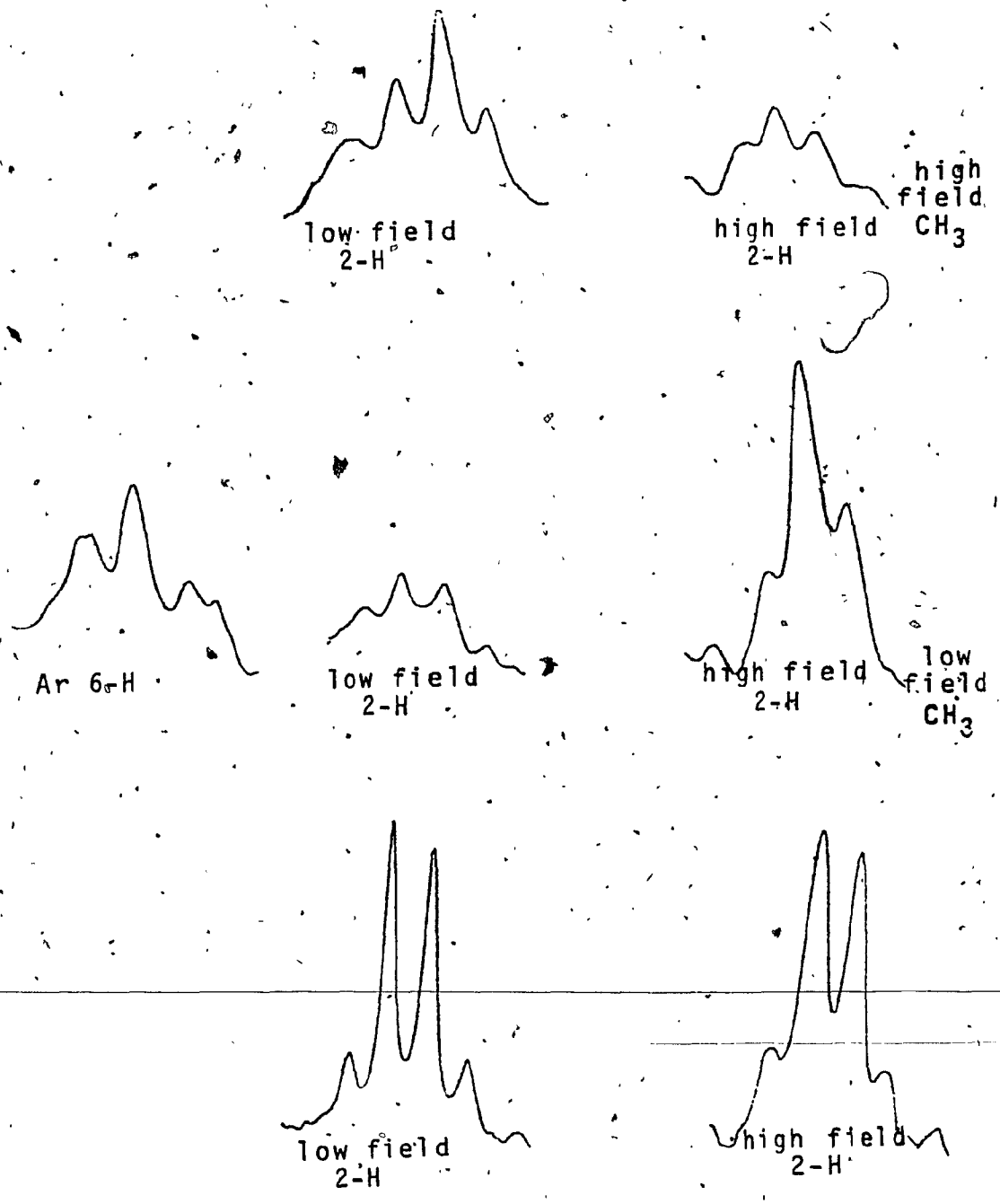


Figure 3.2 NOE difference spectra of compound 4, after irradiation of low field and high field methyl group.

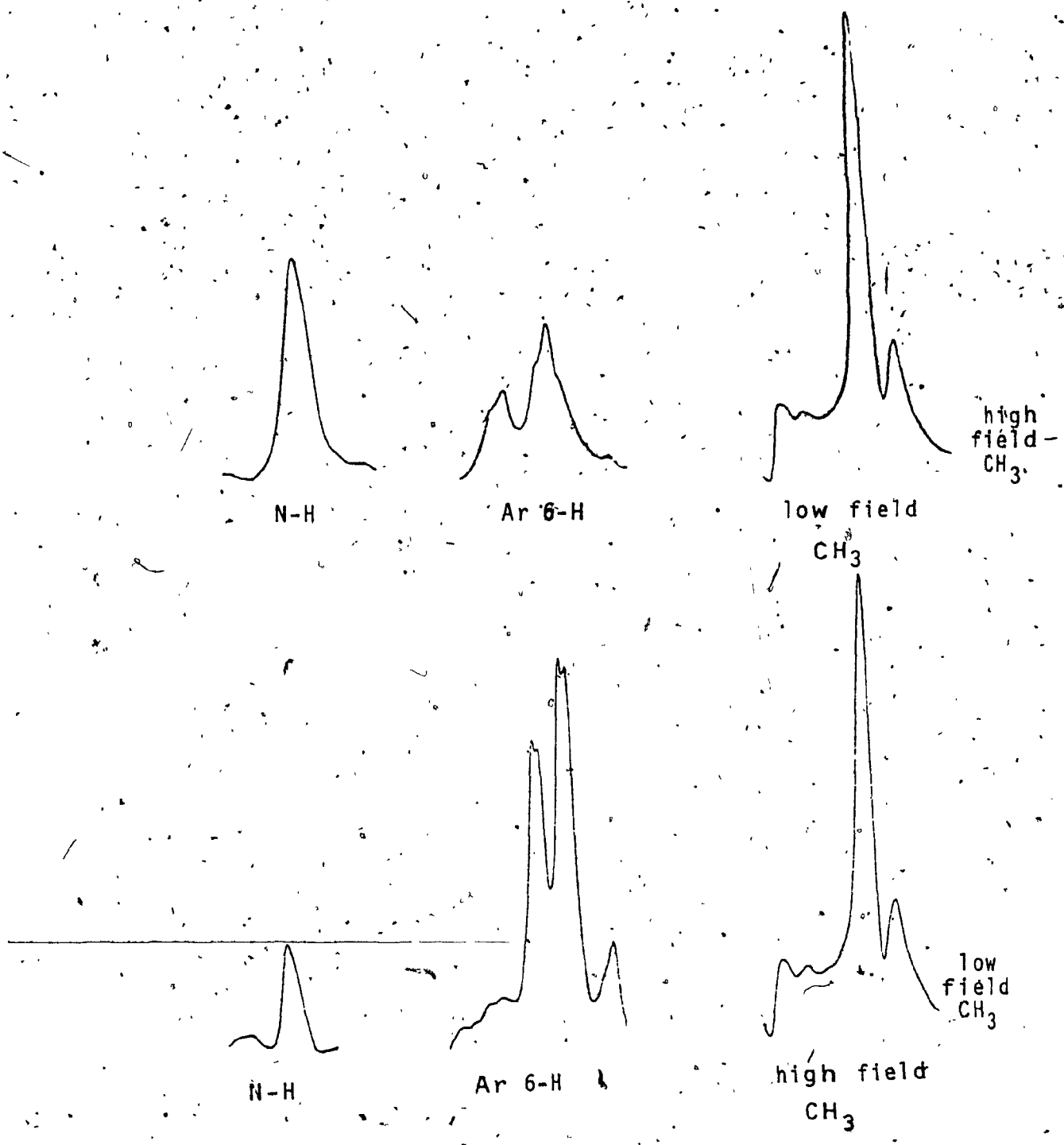


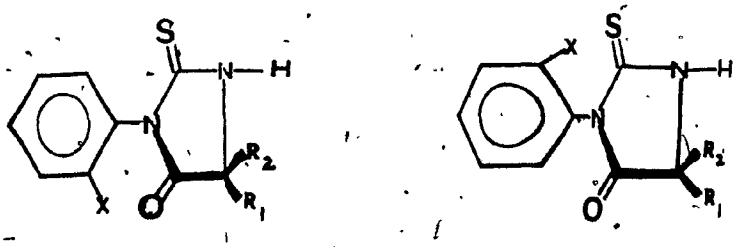
Figure 3.3 NOE difference spectra of 1(2'-chlorophenyl)-4-6-diamino-2,2-dimethyl-S-triazine, 1, after irradiation of low field and high field methyl group.

CHAPTER IV

INTRODUCTION

Studies of conformational isomerism in a number of types of N-aryl substituted heterocyclic compounds using proton NMR have previously been reported[69,70,71]. In particular, restricted rotation about the aryl C-N bond in 3-aryl-5,5-dimethyl-2-thiohydantoins (3-aryl-5,5-dimethyl-2-thio-4-imidazolidinones), and their 5-monomethyl analogues has been investigated, and barriers to rotation have been measured[69,70,71]. The barrier to internal rotation in ortho aryl substituted compounds is consistent with the relative sizes of these substituted groups, i.e. the barrier is largely steric in character. It has been shown that the rotational barrier to internal rotation in the thiohydantoins is much higher than the corresponding hydantoins[69].

Those thiohydantoins with unsymmetrically substituted aryl groups can exist as two major enantiomeric rotational isomers, II and III, when $R1 = R2 = CH_3$.



$R_2 = H, CH_3$

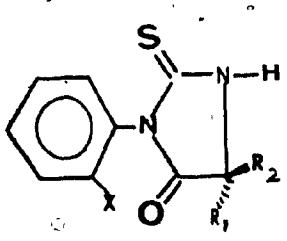
II III

The two ring systems are depicted here as being at right angles, for convenience. The actual angles are not likely to be 90 degrees. In each of these rotational isomers, ($R1 = R2 = CH_3$), the geminal methyl groups

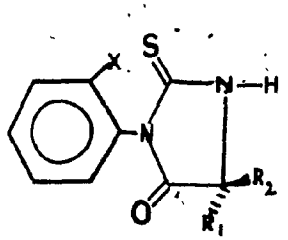
are diastereotopic (i.e. they have different environments) and should have different chemical shifts, so that the methyl spectrum would consist of a doublet. The two enantiomeric forms would be indistinguishable in achiral media. If rotation about the aryl C-N bond were rapid on the NMR time scale, i.e. the rotational isomers were undergoing rapid interconversion, the doublet would collapse to a singlet. For intermediate rates of interconversion, partially collapsed spectra would be observed. No such partially collapsed spectra, or significantly broadened lines, were observable at normal temperature at 400 MHz in the present case.

If R1/=R2, the rotational isomers, II and III, are diastereomers and are expected to have distinguishable spectra of unequal intensity at conformational equilibrium provided that the conditions for slow rotation and chemical shift differences are met. Each diastereomeric rotamer should give rise to a 5-methyl doublet resulting from spin coupling to the proton at C-5. Similarly, the 5-H should give two quartets for these two diastereomers. Under conditions of fast rotation the time averaged spectrum should be obtained so that the pair of 5-methyl doublets and the pair of 5-H quartets should collapse to a single doublet and a single quartet.

There exist two possible transition states for interconversion of the rotamers, namely the states in which the two rings are coplanar.

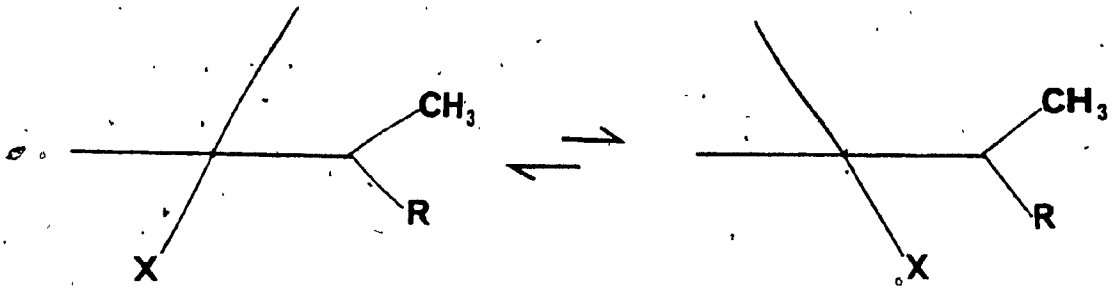


and



In both forms, severe steric interaction between the aryl ortho substituents and the carbonyl oxygen atom and the thio group is expected. The relative severity of these interactions is expected to be the major factor which determines the relative importance of the two possible interconversion pathways.

In the conformational ground states of the molecules, two conformations of the two rings separated by a low energy barrier can be envisaged. In these, the driving force towards coplanarity of the rings, namely conjugation, is balanced by a repulsive steric interaction which is a maximum when the rings are coplanar. These two sub-conformations can be represented as shown below.



Interconversion of these sub-conformations (i.e. libration about the aryl C-N bond) must be fast on the NMR time scale, so that only the spectrum of the time averaged conformation can be observed. The averaged conformation is unlikely to involve a 90° dihedral angle in compounds such as in the present series, unsymmetrically substituted in both rings. The aryl ortho substituent (X) is likely to lie towards the less hindered transition (co-planar) state. Since the degree of steric repulsion between the two ring systems must depend on the steric bulk of the ortho substituent, the averaged dihedral angle must be dependent on the steric bulk of the substituent.

While a chemical shift difference between the geminal methyl groups can be predicted as a matter of stereochemical principle, its physical origin is of interest. There must be a direct contribution from the ortho substituents themselves associated with the electrons in the C-X bond (vs the electrons on the C-H bond in the other ortho position). Differential influences at the two geminal methyl sites are expected to be different because of the "cisoid" and "transoid" relationships to the X-groups. However, this influence might be expected to be small at the relatively remote methyl group sites.

The major contribution to the chemical shift difference probably arises from the magnetic anisotropy associated with the aromatic ring currents of the aryl groups. Unless the "averaged " dihedral angle between the ring is 90°, the two methyl groups will lie in different "shielding-deshielding" regions of the aryl group. Such ring current effects produce some of the largest influences on chemical shifts observable in proton NMR spectra, and are thoroughly documented[72,73].

Another possible contribution to the chemical shift difference between geminal methyl groups is the differential effects of specific solvation of the heteroatoms of the hetero ring. From X-ray crystallographic studies of the thermodynamically less stable (in solution), diastereomeric rotational isomer of 3-(2-bromophenyl) 5-methyl-2-thiohydantoin, it has been shown that the heterocyclic ring is planar with a dihedral angle between the heterocyclic and the aryl ring of 82°, and the bromine is transoid to the 5-CH_3 group[71]. In the preferred rotational isomer, which should be more highly solvated, the bromine would be transoid to the solvent shell and hence cisoid to the 5-CH_3 group. The solution geometry of a molecule may very well be

different from that in the solid state, and unfortunately, not much is known about this particular aspect of these molecules. Further, the X-ray crystal structure of 3-(2-bromophenyl) 5-methyl-2-thiohydantoin[71] shows that the C=S bond length is considerably greater than the C=O bond length (1.67 vs 1.23 ^{o}A). In addition, S is larger than O (1.85 vs 1.40 ^{o}A). In consequence, there occurs a stronger repulsive interaction between the S atom and the groups in the ortho position on the aryl ring, when the thio compound is in its rotational transition state. Since a C=S group is more polarizable than a C=O group (especially in a highly polar solvent, (e.g. DMSO), solvation around a thio carbonyl group is expected to occur to a considerable extent. The ^{13}C NMR study of 3-aryl-2-thiohydantoins[74] shows that this is, indeed, the case. In thiohydantoins the bulky ortho substituent must pass over the C-5 substituent while the ortho hydrogen atom passes over the thiocarbonyl group in the preferred transition state for rotation. Therefore, it may be concluded that the differences in rotational stabilities of these thiohydantoins principally result from differences in repulsive interactions between the ortho substituent and the thiocarbonyl group, and the ortho substituent and the carbonyl group, respectively. Thus, the larger highly polarizable and hence the solvated thiocarbonyl group firmly "locks" the N-aryl moiety out of plane giving extra stability to the ground state of these compounds.

RESULTS AND DISCUSSION

3-ARYL-5-METHYL-2 THIOHYDANTOINS

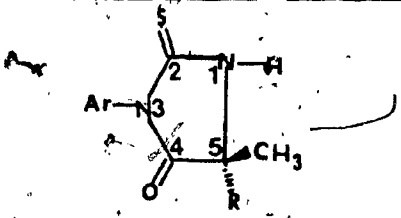
All the monomethyl compounds with diastereomeric rotational isomers show two doublets for the 5-methyl group, two quartets for the 5-H protons, and also separate peaks for the 3'-H, 4'-H, 5'-H, 6'-H and 2'-CH_3 protons, indicating that the 5-methyl groups and 5-H's are anisochronous under the conditions of the experiments. Had internal rotation been fast on the PMR time scale single, time averaged signals would have been shown in all cases.

The aromatic proton signals in both diastereomeric rotamers are sufficiently dispersed at 400 MHz that R_1 values could be determined for all of the protons. It should be noted (Table 4.1) that the absolute R_1 values of protons remote from the direct influence of changes in aryl group substituents, i.e., 5-CH_3 and 5-H, are not constant throughout the series. In particular, the R_1 values are large for compounds 4, 5, and 6, with large aryl ortho substituents, whereas the range of values in the remaining compounds is small. The faster uncorrected rates in 4, 5, and 6 are evidently due to the reduced molecular tumbling rate caused by the relatively large substituent group. The small range of normalized rates for the 5-H protons indicates that the relaxation rates of 5-H protons are insensitive to change in the ortho substituents of the aryl group.

The fastest relaxing protons in these compounds are those of the 5-methyl groups, which relax much faster than the aryl methyl protons. The absolute relaxation rates of the 5-methyl protons range from 1.98-2.57 sec^{-1}. The fastest rate occurs in the 2'-tolyl compound, i.e. 4, whereas the range of values in the remaining compounds is small.

TABLE 4.1

PROTON SPIN LATTICE RELAXATION RATES (R_1 sec^{-1}) OF 3-ARYL-5-METHYL-2-THIOHYDANTOINS (determined by the null point method, absolute values)



No	Ar	Aryl protons 2'	3'	4'	5'	6'	5-CH_3	2-CH_3	5-H	N-H
1	Phenyl	.44	.45	.45	.45	.59	2.17	-	.59	1.26
2	2'-Fluorophenyl	-	53	.63	.47	.45	1.98	-	.59	1.16
		-	.53	.63	.47	.47	1.98	-	.60	-
3	2'-Chlorophenyl	-	34	.64	.65	.45	2.10	-	.60	1.54
		-	.34	.65	.65	.45	2.10	-	.64	-
4	2'-Methylphenyl		.79	.87	.87	.59	2.57	1.47	.69	1.61
		-	.79	.87	.87	.59	2.57	1.47	.71	-
5	2'-Methyl 4 -	-	.69	-	.50	.75	2.31	1.31	.67	1.39
	methoxyphenyl	-	.69	-	.50	.75	2.31	1.31	.66	-
6	2'-Methyl 4 -	-	.39	-	.46	.51	2.48	1.39	.75	1.54
	nitrophenyl	-	.39	-	.46	.51	2.48	1.39	.73	-

In principle, due to differences in their environments one should expect different R_1 values for the 5-methyl groups in two different diastereomeric rotational isomers. The relaxation rates (absolute) for 5-methyl groups in both rotamers are the same in all the compounds, showing the insensitivity to the ortho substituent on the aromatic ring.

TABLE 4.2

PROTON SPIN-LATTICE RELAXATION RATES (R1) OF 3-ARYL-5-METHYL 2 THIOHYDANTOINS (normalized value)

No	Ar	Aryl protons 2'	3'	4'	5'	6'	5-CH_3	2'-CH_3	5-H	N-H
1	Phenyl	.20	.29	.29	.29	.20	1.00	-	.27	.58
2	2'-Fluorophenyl	-	.27	.32	.24	.22	1.00	-	.30	.58
		-	.27	.32	.24	.24	1.00	-	.30	-
3	2'-Chlorophenyl	-	16	.31	.31	.21	1.00	-	.30	.73
		-	.16	.31	.31	.21	1.00	-	.29	-
4	2'-Methylphenyl	-	.31	.34	.34	.23	1.00	.57	.27	.63
		-	.31	.34	.34	.23	1.00	.57	.28	-
5	2'-Methyl-4'-	-	.30	-	.21	.33	1.00	.57	.29	.60
	methoxyphenyl	-	.30	-	.21	.33	1.00	.57	.29	-
6	2'-methyl-4'-		.16	-	.19	.20	1.00	.56	.30	.62
	nitrophenyl	-	.16	-	.19	.20	1.00	.56	.30	-

In most cases, methyl protons will relax each other very efficiently because of their close proximity, hence relaxation contributions from protons external to the methyl group are of minor importance. Therefore, the major factor which influences methyl group relaxation is the rotational correlation time (i.e. Tc). Thus differences in R_1 values of methyl groups reflect differences in their respective Tc values. For different methyl groups in a single molecule, the differences in R_1 values, hence Tc values, are a reflection of the respective steric environments. Assuming that the heterocyclic ring is

not changing its conformation, in both isomers II and III, the 5-CH_3 group has the same steric environment. Therefore, the methyl group rotates freely in both isomers, and thus they have the same relaxation rates.

The aryl methyl (2'-CH_3) protons have almost identical rates (normalized) in all three compounds, i.e 4, 5, and 6 indicating the free rotation of the methyl group. The difference between compounds 4, 5, and 6 is the substituent at the 4' position, which does not have much effect on free rotation of the 2' methyl group. Therefore, it is reasonable to expect the same relaxation rate for the 2' methyl group in all three compounds.

In all compounds, the absolute relaxation rate values for the 5-H of both rotational isomers are very slightly different. In both isomers 5-H is relaxed primarily by the 5-methyl protons and the proton at the 1-N position, because the other protons are far away. Therefore, 5-H R_1's are expected to be approximately equivalent for both isomers as well as for all the compounds.

N-H Protons in all compounds relax faster than the protons in the aryl ring. ^{14}N is a quadrupolar nucleus, with spin $I>1/2$. Since the quadrupolar interaction is usually the dominant one for quadrupolar nuclei (unless, due to molecular symmetry, $e^2qQ/\hbar = 0$), the protons which are attached to nitrogen atom might get some relaxation via the quadrupolar relaxation mechanism. This is the most probable explanation for the elevated R_1 values of the N-H protons.

Excellent dispersion of the aromatic proton signals of 3, 4 and 5, at 400 MHz permitted the measurement of the relaxation rates of all four aromatic protons. If this four proton system formed a completely

isolated group which was tumbling isotropically, calculations based on distances measured from Dreiding models, show that the 4'- and the 5'-protons would have identical relaxation rates, 1.94 times faster than the relaxation rates of the 3'- and the 6'- protons. In fact, the 4'- and 5'-protons have similar relaxation rates while the 3'- and the 6'-protons have smaller relaxation rates. H-4' and H-5' have two neighbours each to relax, compared to H-6' and H-3' which have only one neighbour.

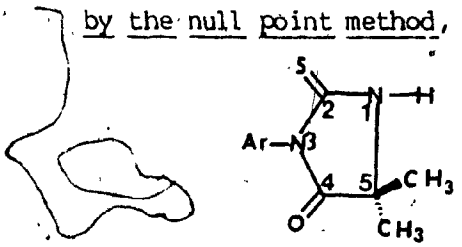
Although both the 3' and 6' protons in 3 have one neighbour, the 6' proton relaxes somewhat faster than the 3' proton, possibly due to the anisotropic motion of the molecule (see later). In contrast, the 3' proton in 4 relaxes faster than the 6" proton, confirming that 3'-H can get some relaxation from the 2'-CH_3 group in addition to that from its neighbour (i.e. 4'-H). Similarly, the 3'-H of 2 relaxes faster than the 6'-H because of the influence of the 2'-fluorine (I=1/2) atom.

3-ARYL-5,5-DIMETHYL-2-THIOHYDANTOINS

The proton chemical shifts for derivatives 7-12 have been reported by Khadim[75] and the proton R_1 values for them are summarised in Table 4.3 and 4.4. With the exception of 9, all the compounds (with an ortho substituted aromatic ring) with enantiomeric rotational isomers showed two sharp signals arising from the 5,5-dimethyl groups, indicating that these groups are diastereotopic under the conditions of the experiments. Since the barriers to internal rotation of these compounds are known to be high, it is assumed that the failure to observe separate 5,5-dimethyl group signals in 9 results from inadequate chemical shift differences rather than from the effects of fast internal rotation.

TABLE 4.3

PROTON SPIN-LATTICE RELAXATION RATES (R_1, sec^{-1}) OF 3-ARYL-5,5-DIMETHYL-2-THIOHYDANTOINS (determined by the null point method, absolute value)



Ar. Aryl protons

No		2'	3'	4'	5'	6'	5-CH_3	2'-CH_3	N-H
7	Phenyl	.46	.61	.61	.61	.44	2.39	-	1.26
8	2'-Chloro phenyl	-	.36	.68	.68	.63	2.48,2.62	-	1.26
9	2'-Bromo phenyl	-	.27	.75	.75	.50	2.67	-	1.39
10	2'-Methyl phenyl	-	.46	.66	.66	.40	2.57,2.62	1.15	1.26
11	2'-Methyl-4' nitrophenyl	-	.41	-	.51	.53	2.89,2.77	1.41	1.39
12	1'-Naphthyl	-	-	.67	.89	.67	3.15,3.01	-	1.73

The aromatic proton signals are sufficiently dispersed at 400 MHz, that R_1 values could be determined for all of these protons in almost all compounds. The multiplet arising from the aryl H-3' was chemically shifted from the other aromatic proton signals in the remaining compounds, so that measurement of its R_1 value was possible in all cases except 12.

TABLE 4.4

PROTON SPIN-LATTICE RELAXATION RATES (R1) OF 3-ARYL-5,5-DIMETHYL 2-THIOHYDANTOINS (determined by the null point method, normalized value)

	Ar	Aryl protons							
No		2'	3'	4'	5'	6'	5-CH_3	2'-CH_3	N-H
7	Phenyl	.19	.26	.26	.26	.19	1.00	-	.53
8	2'-Chloro phenyl	-	.14	.26	.26	.24	.97,1.03	-	.48
9	2'-Bromo phenyl	-	.10	.28	.28	.19	1.00	-	.52
10	2'-Methyl phenyl	-	.25	.27	.27	.16	.99,1.00	.43	.49
11	2'-Methyl-4'-nitrophenyl	-	.14	-	.18	.18	.98,1.02	.49	.48
12	1'-Naphthyl	-	-	.21	.28	.21	.98,1.03	-	.55

It will be noted (Table 4.3) that the R_1 values of protons remote from the direct influence of changes in aryl group substituents, e.g., those of 5,5-dimethyl groups, are not constant throughout the series. In particular, the R_1 values are largest for the naphthyl compound 12, with the largest aryl substituent. These data demonstrate the sensitivity of relaxation rates to changes in rates (and possibly preferred axis) of molecular tumbling. Fortunately, these effects can be eliminated effectively[76] by using the R_1 values of the 5,5-dimethyl group to normalize the relaxation rates of other protons. The

5,5-dimethyl protons are chosen because their rates could not be directly affected by chemical changes in the aryl substituents. Normalized rates are shown in Table 4.4.

The fastest relaxing protons of these compounds are those of the geminal dimethyl groups, which relax notably faster (2-2.5 times) than the aryl CH_3 protons. The absolute relaxation rates for the 5,5-dimethyl protons range from 2.48 to 3.15 sec-1, the fastest rate occurring in the 1-naphthyl compound, 12, whereas the range of values in the remaining compounds is small. The faster rate in 12 is evidently due to the reduced tumbling rate caused by the larger naphthyl group.

The higher R_1 values (absolute) for the geminal 5,5-dimethyl groups could be due to the Tc values. 5,5-Geminal methyl groups may not rotate freely because of steric interference from each other, resulting in large Tc values. Therefore, higher R_1 values for the geminal 5,5-dimethyl groups are expected, compared to the methyl groups in the aromatic ring. 5,5-Dimethyl groups can also get some relaxation from each other via dipole-dipole interaction. This could be another reason for having higher R_1 values for them compared to the aromatic methyl group.

After normalization (Table 4.4), the relative relaxation rates between the geminal 5-methyl groups in a compound are seen to exhibit very small differences. Even though these differences are very small in all the compounds they could be significant because both methyl groups experience the same experimental conditions during the R_1 measurements, and the differences are clearly visible on the stack plots. The small differences in R_1 values between 5,5-methyl groups in these compounds may be explained by considering preferred conformations.

Previous studies of equilibrium constants[75] of the monomethyl analogues of these compounds suggest that there should be a preferred conformation which is determined by the solvation effects of the hetero atoms in the heterocyclic ring. The difference of R_1 values of geminal 5-CH_3 groups of rotational isomers could be due to the difference in free rotation of methyl groups. As explained before, in a highly polar solvent, e.g DMSO-d_6, preferential solvation around the thiocarbonyl group would be likely on the side of the molecule transoid to the bulky ortho substituent. Hence one of the methyl groups may experience greater steric hindrance than the other, which would affect its rate of rotation thus the Tc value. Differences in R_1 values of methyl groups reflect differences in the respective Tc values. Therefore, one could expect to have different R_1 values for the geminal 5-methyl groups.

The aryl methyl protons in 10 and 11 relax with different rates (absolute and normalized) which are much slower than those of the 5,5-dimethyl groups. The 2'-CH_3 group evidently does not have a preferred conformation, i.e. a low rotational barrier facilitates free rotation which, in turn, leads to a marked decrease in R_1 values, compared to the geminal 5,5-dimethyl groups.

The aryl ring protons of 11 show well dispersed signals, so that their relaxation rates could be determined. If the 3'-, 5'- and 6'-protons of the 2'-methyl-4-nitro compound, 11, formed an isolated spin system, tumbling isotropically, calculations based on distances measured from Dreiding models show that the 5'- and 6'-protons should relax almost at the same rate, as observed. Similarly, 3'-H relaxes slower than the other two, as expected, although it must get some relaxation from the 2'-methyl group.

The 4'-H protons of 7, 8, 9 and 10 have very similar normalized relaxation rates, indicating, as expected, that their significant relaxation pathways are to the neighbouring 3'- and 5'- protons.

In compound 10, the 4' and 5' protons relax at almost the same rate, and have higher R_1 values compared to the 3' and 6' protons. In addition, the 3' proton relaxes a little faster than the 6' proton, even though each has one neighbor to relax, confirming that 3'-H gets some additional relaxation from its neighbouring 2'-CH_3 group.

Good dispersion of the aromatic proton signals of 7 at 400 MHz permitted the measurement of the relaxation rates of all five aromatic protons. The relaxation rates of the 3'-, 4'- and 5'- protons are almost identical (Table 4.3 and 4.4), while the R_1 values of the 2'- and 6'-protons are identical and smaller than the others This indicates, as expected, that the significant relaxation pathways of the 3'-, 4'-, and 6'-protons are due to the neighbouring protons.

As seen before, the N-H in almost all compounds relaxes somewhat faster than the aryl protons, probably due to the effect of quadrupolar nitrogen, but only half as fast as the 5,5-dimethyl protons.

Two external factors which may produce differential relaxation rates within the protons of the aryl groups may be identified, namely, anisotropic molecular motion and inter-ring relaxation. The most likely axis for preferred molecular rotation would be approximately parallel to the bond linking the aryl and the heterocyclic moieties. Thus, the relaxation vector between 5'-H and 6'-H would be approximately parallel to this axis whereas the relaxation vectors between 3'-H and 4'-H, and 4'-H and 5'-H would make a large angle to this axis. The theory of dipole-dipole relaxation in anisotropically tumbling molecules predicts

that relaxation vectors which lie on or parallel to the principal axis of rotation are more efficient than vectors at an angle to the axis. It follows that the 5'-H, 6'-H pathway is expected to be more efficient than the 3'-H, 4'-H, and the (similar) 4'-H, 5'-H pathways.

The relaxation rates of the 4' and 5' protons of 9 are similar and higher compared to the R_1 values of the 3'- and 6'-protons, as expected, since their significant relaxations are due to neighbouring protons. But 6'-H relaxes much faster than the 3'-proton, indicating the anisotropic motion of the molecule. For the same reasons, in 8 the 4'- and 5'-protons also have higher R_1 values than the 6'- and 3'-protons, but 3'-H relaxes much slower than 6'-H.

Conclusion

It is apparent that significant differences between methyl R_1 values of different rotamers exist only in one group of compounds (i.e. 3-aryl-5,5-dimethyl-2-thiohydantoins). No inter ring relaxation has been observed for these compounds.

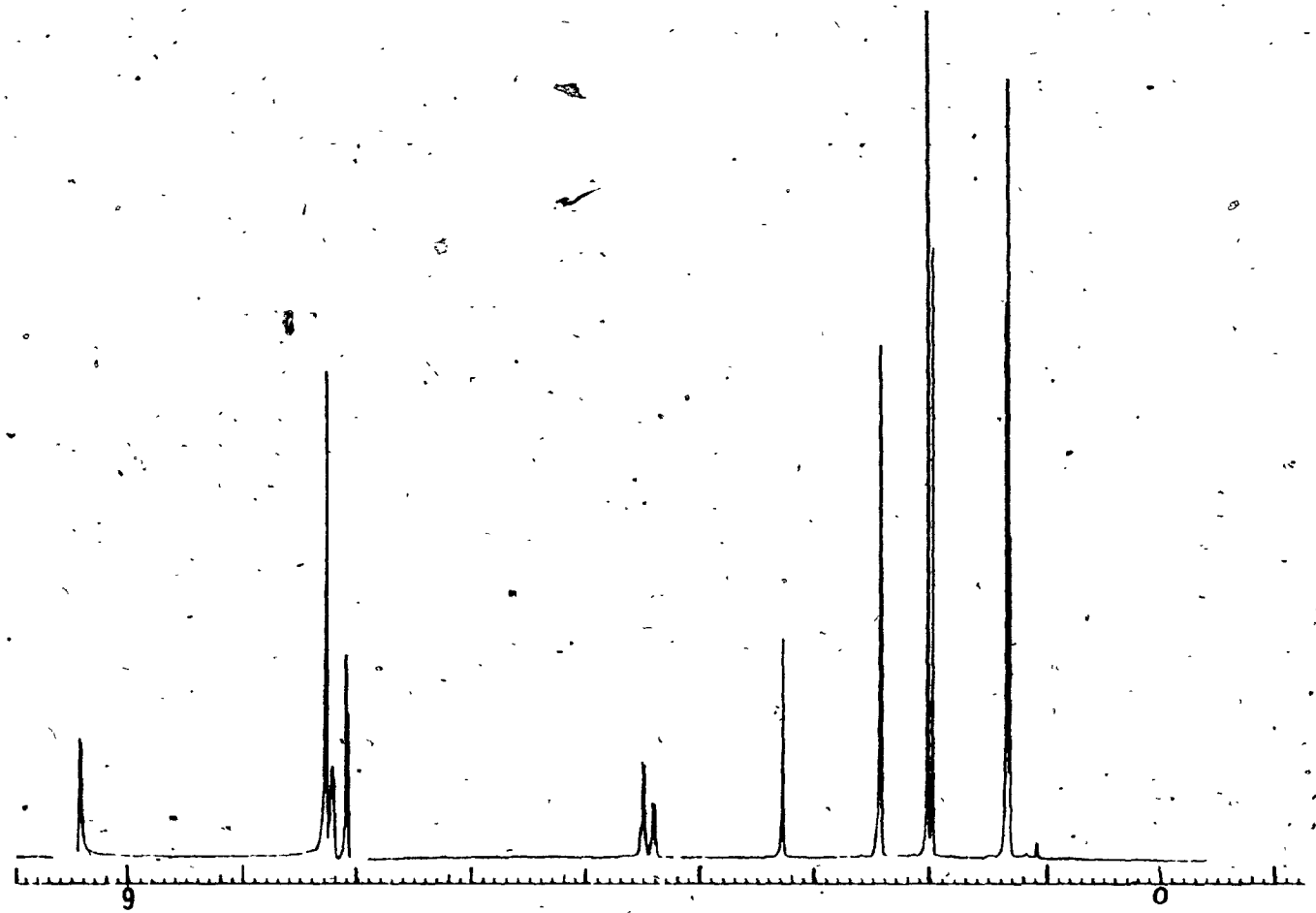


Figure 4.1 400 MHz proton NMR spectrum of 1(2'-methylphenyl)
-5-methyl-2-thiohydantoin

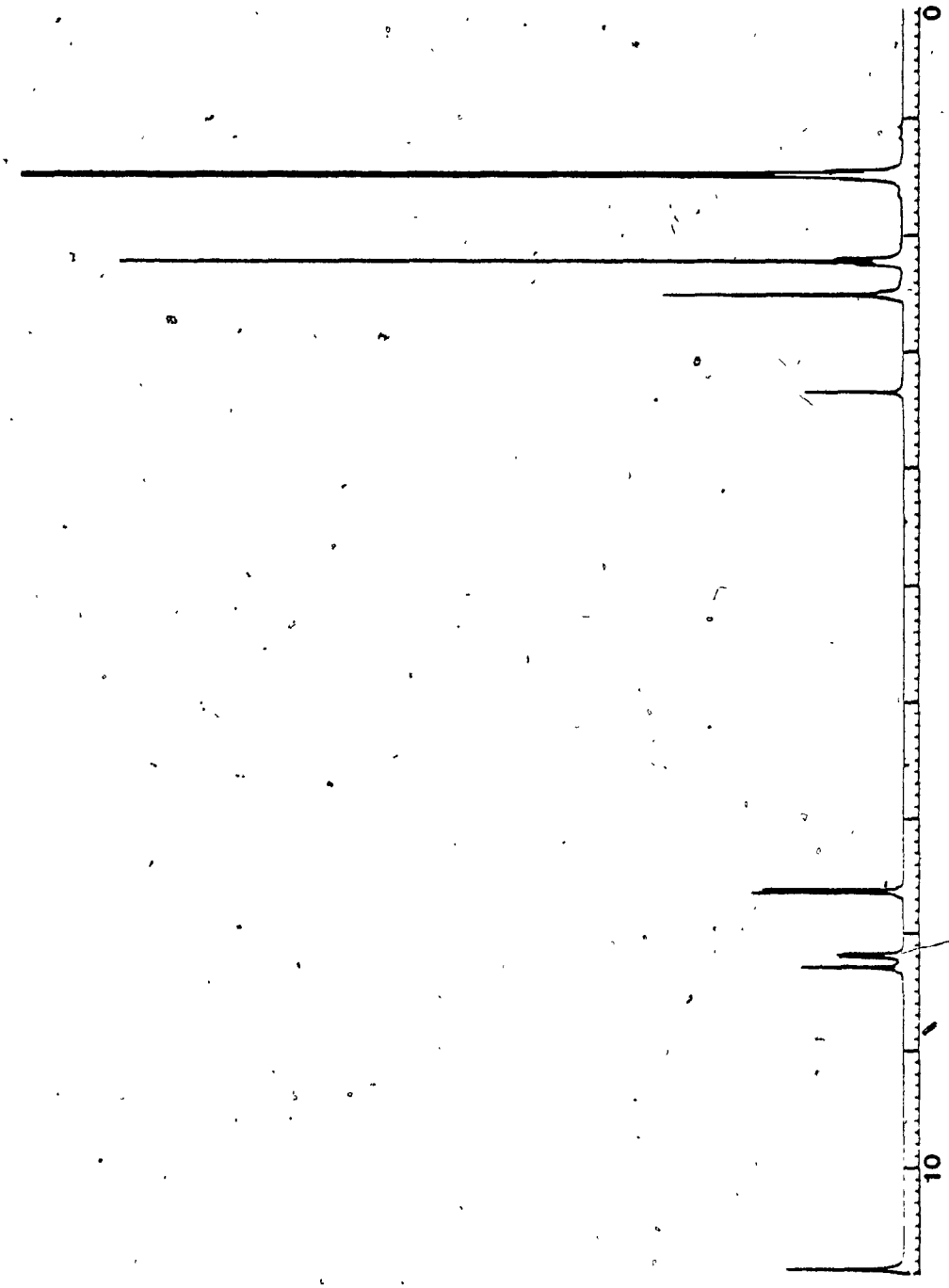


Figure 4.2.400 MHz proton NMR spectrum of 1(2'-methylphenyl)-5,5-dimethyl-2-thiohydantoin

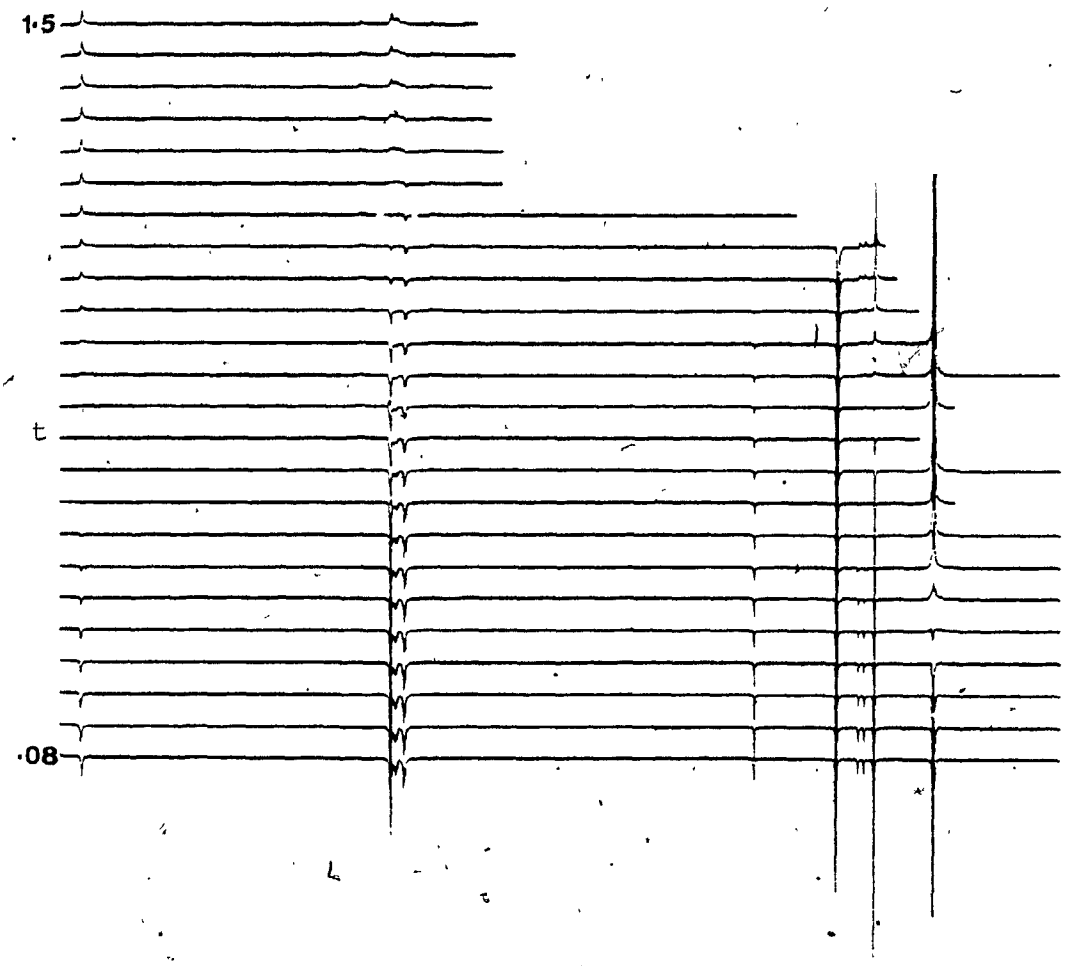
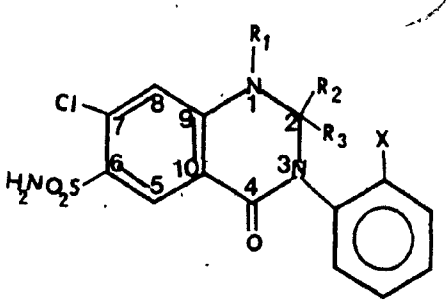


Figure 4.3 Stack plot displaying a selected series of partially relaxed spectra of 1-(2'-methylphenyl) -5,5-dimethyl-2-thiohydantoin

CHAPTER V

INTRODUCTION

Derivatives of 3-aryl-2,3-dihydro-4(1H)-quinazolinones, I are diuretic agents, some of which are used in the treatment of diuresis, natriuresis and kaluresis. The diuretic activity is dependent on the various substituents on the quinazolinone nucleus and the substituents on the N-aryl ring. The highly active compounds have at least one hydrogen in the 2-position, a primary SO_2NH_2 in the 6-position and an ortho or para alkyl substituent on the aromatic ring in the 3-position of the quinazolinone nucleus[77].

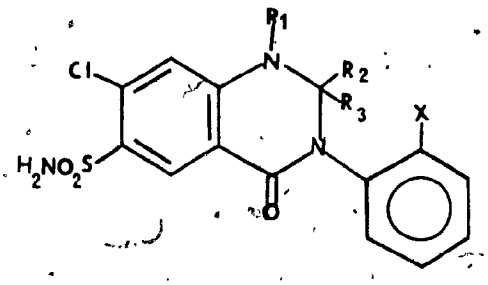


I

Proton magnetic resonance studies of 3-aryl-2,3-dihydro-4(1H)-quinazolinones were initiated by Colebrook and Fehlner[78] in 1956. The thermodynamic activation parameters for restricted internal rotation about the C-N bond for a number of 3-aryl 2,3-dihydro-4(1H) quinazolinones have been determined[78] by complete lineshape analysis of the temperature dependent proton NMR spectra.

^1H and ^{13}C NMR studies of these compounds[79], show that these compounds exist as mixtures of enantiomeric or diastereomeric rotational isomers at normal temperatures. The steric interactions between the

ortho substituent on the 3-aryl group and the substituent on the 2- and 4-positions of the hetero ring in the 3-aryl-2,3-dihydro-4(1H) quinazolinone, II, force the aryl group out of the plane of the rest of the molecule in the conformational ground state.



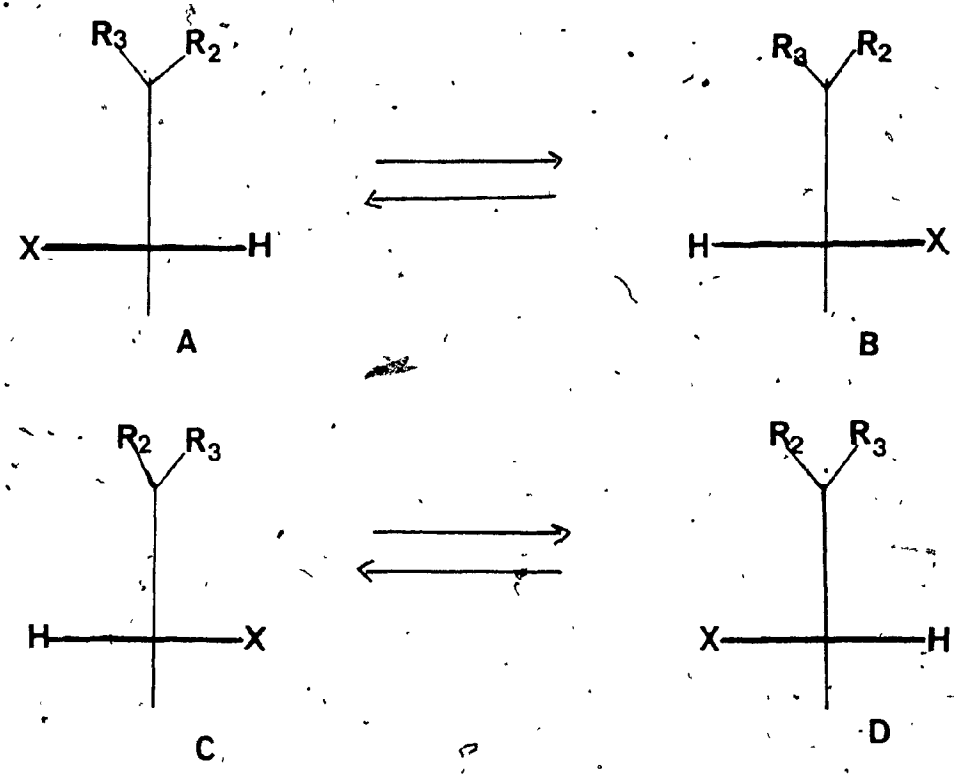
II

CAUSES OF NON EQUIVALENCE AND SPECTRA OBSERVED

If the aryl ring is not coplanar with the hetero ring in the quinazolinone, then the molecule may have 4 possible isomers. These isomers can be represented in a simplified form by A, B, C and D. These drawings represent a view of the molecule along the aryl C-N bond from the para- position of the aryl ring.

If R_2 and R_3 are identical then A will be identical to D; B will be identical to C, and A will be enantiomeric to B. As enantiomers, A and B will have indistinguishable spectra. However, an examination of A shows that R_2 and R_3 should be in different magnetic environments and, therefore, they will be expected to have different chemical shifts. If both R2 and R3 are protons, the chemical shift between them would not be expected to be very large, and of course, they would be coupled to each other. In such a case one would expect mixing of the energy levels to give the familiar AB quartet under conditions of slow rotation. When the rotation around the the aryl C-N bond is fast, the spectra will

collapse to a time averaged singlet.



When R2= R3= CH_3 the coupling between the protons of the two methyl groups is expected to be very small and the spectrum will consist of a pair of singlets of equal intensity. In the time averaged spectrum there will be a single peak centered on the original positions of the two collapsed peaks. This behaviour has been observed by Fehlner[78].

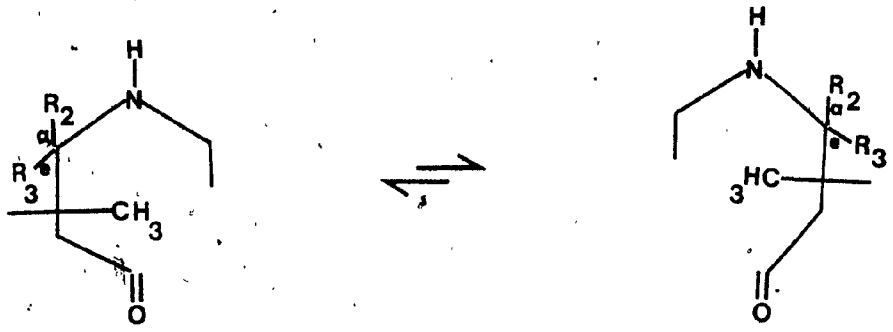
This situation becomes more complicated when R2 ≠ R3. Now A becomes diastereomeric to B, and C becomes diastereomeric to D while A and C, B and D are enantiomeric pairs. Each of the two sets of enantiomers will have its own individual spectrum. These two spectra are superimposed to give the observed spectrum. The two pairs of enantiomers do not have to be present in equal concentration since they should have different free energies. If R2 is a proton and R3 is a methyl group then these will couple with each other. The spectrum of

the methine protons will be a pair of quartets, while methyl protons will produce a pair of doublets. At high temperatures these spectra will collapse to a single quartet and a single doublet.

In principle, not only the substituents on the C-2 carbon, but all protons should have different absorptions for each diastereomer. Even the phenyl protons in the 5 and 8-positions of the quinazolinone ring are occasionally resolved into individual peaks with a chemical shift difference of 1 to 12 Hz (400 MHz). The ratio of the diastereomers is not generally 50:50.

Two major motions of the 3-aryl quinazolinone molecule are involved in the rotation of the N-aryl ring. The actual rotation of the ring is believed to occur when the bulkier ortho substituent passes the C-2 carbon. The other motion that is involved in the rotation process is the flipping of the non-planar hetero-ring. This probably has a very low energy barrier and is flipping very quickly at room temperature.

As can be seen in the diagrams below, each conformer of the hetero-ring has one of the C-2 substituents pseudo axial and one pseudo equatorial.



In a compound where R2= R3= H, it will not matter which form the

hetero-ring is in, since the tolyl methyl will always be passing a hydrogen atom during the rotation. But when R2= H, and R3= CH_3 the positioning of the hetero-ring is of interest. When the C-2 methyl is in the pseudo equatorial position it is pointed towards the aryl ring and interferes directly with the rotation. However, when the C-2 methyl is on the pseudo axial position it is turned away from the aryl ring and has little effect on rotation. Since the barrier to conformational change in the hetero-ring is low, the conformation adopted should be such as to minimize steric interference with the 3-aryl group.

In a compound where R2= R3= CH_3, similar to the case where R2= R3 = H, it will not matter which form the hetero-ring is, since the tolyl methyl will always be passing a methyl group during the rotation.

In principle, diastereotopically related protons, or groups of protons within a molecule, or corresponding protons on diastereomeric isomers, should have different R_1 values. The magnitudes of the differences must depend on the net differences in the relaxation pathways in the two environments and may, in practice, be too small to be observable. When differences in R_1 values are observable, however, they are a potential source of steric and structural information.

A complicating factor in the case of molecules which undergo a conformational exchange process is that there is an effect on the measured R_1 values associated with the molecular motion. If the conformational lifetimes are short with respect to the relaxation times of the protons under study, a given proton must change its environment before its relaxation is complete. Under these circumstances, the differential between the relaxation rates of protons exchanging between different environments should be reduced. In the extreme situation of

very slow exchange the relaxation rates should accurately reflect differences in environments.

RESULTS AND DISCUSSION

The ^1H R_1 values (sec^{-1}) (absolute and normalized) for the series of 3-aryl-2,3-dihydro-4(1H)-quinazolinones are given in Table 5.1 and Table 5.2, respectively.

The relaxation rates (R_1 values) in this series of compounds range from 0.30 to 4.08 sec^{-1}. The fastest relaxing are the protons of SO_2NH_2 groups, the slowest are the more isolated aryl protons, in particular the 5-proton of the 4(H)-quinazolinone ring.

2-Methylene and 2-Methine Protons

The relaxation rates (R_1 values) of the 2-methylene protons (compounds 1 and 2) fall within the range 1.07-2.04 sec^{-1} (Table 5.1). These rates increase roughly in parallel with increasing molecular weight, indicating their sensitivity to changes in rates of molecular tumbling. After normalization with respect to the 5-H rate, the relative 2 methylene rates fall within the range 5.85-6.71 (Table 5.2). Because of their short internuclear distance and their location in a relatively rigid portion of the molecule, the 2-methylene protons relax each other efficiently. Less efficient relaxation pathways which may also contribute to the relaxation rates are to the protons at the N-1 position, and the protons attached directly or indirectly to the ortho positions of the 3-N-aryl group. Since both of the compounds have identical quinazolinone moieties, no information on the contribution of the former relaxation pathway can be obtained. Thus, external

influences on the 2-methylene proton relaxation rates must be due to relaxation to N-aryl substituents, modulated by the effect of changes in substituents on the overall tumbling rates of the molecules in solution, and changes in rates of segmental motion, i.e. rotation or libration about the aryl C-N bond.

Comparison of relaxation rates between compounds is best done using the normalized rates in Table 5.2, so as to reduce correlation time effects as much as possible. The most striking feature of the relative rates of the 2-methylene protons is the higher values for the 5',7',8'-trimethyl phenyl compound, 2, compared to the 5'-tolyl compound, 1. Since the ortho substituents are identical in 1 and 2, the origin of this difference is not clear.

The relaxation rates (R_1 values) of 2-methine protons (compounds 3-5, 8-10 and 12) fall within the range 1.07-1.93 sec^{-1}. These rates increase roughly in parallel with increasing molecular weight, indicating their sensitivity to changes in rates of molecular tumbling. After normalization with respect to the 5-H relaxation rate, the relative 2-methine proton rates fall within the range 3.23-6.33. The 2-methine proton should get most of its relaxation from the substituent at the same carbon atom. Less efficient relaxation pathways which may also contribute to the relaxation are to the protons at the N-1 position, and the protons attached directly or indirectly to the ortho positions of the 3-N-aryl group.

The 2-methine protons in compound 5, which has a benzyl substituent at the N-1 position, have the highest R_1 values compared to other compounds without a substituent at the N-1 position, confirming that these protons get some of their relaxation from the substituents at the N-1 position.

Table 5.1

RELAXATION RATES (sec^{-1}) OF 3-ARYL-2,3 DIHYDRO-4-(1H)-QUINAZOLINONES (determined by the null point method)

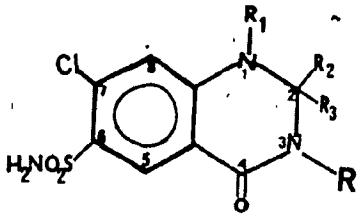
No	2-H	2-CH3	5-H	8-H	N-aryl protons 5', 6', 7', 8', 9'	5'CH3	NH2	NH	6'CH3	7'CH3
1	1.78	-	.30	.54	.71	1.22	3.46	1.87	-	-
	1.82									
2	2.04	-	.30	.55	.63 .71	1.26	4.08	2.10	1.47	1.47
	1.98									
3	1.15	3.15	.31	.54	.48 .71 .48	1.20	3.65	2.31	-	-
	1.07	3 65	.31	.54		1.31		2.31		
4	1.39	4.08	.31	.63	.69	1.57	3.85	2.16	-	1.44
5	1.51	4.33	.35	.82	.81	2.10	3.85	-	-	-
	1.44	3.85	.31	.82		2.10				
6	1.82	5.33	.30	1.16	.80	1.58	3.01			
	1.93	4.08			.80	1.47				
7	-	4.62	.29	.58	.92	1.47	3.47	2.39	-	-
		4.33				1.47				
8	1.20	-	.31	.58	.87	1.47	3.01	2.31	-	-
	1.24					1.44		2.31		
9	1.31	3.96	.33	.59	.90	1.47	3.85	2.39		
10	1.61	-	.50	.60	.89	1.61	3.85	2.39	-	-
	1.58			.60		1.61		1.39		
11	-	3.85	.32	.53	.79	1.44	3.85	2.31		
	-	5.33	.32	.53		1.44	3.85	2.31		
12	1.61	-	.31	.59	.86 .99 .86	1.57	3.85	2.77	-	-
	1.73					1.47	3.85	2.77		

Table 5.2

NORMALIZED RELAXATION RATES OF 3-ARYL-2,3-DIHYDRO 4-(1H)-QUINAZOLINONES

No	2-H	2-CH3	5-H	8-H	N-Aryl protons 5', 6', 7', 8',9'	5'CH3	NH2	NH	6'CH3	7'CH3
1	5.85	-	1.00	1.77	2.36	4.00	11.40	6.16	-	-
	6.00									
2	6.71	-	1.00	1.82	2.07 2.33	4.15	13.41	6.90	4.9	4.9
	6.51									
3	3.75	10.23	1.00	1.74	1.57 2.32 1.57	3.88	11.84	7.50	-	-
	3.46	11.84	1.00	1.74		4.25		7.50		
4	4.50	13.24	1.00	2.04	2.25	5.23	12.50	7.03	-	4.68
5	4.85	13.94	1.12	2.62	2.62	6.76	12.38	-	-	-
	4.65	12.34	1.00	2.62		6.76				
6	6.00	17.54	1.00	3.80	2.62	5.18	9.91	-	-	-
	6.33	13.41				4.85				
7	-	16.00	1.00	2.00	3.20	5.11	12.00	8.28	-	-
		15.00								
8	4.02		1.00	1.88	2.81	4.69	9.78	7.50	-	-
	3.88					4.79		7.50		
9	3.96	12.00	1.00	1.79	2.73	4.46	11.67	7.24	-	-
10	3.29	-	1.00	1.22	1.82	3.29	7.86	-	-	-
	3.20			1.22		3.29				
11	-	12.22	1.00	1.69	2.50	4.58	12.22	7.33	-	-
		16.92	1.00	1.69		4.58	12.22	7.45		
12	5.11	-	1.00	1.86	2.75 3.14 2.75	4.68	12.22	8.80	-	-
	5.50					5.00		8.80		

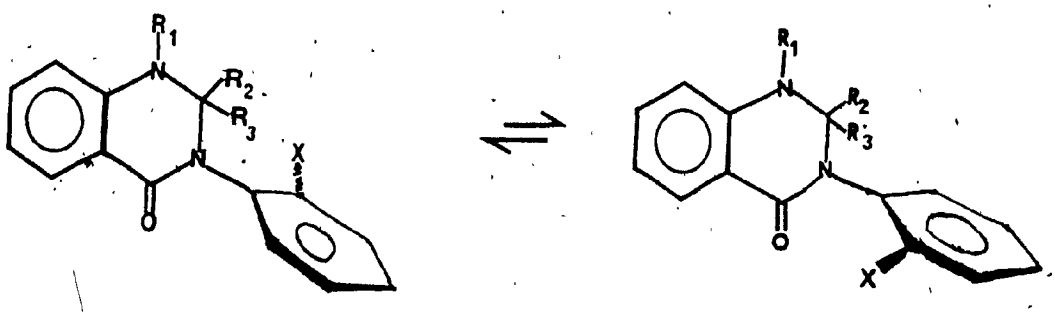
LIST OF COMPOUNDS



No.	R	R1	R2	R3
1	5'-Tolyl	H	H	H
2	5',7',8'-Trimethylphenyl	H	H	H
3	5'-Methyl-6'-chlorophenyl	H	H	CH_3
4	5',7',9'-Trimethylphenyl	H	H	CH_3
5	5'-Tolyl	CH_3	H	CH_3
6	5'-Tolyl	CH_2Ph	H	CH_3
7	5'-Tolyl	H	CH_3	CH_3
8	5'-Tolyl	H	H	$CHCl_2$
9	5',9'-Dimethylphenyl	H	H	CH_3
10	5'-Tolyl	H	H	CH_2Cl
11	5'-Tolyl	H	CH_3	$COCH_2CH_3$
12	5'-Tolyl	H	H	CH_2OCH_3

Apart from a direct inter-ring dipole dipole contribution, an ortho aryl substituent may influence the relaxation rates of the 2-methylene and 2-methine protons by changing the average dihedral angle between the aryl and the heterocyclic moieties through a steric bulk effect, thereby changing inter-nuclear distances between 2-methylene or 2-methine protons and the substituent at N-1 or the ortho substituents of the 3-aryl group. An increase in the steric bulk of the ortho substituent, X, is expected to increase the dihedral angle between the rings, III and IV. An associated influence on freedom for segmental motion within the

molecule may affect relaxation rates through Tc effects.



III IV

C-5 Protons

5-H has almost the same relaxation rate (absolute) in most of the compounds in this series. It does not change much with the substituent at C-2 or the ortho substituent of the N-aryl ring. This lack of sensitivity is due to the isolation of this proton from the rest of the aromatic ring and the quinazolinone ring.

Protons at C-8

The protons at the 1 position (on the N atom) are the only ones which can contribute significantly to the relaxation of the protons at C-8, since the C-2 substituents and the ortho substituents on the aromatic ring are not close enough to contribute.

For most of the diastereomeric compounds H-8 shows two signals, one from each diastereomer. However, both signals have the same relaxation rate. Relaxation rates of H-8 of those compounds with a proton at the N-1 position (R1=H) range from 0.54- 63 sec^{-1}. For the compounds with a substituent at the N-1 position (e.g.compound 5 and 6), H-8 has higher relaxation rates (0.82-1.16 sec^{-1}), i.e. an increase of about more than

100%. The highest relaxation rate has been seen for the N-benzyl substituted compound. It is obvious, therefore, that H-8 can pick up some relaxation from the protons of the N-1 substituent. The relaxation rate of H-8 is also elevated in the N-methyl compound, 5, but to a lesser extent than in the N-benzyl compound. This suggests that the N-benzyl group may have a preferred conformation which favours H-8 relaxation.

2-Methyl protons

The relaxation rates (R_1 values) of these protons of the mono-methyl compounds fall within the range 3.15-5.33 sec^{-1}, whereas in the dimethyl compound, 7, they fall within the range 4.33-4.6 sec^{-1}. Most of the diastereomeric 2-methyl groups have different rates, higher than those of methyl groups on the N-aryl ring. The most striking feature of the normalized and the absolute rate is the relatively fast relaxation rate of one of the isomers in 6 and 11. This methyl group relaxes 30% faster than the same group in the other isomer of the same compound. These data suggest that steric interference between the N-1 substituent and a 2-methyl group has the effect of slowing the rate of methyl group rotation, thereby increasing the relaxation efficiency by a Tc effect. The 2-methyl group may also experience a direct dipolar relaxation contribution from the N-1 substituent, probably of minor importance due to the efficiency with which methyl protons relax each other.

In the 2,2-dimethyl compound, 7, the methyl groups have relatively large R_1 values compared to the R_1 values of the methyl groups in the mono-methyl compounds without any substituent at the N-1 position. In

most cases methyl protons relax each other very efficiently, thus differences in R_1 values of methyl groups are largely a reflection of their respective τ_c values. In the case of the 2,2-dimethyl compound, the geminal methyl groups may not rotate freely because of steric interference from each other, resulting in large τ_c values, which, in turn, lead to a marked increase in the R_1 values, as observed. In addition, 2,2-dimethyl groups get some relaxation from each other via dipole-dipole interaction.

In principle, it should be possible to differentiate R_1 values for different rotamers, and to correlate chemical shifts with respect to the transoid or cisoid conformations of the molecules, as in the case of the triazines. But in the quinazolinone case there are difficulties in differentiating R_1 values for diastereotopic rotamers, because of the effects of the rotational process.

As mentioned earlier, most of the 2-CH_3 groups and the 2-methine protons in the two diastereotopic rotamers have different relaxation rates (see Table 5.1). If one considers the two diastereotopic rotamers for monomethyl compounds, in one rotamer the 5'-methyl group is cisoid to the 2-methyl group whereas in the other it is transoid. Due to steric interactions, one could expect that the transoid conformation would be in higher concentration at conformational equilibrium, i.e. it should be more stable compared to the other. As one can see from molecular models, in the transoid conformation the 2-H proton is close enough to the N-aryl ring protons to get some relaxation, while in the cisoid conformation (less stable) the 2-H proton can get some relaxation from the 5'-methyl group. It is not clear from a study of models which of these processes should be more efficient. However, experimental data

show that the relaxation pathway to an ortho proton is more efficient than to an ortho methyl group (assuming that the conformational assignments are correct).

Further, if one considers the effect of solvent, there is a possibility that the C-4 carbonyl group is solvated by DMSO-d_6. This solvent shell could affectively increase the bulkiness of the carbonyl group. Therefore, the cisoid conformation might very well be the more stable one, so that it would be present in higher concentration at equilibrium. If this is so, the above inferences on the relative efficiencies of relaxation pathways would need to be reversed.

The few studies of solvent effects that have been done for one of these compounds[78] show that there are significant changes in thermodynamic parameters in different solvents. Investigation of some other aryl-substituted heterocyclic compounds which are subject to restricted internal rotation has shown that conformational preferences may be dominated by the effect of solvation rather than by steric interactions within the solute molecule[75]. It might be worthwhile, therefore, to study solvent effects on the thermodynamic parameters for more of these compounds. Such studies might lead to a better understanding of the solvation process, which could help to answer the question of the preferred conformation of these compounds.

The difficulties in interpreting these R_1 values due to uncertainty in the assignment of the conformation are compounded by the knowledge that the relaxation rates are of the same order of magnitude as the rates of internal rotation about the aryl C-N bond[78] i.e. the molecule may change its conformation before relaxation is complete.

Aryl methyl (5') protons

The spin-lattice relaxation rates for the methyl substituent at the C-5' position of the aryl moiety fall in the range 1.20 to 2.10 sec^{-1}. These protons relax much slower than the 2-methyl protons. This difference is a consequence of the freedom of segmental motion available to the methyl group, which influences the observed R_1 values through the Tc term.

As mentioned before, methyl protons relax each other very efficiently. Hence, differences in R_1 values of the methyl groups are related to their respective Tc values. The 5'-CH_3 group does not have as much steric interference as the 2,2-dimethyl groups, and hence rotates more freely, resulting in a small Tc value and small R_1 values.

Interpretation of the variations in the normalized relaxation rates of the aryl methyl groups within the series (Table 5.2) in terms of substituent effects is complicated by the possibility of concomitant changes in the rates of internal motion within the molecules. The most striking feature of the normalized rates is the relatively fast relaxation of the methyl group in compound 5 which has a methyl group at the N-1 position. The preferred conformation for the heterocyclic ring of this compound would be the one where the 2-methyl group is in the pseudo axial position to minimize the steric interaction between the N-CH_3 and the 2-CH_3 group. In this conformation, the 5'-CH_3 group would experience some restriction to rotation, leading to a higher Tc and a higher R_1 value. In addition, if the molecule is in the above conformation, the 5'-CH_3 group can get some relaxation from the 2-CH_3 group so that it has a higher R_1 value than the 5'-CH_3 groups in the other compounds.

N-Aryl protons

In most cases the protons on the N-aryl group give rise to complex multiplets, so that R_1 values could not be measured for individual protons, and only the approximate range of values could determined (Tables 5.1 and 5.2). Only in the case of the trisubstituted aryl systems, 4 and 2, could all of the aromatic proton R_1 values be measured.

The relaxation rates of the N-aryl protons fall in the range 0.48 - 0.99 sec^{-1} (Table 5.1), and the normalized rates in the range 1.57- 3.20 (Table 5.2). The highest R_1 value (i.e. 3.20 sec^{-1}) for the N-aryl protons has been seen for the 2,2-dimethyl compound, since an N-aryl proton may pick up some relaxation from the methyl groups at the C-2 position. Further, because of the bulky substituent at the C-2 position, the rate of rotation of the 3-N-aryl ring will be reduced to a certain extent. This factor leads to a large Tc value and a high R_1 value.

In compound 3 (i.e. 5'-methyl-6'-chlorophenyl-2,3-dihydro-4-(1H) quinazolinone) 8'-H relaxes faster than the 7' and 9' protons. 8'-H has two neighbours to relax to compared to the 7' and 9' protons which have only one neighbour each. For the same reason, a comparatively higher R_1 value has been observed for the 7' and 8' protons in compound 12. Normally the compounds with large substituents at C-2 have higher R_1 values for some N-aryl protons, implying that N-aryl protons can get some relaxation from the groups at the C-2 position. Further, in compound 12, free rotation of the N-aryl ring may be reduced because of steric interference from the bulky substituent at the C-2 position,

leading to a higher Tc value, and hence higher R_1 value for N-aryl protons.

Conclusion

The proton relaxation data reported here clearly evidence the transfer of relaxation contributions between the protons of the aryl ring and the C-2 methyl and methylene protons of the quinazolinone ring. Although this cannot be interpreted in terms of a unique conformational model, it is clear that such inter-ring relaxation offers a new source of structural data which helps further study in other heterocyclic molecules. It is also clear that a substantial differential exists between the R_1 values of 2-CH_3 protons and 2-H protons in the two different diastereomers. Interpretation of these data in terms of preferred conformations should be feasible, but it is difficult to identify the more stable conformation because of difficulties associated with relatively fast rotation and possible solvent effects.

Future work

As far as future work on this series of compounds is concerned, some experiments could be done which would be of value in determining which isomer is thermodynamically more stable, i.e. the major isomer. One of these experiments would be involve studies of solvent effects on thermodynamic parameters of these compounds.

At room temperature, the rotational barriers of these compounds are known to be relatively small[78]. Therefore, it might be useful to study R_1 values at sufficiently low temperatures that internal rotation is inhibited. Since there are difficulties associated with identifying

different rotamers from R_1 values, another way to solve this problem could be by NOED experiments. But since it is known that these compounds rotate relatively fast around the C-N bond at room temperature, NOED experiments at normal temperatures would not be a useful source of information. Therefore, it would be worthwhile to do NOED experiments at relatively low temperatures.

In principle, NOE experiments give a measure of how much relaxation a particular proton or a methyl group can get by the dipole-dipole relaxation mechanism. Hence, studies of ^{13}C NOE's of the C-2 methyl groups of these compounds might also be useful in helping to identify the steric interactions on C-2 substituents from the N-aryl ring and the N-1 substituents.

A study of the ^{13}C spin-lattice relaxation rates of these compounds should yield data on segmental motion, particularly of methyl groups, and hence provide a source of information on steric interactions within the molecules.

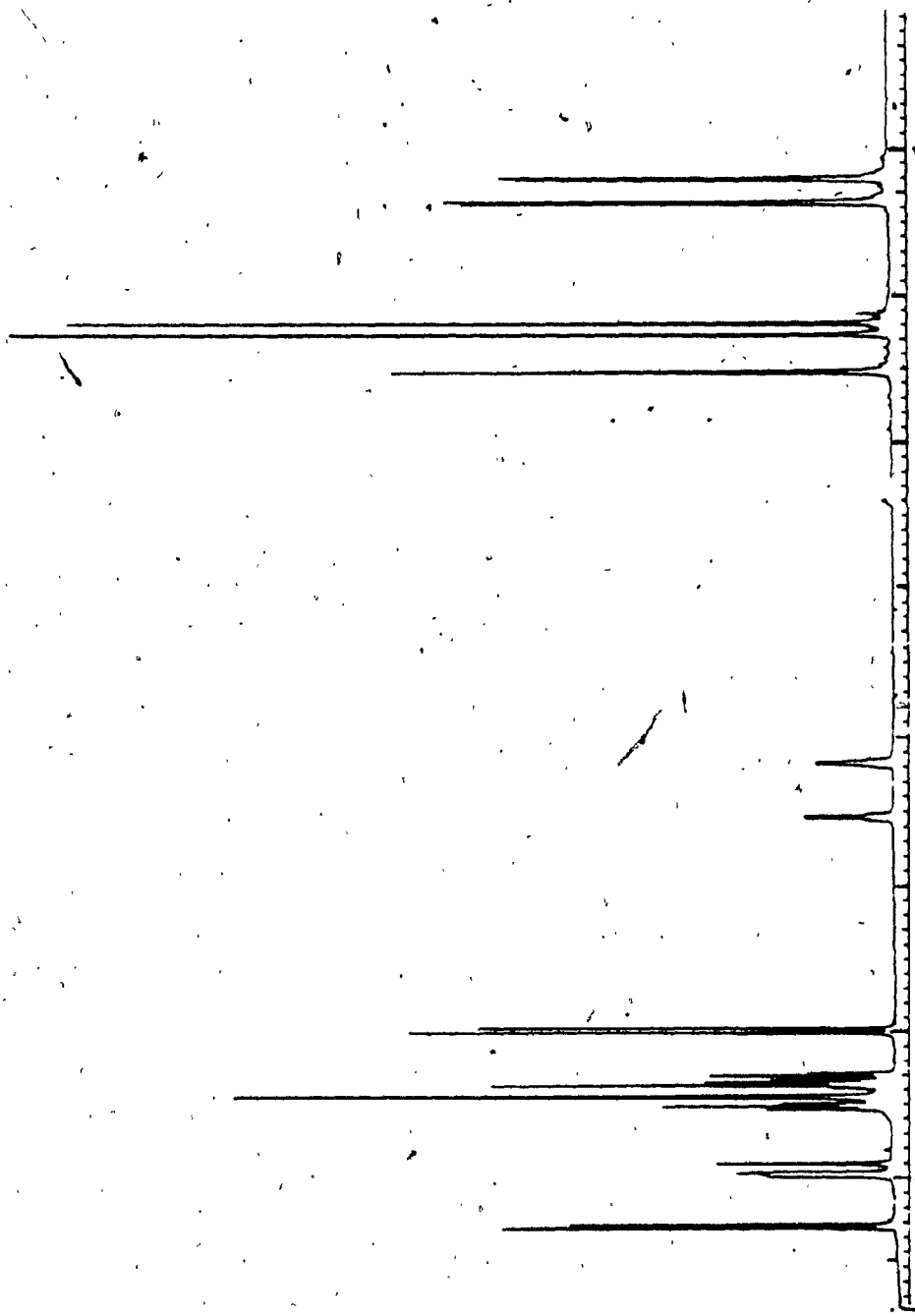


Figure 5.1 400 MHz proton NMR spectrum of 3(5'-methyl-6'-chlorophenyl)-2,3-dihydro-4(1H)-quinazolinone, 3.

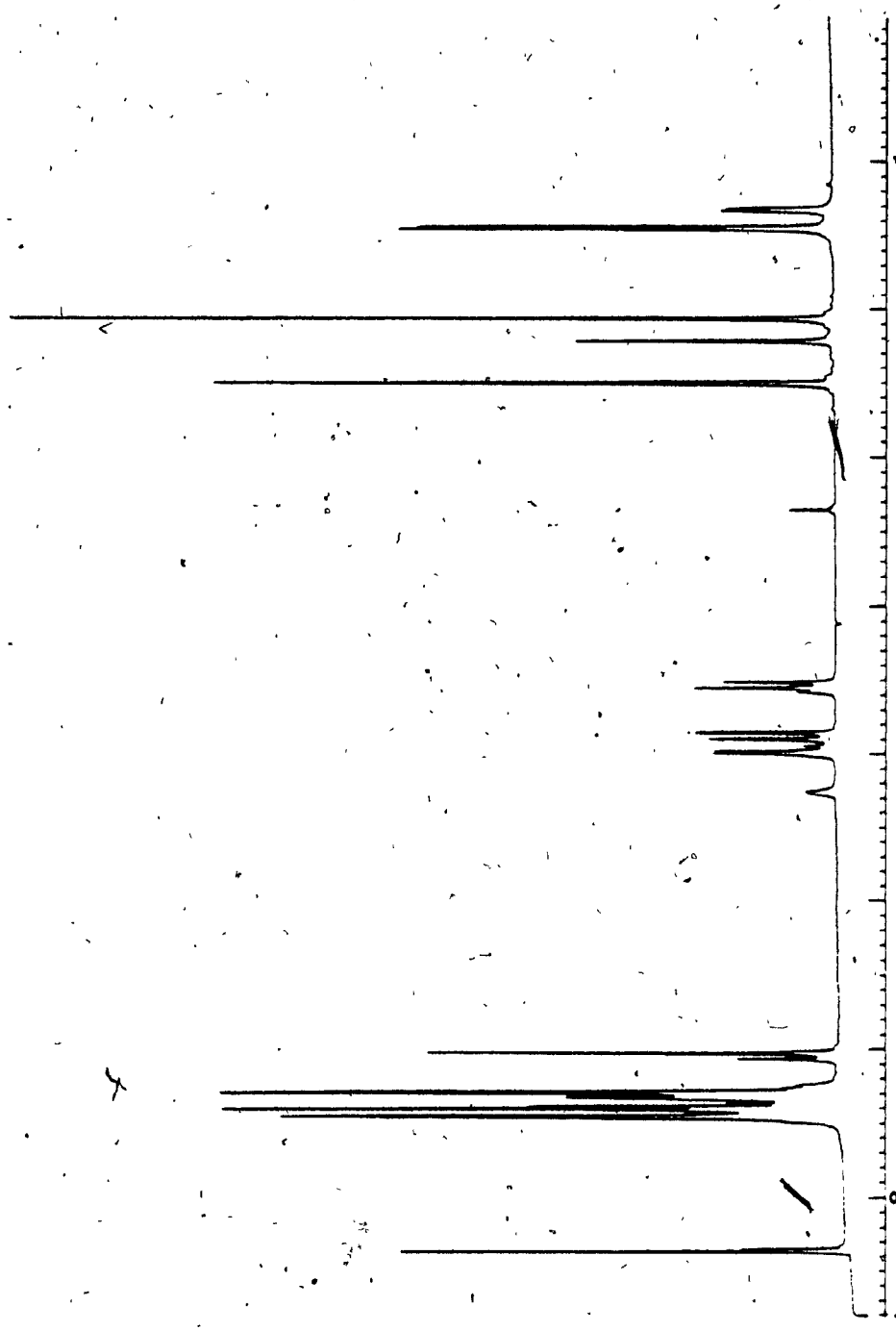


Figure 5.2 400 MHz proton NMR spectrum of 3(5'-methylphenyl)-1-benzyl-2,3-dihydro-4-(1H)-quinazolinone, 6.

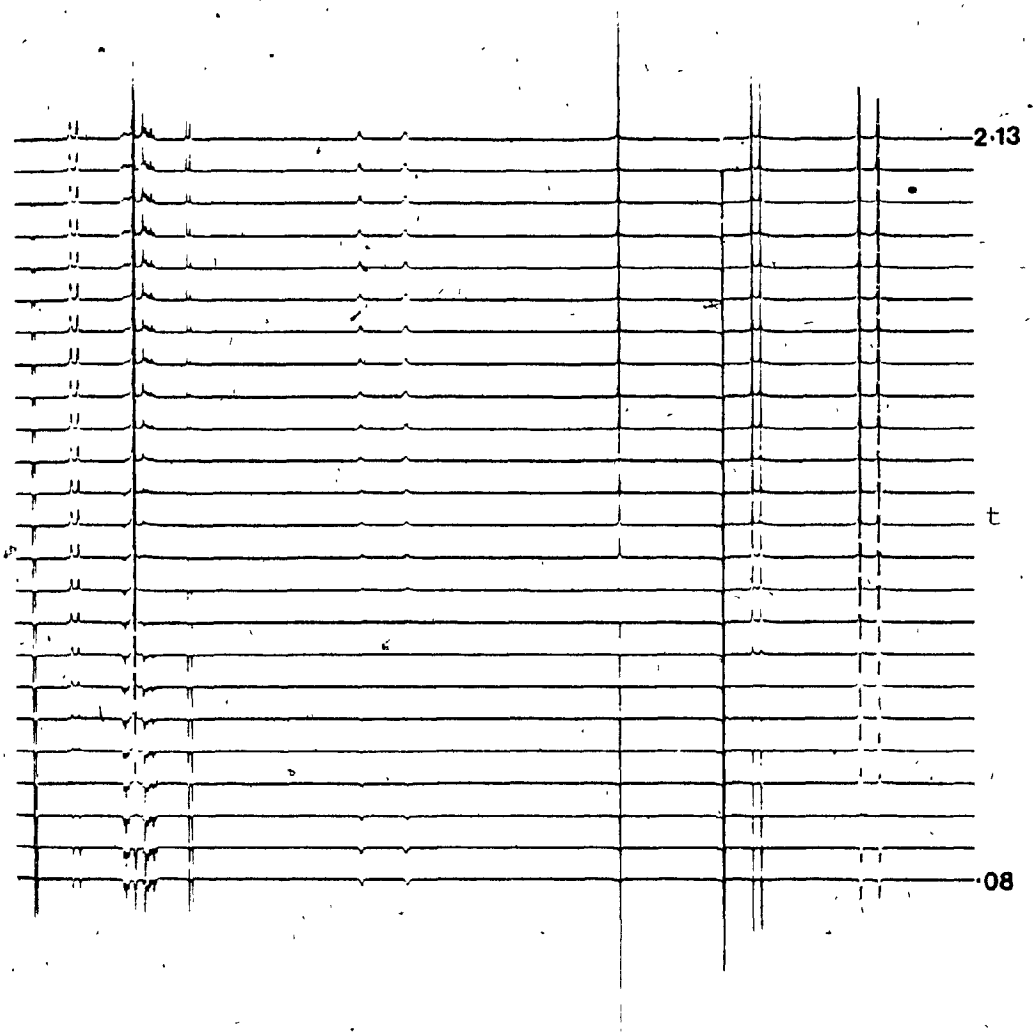


Figure 5.3 Stack plot displaying a selected series of partially relaxed spectra of compound 3, taken for various delay times, t, in the inversion recovery pulse sequence.

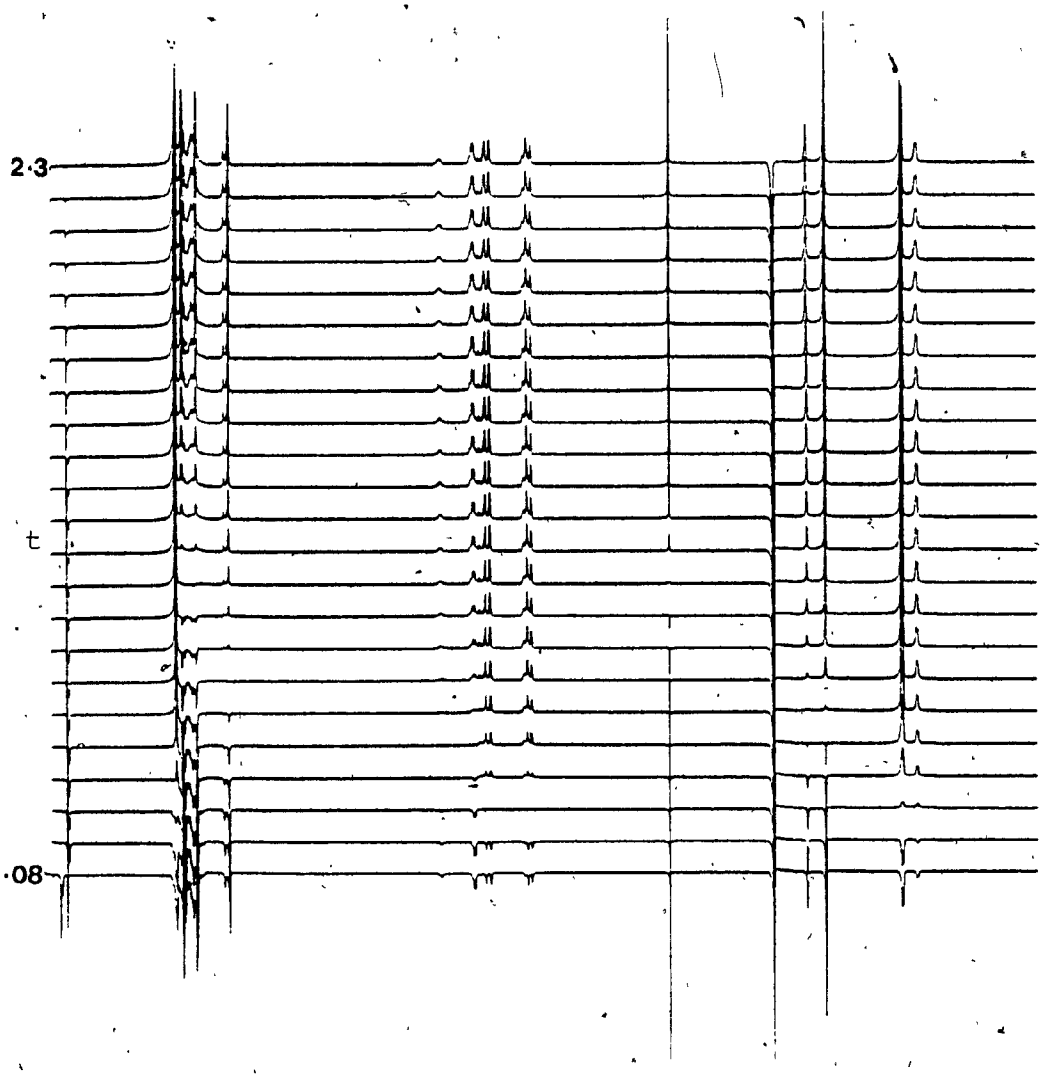


Figure 5.4 Stack plot displaying a selected series of partially relaxed spectra of compound 6, taken for various delay times, t, in the inversion recovery pulse sequence.

CHAPTER VI

INTRODUCTION

Heterocyclic compounds form some of the largest, and most important, subclasses of organic compounds. These include naturally occuring compounds, pharmacologically active compounds, and compounds of intrinsic theoretical interest. Heterocyclic compounds also play an important role in mediating many biological processes.

The genetic material DNA is heterocyclic, as are many useful alkaloids such as the anaesthetic cocaine, the insecticide nicotine, the antimalarial quinine, and the amoebicide emethine. The antibiotics penicillin and cephalosporin and a variety of vitamins, such as riboflavin and biotin, are heterocyclic.

A knowledge of heterocyclic chemistry, therefore, is important in areas of natural product chemistry, biosynthesis, and in studies of drug metabolism. A large number of coenzymes, vitamins, and drugs rely on heterocyclic reactivity for their actions. Therefore, the understanding of structures and reactivities of simple heterocyclic compounds, which are structural units of more important compounds like nucleic acids, can help to achieve an understanding of the mode of action of such compounds.

Purines and pyrimidines are heterocyclic systems which are important in the most basic biological processes of heredity and evolution. Pyrimidine is the parent heterocycle of a very important group of compounds such as nucleic acids and certain coenzymes, which have been studied for many years. Pyrimidine derivatives occur in living systems and some derivatives are found to have biological

activity. There are in addition to the above mentioned naturally occurring pyrimidine derivatives, many pyrimidines of synthetic origin that are widely used as therapeutic drugs, e.g. sulfonamide drugs and sulfadiazine drugs. Further, certain pyrimidines, purines, and related compounds are used as antibacterial and anticancer agents, and have various other physiological activities. Therefore, pyrimidines, pyrimidones and purines are important compounds in their own right as well as because of their role in nucleic acid chemistry.

Because small ring aliphatic compounds are reactive and there is a large number of drugs which are seen to owe their activity to the reactivity of small heterocyclic rings, a considerable amount of research has been done to deduce some relationship between the structure of a compound and its activity.

The study of ^{1}H spin-lattice relaxation rate studies of simple ring N-heterocyclic compounds reported in this thesis was undertaken in order to obtain information on their structures. It was expected that the information obtained would be valuable for structure determination purposes in future studies of compounds of similar type.

The direct N-alkylation of basic moieties of nucleic acids has been the subject of considerable chemical and biological interest in recent years. Such reactions may be not only useful from a synthetic point of view, but also relevant to the study of mutagenic and carcinogenic effects which occur in living systems, caused by alkylating agents. Hence, the correct assignments of N-alkyl groups of basic moieties of nucleic acids are very important.

Assignment of the structures of the mono-N methyl and di-N-methyl derivatives of uracil and pyrimidones was originally a non-trivial

problem whose solution required some time by chemical means. We were interested in finding out how readily this problem could be solved using ^1H spin-lattice relaxation rate measurements (R_1 values).

The unusually high relaxation rates observed for protons α-to an sp^2 hybridized nitrogen atom in 2- and 4-pyrimidones prompted us to continue these studies on similar types of compounds.

In the course of the research described in this thesis, proton spin-lattice relaxation measurement experiments were carried out for a series of uracil compounds, 2-pyrimidones, 4-pyrimidones, and some pyrimidine type bicyclic compounds. Most of these compounds were obtained from Dr O. S. Tee of this University, but some methyl substituted pyrimidones were synthesised according to the methods described in the literature.

Under suitable conditions, proton spin-lattice relaxation involves through space interactions between individual protons in the same molecule. Since the efficiency of these interactions decreases with distance, each proton receives most of its relaxation from its near neighbour protons. This property can be used as a possible way to determine the structure and conformation of the molecule.

The importance of nucleic acids rests in their role in storage and transmission of biological information. Expression of this information involves changes in structure at all levels, secondary, tertiary and quaternary. Consequently, any technique capable of providing detailed structural information, especially changes in structure, will play a significant role in our understanding of the biological function of these macromolecules.

In general, R_1 measurement data can provide information on

substituents, especially methyl groups , and steric effects on the motional correlation times of those substituents. In certain cases, this information i.e. R_1 values of methyl groups, can be used to correlate chemical shifts in a straight forward and unambiguous manner e.g. for 1,3-dimethyl uracil and 1,4-dimethyl-2-pyrimidone.

Further, R_1 measurements of these simple nitrogen heterocyclic compounds have been found to reflect the electronic structure and geometry of the ring nitrogen atoms to which protons are adjacent or attached. Therefore, these studies might be particularly useful as probes for the study of complex molecules such as proteins, DNA, and RNA.

RESULTS AND DISCUSSION

A) Uracils

TABLE 6.1

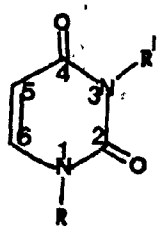
PROTON SPIN-LATTICE RELAXATION RATES ($R1\ sec^{-1}$) OF URACIL COMPOUNDS (determined by non-linear regression method)

No	R	R'	1-H	3-H	5-H	6-H	1-CH_3	3-CH_3
1a	H	H	1.03	0.87	0.54	0.81	-	-
1b	D	D	-	-	0.33	0.44	-	-
2a	CH_3	H	-	0.49	0.26	0.40	0.61	-
2b	CH_3	D	-	-	0.33	0.50	0.74	-
3a	H	CH_3	0.75	-	0.37	0.56	-	0.65
3b	D	CH_3	-	-	0.39	0.48	-	0.66
4	CH_3	CH_3	-	-	0.20	0.30	0.47	0.42

TABLE 6.2

PROTON SPIN-LATTICE RELAXATION RATES (normalized) OF URACIL COMPOUNDS

No	R	R'	1-H	3-H	5-H	6-H	1-CH_3	3-CH_3
1a	H	H	1.91	1.61	1.00	1.50	-	-
1b	D	D	-	-	1.00	1.33	-	-
2a	CH_3	H	-	0.80	0.43	0.66	1.00	-
2b	CH_3	D	-	-	0.45	0.68	1.00	-
3a	H	CH_3	1.15	-	0.57	0.86	-	1.00
3b	D	CH_3	-	-	0.59	0.73		1.00
4	CH_3	CH_3	-	-	0.43	0.64	1.00	0.89



I

Structural information on uracil compounds, I, R= R'= H, can be obtained from the relaxation rates of the ring protons, in particular that of H-6. This proton must be relaxed most efficiently (because of the $1/r^6$ distance dependence for dipole-dipole relaxation) by H-5 and protons located at N-1 (H or CH_3). H-6 relaxes about 50% faster than H-5 in non deuterated compounds (uracil, 50%, 1-methyl uracil, (2a), 53%, 3-methyl uracil, (3a), 51%, 1,3-dimethyl uracil, (4), 50%) (Table

6.2). There appears to be a small enhancement of the relaxation rate of H-6 when N (1)-H is replaced by a methyl group.

A clear cut distinction between the monomethyl compounds, 2a and 3a, can be made when the remaining N-H is replaced by deuterium (2a vs 2b). When the relaxation rates are normalized with respect to the methyl group rates (1.00), the R_1 value of H-5 and H-6 in the 1-methyl compounds (2a and 2b) are essentially unaffected by replacement of the relatively remote 3-H by deuterium (2a vs 2b). In contrast, while the R_1 value of H-6 is decreased by 15% when the neighbouring 1 position is deuterated (3a vs 3b) the R_1 value of H-5 remains unchanged (see Table 6.1 and 6.2).

As in the case of structural information, the chemical shift assignments of the methyl groups in dimethyl uracil can be obtained from the relaxation rates of the methyl groups. Since protons within methyl groups relax each other efficiently because of their close proximity, relaxation from other ring protons to the 1-CH_3 and 3-CH_3 groups is of minor importance, so that the major factor which influences methyl group relaxation is the rate of internal rotation about the three-fold axis (i.e. a Tc effect). The differences between 1- and 3-methyl group R_1 values are, therefore, attributed to steric influences on the barriers to internal rotation of the methyl groups.

In 1,3-dimethyl uracil, 4, the R_1 values for the two methyl groups differ by 11%. On the basis of steric interactions with adjacent substituents, it can be predicted that the 1-CH_3 group will have a preferred conformation compared to the 3-CH_3 group. Hence, the 3-CH_3 group may rotate freely compared to the 1-CH_3 group and so have a lower Tc value, which in turns leads to a smaller R_1 value. Therefore, the

slower relaxing methyl group can be assigned to 3-CH_3 and the faster to the 1-CH_3.

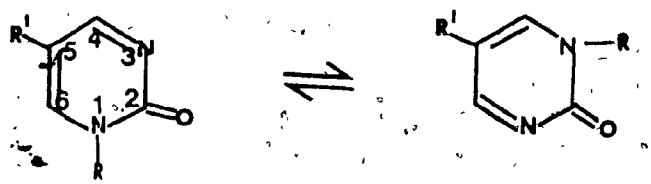
For all uracil compounds, the calculated relaxation rates agree with experimental values qualitatively. Because of the relative agreement of the experimental and the calculated R_1 values, it is clear that all protons in uracil compounds relax mainly by the intramolecular dipole-dipole mechanism.

B) 2-PYRIMIDONES

1. N-SUBSTITUTED PYRIMIDONES

In the study of proton spin-lattice relaxation rates of 2-pyrimidones, significantly elevated relaxation rates for the protons which are adjacent to sp^2 hybridized N, or sp^3 hybridized N which are influenced by chemical exchange, were observed. Experimental and calculated R_1 values (using a program which assumes isotropic motion and compares the relative inter-proton distances as measured in Dreiding models) of 2-pyrimidones do not agree qualitatively, indicating a contribution of a relaxation mechanism for the ring protons of 2-pyrimidones, in addition to the dipole-dipole relaxation mechanism. In the following discussion, the possibility of significant contributions from other intramolecular mechanisms has been explored.

Theoretically, in 2-pyrimidones, H-5 should be relaxed efficiently by H-6 and H-4. H-6 should be relaxed by H-5 and by protons located at N-1, whereas H-4 should be relaxed almost exclusively by H-5. In the first three compounds, 5-6, (Table 6.3) hydrogen exchange takes place between N-1 and N-3, making H-4 and H-6 symmetrically equivalent (Figure II and III). Hence both H-4 and H-6 have the same chemical shift and



II III

the same relaxation rate values.

If all the ring protons relax only by the dipole-dipole relaxation mechanism, H-5 should have the highest relaxation rate among all the ring protons. But experimentally 5-H has a smaller R_1 value than H-4 and H-6. This higher R_1 value for H-4 and H-6 (29%, 2-pyrimidone) could be due to scalar relaxation of the first kind which arises when chemical exchange occurs. When the remaining N-H is replaced by deuterium, i.e. compound 5b, the R_1 of H-5 remains unchanged (Table 6.3), confirming, as expected, that its significant relaxation pathways are due to H-4 and H-6. In contrast, the R_1 value of H-4 and H-6 has decreased by 22%, confirming that both H-4 and H-6 get some relaxation from the protons at the N-1 or N-3 position.

In 1-methyl-2-pyrimidone, 7a, and 1-ethyl-2-pyrimidone, 8a, no exchange can take place between N-1 and N-3. As in the above compounds, H-6 can get some relaxation from H-5 as well as from protons located at N-1 (CH_3 or C_2H_5). Similarly, H-5 has two neighbour protons to provide relaxation, hence, one can expect to have the highest R_1 value for H-5 as compared to other ring protons. But in both cases H-4, although it has only one neighbour proton, relaxes much faster than the other ring protons. Some relaxation rate enhancement could be due to scalar

relaxation of the second kind to the ^{14}N nucleus.

As explained before, the quadrupolar ^{14}N nucleus undergoes fast relaxation, providing a relaxation mechanism for the protons α to the N atom through the scalar relaxation mechanism. The quadrupolar N^{14} nucleus is itself relaxed primarily by the quadrupolar interaction. The quadrupolar relaxation time depends on Tc (rotational correlational time) and upon the quadrupolar coupling constant. Since, in mobile liquids the molecular correlational times are very small (10^{-11}-10^{-12} sec^{-1}), the relaxation rate is governed primarily by the magnitude of the quadrupolar coupling constant. The quadrupolar coupling constant, in turn, depends on the molecular symmetry. N-1 and N-3 have different geometries, and hence have different symmetries. Therefore, one can expect different R_1 values for H-4 and H-6 since they are adjacent to two different nitrogen atoms with different geometries. H-4 is adjacent to an sp^2 nitrogen atom (N-3) and has a higher R_1 value than H-6 which is adjacent to an sp^3 nitrogen (N-1).

When the methyl protons are replaced by deuterium (1-deuteromethyl 2-pyrimidone), the R_1 value of H-6 decreases by 28.5%, confirming that H-6 gets some relaxation from the N-methyl group at the 1-position. But surprisingly, the R_1 of H-4 is increased by 10%. Similarly, in 1-deuteroethyl-2-pyrimidone, the R_1 value of H-6 has decreased by 22% compared to the R_1 value of H-6 of the nondeuterated compound, 8a. In contrast, the R_1 of H-4 has increased by 14.5%. Theoretically, there should not be any change in R_1 values of H-4 in either deuterated 1-alkyl-2-pyrimidone. The significant increment of experimental R_1 values of H-4 in both deuterated 1-alkyl-2-pyrimidones is very unusual.

TABLE 6.3

PROTON SPIN-LATTICE RELAXATION RATES ($R1\ sec^{-1}$) OF 2-PYRIMIDONES

(determined by non-linear regression method).

No	R	R'	1-H	4-H	5-H	6-H	CH_3	CH_2
5a	H	H	1.14	0.40	0.31	0.40	-	-
5b	D	H	-	0.33	0.31	0.33	-	-
6	H	D	0.53	1.15	-	1.15	-	-
7a	CH_3	H	-	0.32	0.21	0.25	0.38	-
7b	CD_3	H	-	0.50	0.28	0.24	-	-
8a	Et	H	-	2.33	0.48	0.58	0.71	0.80
8b	DEt	H	-	2.29	0.46	0.44	-	-

TABLE 6.4

PROTON SPIN LATTICE RELAXATION RATES (normalized)

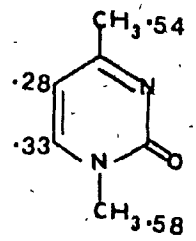
OF 2-PYRIMIDONES

No	R	R'	1-H	4-H	5-H	6-H	CH_3	CH_2
5a	H	H	3.68	1.29	1.00	1.29	-	-
5b	D	H	-	1.01	1.00	1.01	-	-
7a	CH_3	H	-	1.52	1.00	1.19	1.80	-
7b	CD_3	H	-	1.78	1.00	0.85	-	-
8a	Et	H	-	4.95	1.00	1.23	1.51	2.66
8b	D-Et	H	-	5.67	1.00	0.96	-	-

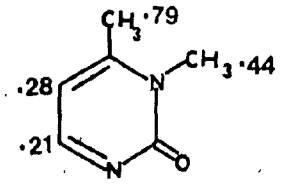
2. 4-SUBSTITUTED 2-PYRIMIDONES

In the study of the proton spin-lattice relaxation rates of 4-substituted 2-pyrimidones, substantial differential rates in methyl group R_1 values were observed. These differences are attributed to differences in Tc values of the methyl groups. Further, the R_1 measurements of these compounds lead to an unambiguous assignment of 1- and 4-methyl groups in 1,4-dimethyl-2-pyrimidone.

In most cases, methyl protons will relax each other very efficiently, thus differences in R_1 values of methyl groups reflect differences in their respective Tc values rather than relaxation contributions from neighbouring protons. Rotational correlation times (Tc values) of methyl groups are a reflection of the steric environments of these groups. Therefore, for different methyl groups in a single molecule, the differences in R_1 values, hence, Tc values, are a reflection of their steric environments. This is clearly evident in the R_1 values of 1,4- and 3,4-dimethyl-2-pyrimidones (IV and V).



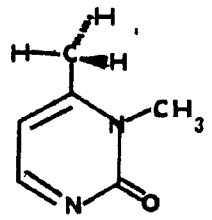
IV



V

In 3,4-dimethyl-2-pyrimidone, V, even though H-6 is adjacent to an sp^2 hybridized N atom (C=N), 6-H relaxes slower (25%) than H-5 because 5-H can get some relaxation from the 4-CH_3 group. Further, the 4-CH_3 group would have a preferred conformation to minimize steric

interference from the adjacent 3-methyl group. Hence the 4-methyl protons can be oriented more towards the 5-H as shown in the diagram below, VI.



VI

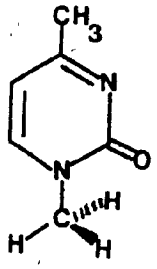
Therefore 5-H can pickup some relaxation from the 4-methyl protons in addition to H-6.

Here the 4-methyl group relaxes much faster than the 3-methyl group. The 3-methyl group does not have any preferred conformation because it experiences steric interference from both sides. Hence it will rotate more freely (i.e. have a low Tc value), and have a lower R_1 value. As mentioned before, the 4-methyl group might have a preferred conformation compared to the 3-methyl group because of steric interference from the 3-methyl group, thereby hindering its rotation and leading to a smaller T_1, and higher R_1 value.

Similarly, in 1,4-dimethyl-2-pyrimidone, IV, the 4-CH_3 group relaxes slower than the 1-CH_3 group for steric reasons. The presence of a 2-carbonyl group results in a preferred conformation for the 1-CH_3 group compared to the 4-CH_3 group, thus increasing the barrier for free rotation, which leads to a marked decrease in the T_1 or a marked increase in the R_1 value for the 1-CH_3 group.

It is interesting to note that, in 1,4-dimethyl-2-pyrimidone, the 6-H proton relaxes 17% faster than the 5-H proton. Both 5-H and 6-H

have one neighbour proton and a methyl group to provide relaxation. 1-CH_3 group might have a preferred conformation compared to the 4-methyl group to minimize steric interference from the 2-carbonyl group. Therefore, in the preferred conformation, 1-CH_3 protons can be locked in such a way that they are closer to the 6-H ring proton than the carbonyl group as shown in the diagram below, VII. Hence, 6-H can get much of its relaxation from the 1-methyl protons as well as from the neighbour 5-H. Thus, one can expect higher relaxation rate for the 6-H compared to 5-H.



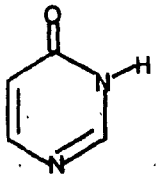
VII

In contrast, the 4-CH_3 group would not have a preferred conformation because it does not experience steric interference from either side. Therefore 5-H will not get much relaxation from the 4-methyl protons as will 6-H from the 1-methyl group. Therefore, it is clear that a distinction between the 1-methyl and 3-methyl groups of substituted 2-pyrimidones can be made from their R_1 values.

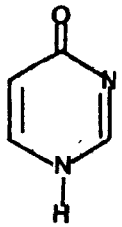
C) 4-PYRIMIDONES

As in the case of the 2-pyrimidones, the 4-pyrimidones, which also have some protons which are α-to sp^2 hybridized nitrogen or attached to an sp^3-hybridized N atom which is affected by chemical exchange, showed unusually high relaxation rates. As in the 2-pyrimidones, these high

R_1 values can be attributed to scalar coupling relaxation of the first kind or the second kind with the ^{14}N quadrupolar nucleus.



VII



VIII

In the first two cases (9a and 9b), hydrogen exchange takes place between N1 and N3 to give two tautomeric structures, VII and VIII. These two tautomeric structures are not identical, hence all the ring protons have different chemical shifts and different R_1 values. Under the experimental conditions, only the spectrum due to one tautomeric structure or a time averaged spectrum, has been observed.

In the 4-pyrimidones, 2-H which is adjacent to an sp^2 hybridized nitrogen atom (i.e. N1 or N3) can get dipolar relaxation only from the protons at N-1 or N-3 (H or CH_3). 6-H has a 5-H neighbour as well as protons at N-1 (because of the exchange process) to provide relaxation. In contrast, 5-H has only its neighbour 6-H to provide relaxation.

Results show (Table 6.5) that, in all cases, 2-H has the highest relaxation rate compared to the R_1 values of other ring protons, though it has only neighbouring protons at N-1 or N-3. These higher relaxation rates may be due, at least in part, to scalar relaxation of the second kind, which arises from the sp^2 hybridized nitrogen atom.

During the exchange process, a proton can be at the N-1 position for a short period of time or at the N-3 position (VII and VIII).

Therefore 6-H can get relaxation from the proton at the N-1 position in addition to its neighbour, 5-H. Hence it is reasonable to expect a higher relaxation rate for the 6-H compared to 5-H. Experimental R_1 values for 4-pyrimidone show that this is indeed the case.

After replacing N-H by deuterium, 9b, the relaxation rates of both 2-H and 6-H have decreased (2-H, 48%, 6-H, 40%), confirming that both of them get some relaxation from the protons at N-1 or N-3.

The other important thing to note with the R_1 values of D-4-pyrimidone, is the slightly higher R_1 value for 6-H compared to 5-H. If the only sources of relaxation for 6-H in 4-pyrimidone were from the neighbouring 5-H and the proton at the N-1 or N-3 position, when N-H is replaced by deuterium one could expect almost the same R_1 value for both 5- and 6-H. Experimental R_1 values show that this is not the case.

Theoretically, 6-H might be a very likely candidate to experience scalar relaxation of the first kind which arises due to the exchange process. As explained before, 1-H, which is attached to an sp^3 hybridized nitrogen atom (N-1) can undergo a hydrogen exchange process with N-3, making 6-H susceptible to scalar coupling relaxation of the first kind. This could be another reason for seeing a higher R_1 value for 6-H.

5-H has only one neighbouring proton (i.e 6-H) all the time and does not experience any direct effect from the exchange process. Therefore, it is expected to have small R_1 values compared to other ring protons.

In 3-methyl-4-pyrimidone, 2-H relaxes faster than the other ring protons. In addition to scalar coupling relaxation of the second kind, 2-H can also get some relaxation from the 3-CH_3 protons. Therefore, 2-H

should have a higher relaxation rate compared to other ring protons. Both 5-H and 6-H have one neighbouring proton each to provide relaxation pathways. The faster relaxation rate of 6-H than 5-H may be due to a contribution to 6-H from the quadrupolar nitrogen nucleus.

In 1-CH_3-4-pyrimidone (bromide salt), 11, as with the other 4-pyrimidones, 2-H relaxes much faster than the other ring protons, probably due to the proton at N-3 as well as the methyl protons at the N-1 position. 6-H relaxes faster than 5-H because of the 1-CH_3 group. 5-H has the smallest R_1, as expected.

TABLE 6.5

PROTON SPIN LATTICE RELAXATION RATES (R1 sec^{-1}) OF 4-PYRIMIDONES (determined by non-linear regression method).

No	R	R'	2-H	N-H	5 H	6-H	N-CH_3
9a	-	H	0.61	0.78	0.25	0.51	-
			(2.44)	(3.12)	(1.00)	(2.04)	-
9b	-	D	0.26	-	0.20	0.23	-
			(1.30)	-	(1.00)	1.15)	-
10	-	CH_3	0.26	-	0.16	0.23	0.41
			(1.63)	-	(1.00)	(1.44)	(2.56)
11	CH_3	H	1.58	-	0.54	0.88	1.52
			(2.93)	-	(1.00)	(1.63)	(2.81)

( ) normalized R_1 values.

SOLVENT EFFECT

The quadrupolar relaxation time of the ^{14}N nucleus can be expressed

by,

$$T_q^{-1} = \frac{3}{8}\left(\frac{e^2qQ}{h}\right)^2 t_q \qquad (2.5)$$

e^2qQ/h = quadrupolar coupling constant

t_q = molecular correlation time.

In the simplified case of the rotation of a sphere of radius a in a medium of viscosity η one has:

$$t_q = \frac{4\pi\eta a^3}{3KT} \qquad (2.6)$$

K = Boltzmann's constant

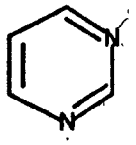
T = absolute temperature

According to equation 2.5 and 2.6, the quadrupolar relaxation time of the ^{14}N nucleus (Tq) depends on the viscosity of the solvent. For example, in a highly viscous solvent, rotational correlation time increases, while Tq (quadrupolar relaxation time) decreases, so that quadrupolar relaxation becomes more effective. Therefore, one could expect, in DMSO-d_6 solvent, scalar coupling relaxation due to a ^{14}N nucleus to be more effective than in acetone-d_6 (a less viscous solvent).

Pyrimidine has two identical resonance structures, IX and X, which make 4- and 6-H chemically equivalent. Therefore, 4- and 6-H have same chemical shifts and same R_1 values.

In both resonance structures, 2-H is adjacent to a C=N bond of bond order 2 compared to 4- and 6-H.

As has been seen with the R_1 values of 2-pyrimidones and 4-pyrimidones, enhanced relaxation rates possibly attributable to scalar



IX

X

relaxation of the second kind were observed for the R_1 values of α-protons to sp^2 hybridized nitrogen atoms in pyrimidine.

According to the scalar coupling relaxation mechanism, it is reasonable to expect higher R_1 values for three protons in pyrimidine (i.e. 2-, 4-, and 6-H) than for 5-H which has only two neighbouring protons to provide relaxation. But 2-H in pyrimidine has much higher relaxation rate compared to 4- and 6-H. This is expected, since all the time 2-H is adjacent to an sp^2 hybridized nitrogen through a C=N bond.

As in the cases of 2-, 4-, and 6-H in pyrimidine, a higher relaxation rate for the 2-H in 3-methyl-4-pyrimidone can be due to scalar relaxation of the second kind. In addition, 2-H can also get some of its relaxation from the 3-methyl protons in the pyrimidone.

Results in Table 6.6 show that in both pyrimidine and $3\text{-}CH_3\text{-}4$-pyrimidone, ring protons have considerably higher R_1 values in DMSO-d_6 than in acetone-d_6. Furthermore, the difference of R_1 values between 2-H and 6-H's in both cases is much more striking in the dimethylsulfoxide-d_6 data (Table 6.6) than in the acetone-d_6 data.

According to equations 2.5 and 2.6, scalar relaxation due to the quadrupolar ^{14}N nucleus can be more effective in highly viscous solvents than in less viscous solvents. The experimental results support the

existence of scalar coupling relaxation of the second kind from the quadrupolar ^{14}N nucleus for pyrimidine and pyrimidone type compounds.

TABLE 6.6

PROTON SPIN-LATTICE RELAXATION RATES OF PYRIMIDINE AND 3-METHYL 4-PYRIMIDONE IN DIFFERENT SOLVENTS (determined by non-linear regression method).

SOLVENT	2-H	4-H	5-H	6-H	3-CH_3
DMSO-d_6	0.54	0.34	0.13	0.34	-
	(4.15)	(2.62)	(1.00)	(2.62)	-
ACETONE-d_6	0.13	0.12	0.12	0.12	-
	(1.02)	(0.98)	(1.00)	(0.98)	-
DMSO-d_6	0.26	-	0.16	0.23	0.41
	(1.63)		(1.00)	(1.44)	(2.56)
ACETONE-d_6	0.16	-	0.15	0.16	0.22
	(1.06)		(1.00)	(1.06)	(1.49)

( ) normalized R_1 value

CONCLUSION

The study of ^1H R_1 measurements of pyrimidones has demonstrated two important factors. One is that scalar relaxation of the first kind becomes dominant over the dipole-dipole relaxation in compounds where exchange takes place, as in 2-pyrimidone, D-2-pyrimidone, 4-pyrimidone and D-4-pyrimidone. Secondly, even in non exchanging systems, scalar relaxation of the second kind may play a part in the relaxation

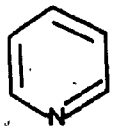
of protons which are adjacent to sp^2 hybridized nitrogen atoms. Further, in certain cases $^1H\ R_1$ values may be used to correlate chemical shifts in a straight forward and unambiguous manner e. g. for 1,3-dimethyl-uracil and 1,3-dimethyl-2-pyrimidone.

The study of $^1H\ R_1$ measurements in different solvents supports the existence of scalar coupling relaxation due to the quadrupolar ^{14}N nucleus for simple pyrimidone and pyrimidine type nitrogen heterocyclic compounds.

MISCELLANEOUS COMPOUNDS

As in the case of the pyrimidones, the effect of an additional relaxation mechanism associated with the ^{14}N quadrupolar nucleus has been seen on the proton spin-lattice relaxation rates of pyridine and some related bicyclic heterocyclic compounds.

In pyridine, XI, the three protons 3-, 4-, and 5-H have two neighbouring protons each, whereas 2 and 6-H have only one neighbouring proton as a source of relaxation. If all the protons relaxed only by the intramolecular dipole-dipole relaxation mechanism, one would expect 3-, 4-, and 5-H to have the same R_1 value, higher than that of 2- and 6-H. However this is found not to be the case. 2-H and 6-H relax much faster than the other ring protons. These high relaxation rates for 2-, and 6-H, which are α-to sp^2 hybridized nitrogen, may be attributable to scalar coupling relaxation of the second kind with the ^{14}N quadrupolar nucleus.



XI

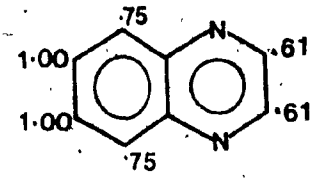
Quinoxaline

In quinoxaline, XII, both 2-, and 3-H are α-hydrogens to sp^2 hybridized nitrogen atoms and have one neighbour each as a source of relaxation. Hence they can relax each other efficiently by the dipole-dipole relaxation mechanism and may also be influenced by scalar coupling relaxation of the second kind with the ^{14}N nucleus. Therefore, one can expect them to have higher relaxation rates compared to other ring protons. But experimentally 2-, and 3-H relax slower than all other ring protons.

According to experimental results, 5- and 8-H, which have one close neighbour and a meta proton each as a source of relaxation, relax faster than 2- and 3-H. The small R_1 values for 2- and 3-H suggest that the less significant scalar coupling relaxation of the second kind may be due to small quadrupolar coupling constants resulting from different geometries of the quadrupolar nitrogen nuclei. Since both 6- and 7-H have two neighbours each as source of relaxation, they have higher R_1 values compared to other ring protons in quinoxaline, as expected.

Quinoline

2-H in quinoline, XIII, is the α-proton to the sp^2 hybridized nitrogen atom, and has one neighbouring proton as a source of

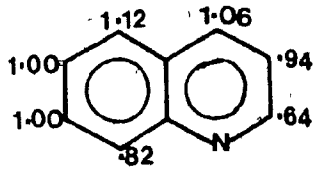


XII

relaxation. 3-H has two neighbouring protons whereas 4-H has one close neighbour and a proton from the carboxylic ring as source of relaxation. If the relaxation of 2-H involves a significant contribution from scalar coupling relaxation of the second kind in addition to dipole-dipole relaxation from its neighbour, one can expect the highest R_1 value for 2-H compared to other protons on the heterocyclic ring. But experimentally it has the smallest R_1 value. This could be due to the effect of a small quadrupolar coupling constant to the ^{14}N quadrupolar nucleus. Scalar coupling relaxation of the second kind is very dependent on the quadrupolar coupling constant.

Both 4- and 3-H in quinoline have the same number of neighbouring protons as sources of relaxation. If the two rings of quinoline molecule are planar, the distance between peri hydrogens and the adjacent hydrogens should be almost the same. Therefore, it might be expected that 3-H and 4-H would relax at almost the same rate. But experimentally 4-H relaxes somewhat faster than 3-H. Both 3- and 4-H are not α-hydrogens to sp^2 or sp^3 hybridized nitrogen atom. Therefore these protons should relax exclusively via dipole- dipole relaxation mechanism. Because the efficiency of dipole-dipole relaxation depends on the distance, higher R_1 value for 4-H may be due to the short distance between peri hydrogen atoms compared to the distance between the adjacent hydrogen atoms.

Further, 5-H relaxes some what faster than 6-H even though both have same number of neighbouring protons as source of relaxation, confirming that 5-H get more relaxation from its neighbour peri hydrogen (4-H). This also suggests the idea of small distance between peri hydrogens compared to distances between adjacent ring hydrogens.



XIII

6- and 7-H have two neighbours each to provide relaxation. Therefore, they should have the same relaxation rates. Experimental results show that this is, indeed, the case.

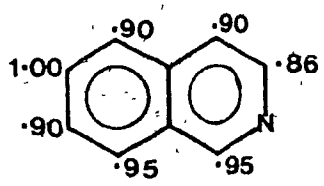
Isoquinoline

In isoquinoline, XIV, 4-H has one neighbouring proton from the carboxylic ring in addition to its immediate neighbour, 3-H, to provide relaxation. 1- and 3-H are α-protons to sp^2 hybridized nitrogen, and both of them have one neighbour each to get relaxation.

In a planar bicyclic compound, the distances between peri hydrogens are almost the same as the distance between adjacent protons on the ring. Therefore, if the isoquinoline ring system is planar it is reasonable to expect similar relaxation rates for 3- and 1-H. But experimentally 1-H relaxes somewhat faster than 3-H. There are two possible reasons for having higher relaxation rate for 1-H compared to 3-H.

One reason could be the scalar coupling relaxation of the second kind of the sp^2 hybridized ^{14}N quadrupolar nucleus. As we noticed in the case of pyrimidones and pyrimidine, protons α-to sp^2 hybridized nitrogen atoms relax much faster than the protons which relax exclusively via the dipole- dipole relaxation mechanism. If the scalar relaxation of the second kind is the reason for the higher R_1 value of 1-H, the same effect could have been observed for 3-H also. Since this is not the case, scalar relaxation of the second kind would not be the reason for the higher R_1 value of 1-H.

The relative insignificance of scalar coupling relaxation of the second kind for 1- and 3-H in isoquinoline suggests that the quadrupolar coupling constants are small.



XIV

If all the heterocyclic ring protons in isoquinoline relaxed only by the dipole-dipole relaxation mechanism, one should expect 3- and 1-H to have the same R_1 values. However this was found not to be the case. This suggests that relaxation between peri-related protons is more efficient than between vicinal protons.

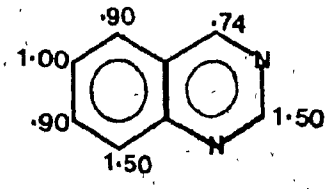
5-H and 8-H in the aromatic ring have the same number of neighbouring protons to provide relaxation. Therefore one could expect the same R_1 value for both. But experimentally 8-H relaxes slightly faster, confirming that 8-H gets much of its relaxation from the peri

hydrogen (1-H).

Quinazoline

Both 2-, and 4-H in quinazoline, XV, are α-protons to sp^2 hybridized nitrogen atoms. In addition, 2-H is located between two sp^2 hybridized nitrogen atoms. If these protons relax with a significant contribution from scalar coupling relaxation of the second kind, one should expect 2-H to relax much faster than 4-H.

Further, 4-H can also get some extra relaxation from its neighbouring peri proton (5-H). Therefore one could also expect a slightly higher dipolar R_1 value for 4-H than 2-H. However, a higher relaxation rate for 2-H is observed.



XV

Both 5- and 8-H have the same number of neighbouring protons on the homocylic ring to provide relaxation. In addition, 5-H has one more proton from the homocylic ring as a source of relaxation. Therefore, 5-H should relax faster than 8-H. Surprisingly, 8-H relaxes faster than 5-H, possibly due to some contribution to 8-H from the quadrupolar ^{14}N nucleus. Both 7-H and 5-H have two close neighbours, and both have the same R_1 value. As in isoquinoline, these two protons are tightly coupled, thus the measured R_1 values are only averages.

Conclusion

Interpretation of the R_1 values of the pyridine and pyrimidine-type bicyclic heterocyclic compounds has been based on the assumption that relaxation proceeds only via intramolecular mechanisms. In order to account for the enhanced relaxation rates of protons α-to nitrogen atoms, it has been necessary to invoke significant contributions from scalar coupling of the second kind. A difficulty with this interpretation is that contributions from this mechanism are expected to be small because of the large difference between the Larmor frequencies of ^{1}H and ^{14}N. The possibility, therefore, that an as yet unaccounted for mechanism contributes must be considered.

The most likely candidate would appear to be contribution from paramagnetic ions specifically coordinated to nitrogen. Although the compounds used in this study were subjected to normal purification procedures and the glassware was cleaned under normal conditions, some contamination may have been present.

It is strongly recommended, therefore, that some of these experiments be repeated following rigorous purification and cleaning procedures.

SELECTIVE PULSE EXPERIMENTS

Protons in pyrimidones, pyrimidine and similar types of bicyclic compounds which are α-to sp^2 hybridized nitrogen atoms or adjacent to sp^3 hybridized nitrogen atoms which are influenced by chemical exchange, have unusually high R_1 values. These high R_1 values have been attributed to scalar coupling of the second kind or first kind with the quadrupolar ^{14}N nucleus.

The selective relaxation rate of a particular proton can be determined simply by using a highly selective 180° pulse for the proton of interest, and then monitoring the recovery rate of that proton using the usual non-selective 90° pulse. This relaxation rate is different from the non-selective value because cross relaxation to the (unperturbed) spins in the system has been effectively shut off. If it is correct to assume that the only relaxation interactions are 100% dipolar the following ratio for a pseudo first order spin system would be observed:

$$\frac{R_1^{\,i}\,(ns)}{R_1^{\,i}\,(s)} = 1.5 \qquad (2.16)$$

where $R_1(ns)$ is the relaxation rate following non-selective excitation, and $R_1(s)$ is the corresponding rate following (single) selective excitation.

Equation 2.16 then embodies the criterion used to define the extent to which a particular proton relaxes via the dipole-dipole mechanism. It is this quality control experiment which confers a major advantage to the relaxation method over the NOE method. The equivalent quality control experiment for the latter would require all but the receptor

resonance to be saturated.

It has been assumed that molecules tumble in the extreme narrowing region ($w_o^2 t_c^2 << 1$) in which case the measurement of spin-lattice relaxation parameters is independent of the observing frequency of the spectrometer. Under this condition it has been shown that for completely dipolar interactions in homonuclear spin systems $R_1(ns)/R_1(s) = 1.5$ (equation 2.16). This is no longer true if the extreme narrowing condition is not satisfied. It is further assumed that the relaxation mechanism is entirely intra- molecular dipolar. Thus for a proton spin system the ratio of R_1 values for non-selective and selective pulse experiments is also a measure of the effectiveness of interproton dipolar interaction. Therefore, theory states that if a particular proton relaxes exclusively via the intramolecular dipole-dipole relaxation mechanism, the ratio given in 2.16 should be 1.5[48,54]. If none of the relaxation comes from this mechanism then the ratio would be unity.

The contribution of non-dipolar mechanisms such as scalar coupling relaxation of the first and second kind due to the ^{14}N nucleus for some of the ring protons in simple nitrogen heterocyclic compounds can be identified from selective pulse experiments.

In parallel to the non-selective relaxation measurement experiments, selective R_1 values of all the ring protons of pyrimidine, 2-pyrimidone 3-methyl-4-pyrimidone and 4-pyrimidone were determined using the standard two pulse[55] (180^o-t-90^o-pd) sequence.

The set of spectra shown in Figure 6.2 illustrate a typical non-selective relaxation experiment using a two pulse sequence. The motion of the nuclear magnetization of each proton can be progressively

followed as one proceeds from spectrum A--->S. The spectra given in Figure 6.3 are typical of a single selective inversion recovery experiment. As the motion of the selectively perturbed spin is followed through the partially relaxed spectra, it is seen that the selectively inverted magnetization relaxes very slowly compared to the non-selective experiment.

One of the other experiments one could perform to confirm that some of the ring protons in simple nitrogen heterocyclic compounds relax by mechanism in addition to the intramolecular dipolar-dipolar mechanism, is the Nuclear Overhauser experiment. The Nuclear Overhauser effect is intimately related to relaxation processes. The NOE specifies a variation in the signal intensity of spins I produced when the resonances of other spins, S, which interact with I through relaxation, are saturated by means of a complementary rf field. Since the Overhauser factors are controlled by dipolar mechanisms they also vary with the inverse sixth power of internuclear distances.

RESULTS AND DISCUSSION

It was shown in chapter 2, equation 2.16, that the ratio of nonselective and selective R_1 values for proton i should be 1.5 if all of the relaxation of spin i arises via dipole-dipole interaction with the other spins which are influenced by the non-selective pulse.

The ratios of $R_1(ns)/R_1(s)$ for H-5 in all the compounds (Table 6.7) range from 1.48-1.51, showing that this resonance relaxes exclusively via dipole-dipole interaction. This is expected because H-5 is not adjacent to an sp^2 hybridized or sp^3 hybridized nitrogen atom in any of

these compounds. Therefore, it can relax only via the dipole-dipole relaxation mechanism from its neighbour protons.

Although this ratio strictly includes both inter and intramolecular contributions, it seems reasonable to assume that, under the condition which pertain here, intermolecular interactions are negligible.

The ratios of $R_1(ns)/R_1(s)$ for H-2 in all three compounds except 2-pyrimidone, range from 1.00-1.15. This indicate that this proton does not relax exclusively by the intramolecular dipole-dipole relaxation mechanism, but also by some extra relaxation mechanism. As suggested before, this extra relaxation mechanism could be scalar coupling relaxation of the first or second kind due to the ^{14}N quadrupolar nucleus.

The 2-H protons in both pyrimidine and 3-methyl-4-pyrimidone are α to sp^2-hybridized nitrogen atoms. In addition, 2-H in 4-pyrimidone is α-to an sp^3-hybridized nitrogen atom which is influenced by proton exchange. Therefore, it is expected that 2-H in all three compounds may relax with contributions from a non-dipolar relaxation mechanism e.g. scalar coupling relaxation.

In pyrimidine and 2-pyrimidone, 4-, and 6-H are chemically equivalent and have the same R_1 values, and hence the same ratio of $R_1(ns)/R_1(s)$. 4- and 6-H in pyrimidine have a ratio of 1.36, indicating that these protons get some relaxation from some other mechanism in addition to intramolecular dipole-dipole relaxation mechanism. This is consistent with their location α-to an sp^2-hybridized nitrogen atom.

Similarly, in 2-pyrimidone, H-4 and H-6, which experience the effect of chemical exchange taking place between protons on the two nitrogen atoms have a $R_1(ns)/R_1(s)$ ratio of 1.00, confirming that these

protons relax mostly by scalar coupling relaxation of first kind, as expected.

H-6 in 4-pyrimidone is α-to an sp^2-hybridized nitrogen atom. In addition, it experiences the effect of chemical exchange process of 1-H between N1 and N3. Therefore, H-6 can also be a potential candidate to experience scalar coupling relaxation of the first kind. The ratio of $R_1(ns)/R_1(s)$ for H-6 is 1.10, again confirming that it relaxes mostly by a non-dipole-dipole relaxation mechanism. In contrast to H-6 in 4-pyrimidone, H-6 in 3-methyl-4-pyrimidone has a ratio of 1.45, showing that it relaxes mainly by the dipole-dipole relaxation mechanism.

NOE difference experiments for pyrimidine showed that irradiation of 2-H, which is α-to sp^2-hybridized nitrogen, caused no observable enhancement of the other proton signals, indicating that 2-H relaxes exclusively by scalar coupling relaxation of the second kind to the ^{14}N quadrupolar nucleus. But an irradiation of 5-H, significant enhancements of the 4-, and 6-H proton signals were observed, confirming that 5-H relaxes primarily or exclusively by the dipole-dipole relaxation mechanism. Irradiation of the 4-, and 6-H transitions produced the expected small enhancement of the 5-H signal, confirming that these protons get some relaxation from 5-H via the dipole-dipole mechanism in addition to other mechanisms.

TABLE 6.7

NON SELECTIVE AND SELECTIVE SPIN-LATTICE RELAXATION RATES OF SOME COMPOUNDS IN DMSO-d6 SOLUTION (degassed)

Compound	Experiment	Relaxation rate (sec^{-1}) values			
		2-H	4-H	5-H	6-H
2-Pyrimidone	Non-selective		.203	.184	.203
	Selective		.184	.124	.184
	Ratio 1/2		1.10	1.48	1.10
Pyrimidine	Non-selective	.601	.385	.136	.385
	Selective	.572	.283	.091	.283
	Ratio 1/2	1.05	1.36	1.50	1.36
4-Pyrimidone	Non-selective	.380		.125	.350
	Selective	.377		.083	.318
	Ratio 1/2	1.00		1.51	1.10
3-Methyl-4-	Non-selective	.126	-	.071	.074
pyrimidone	Selective	.109		.048	.051
	Ratio 1/2	1.15		1.48	1.45

Conclusion

Selective pulse experiments provide evidence for the contribution of mechanisms in addition to the intramolecular dipole-dipole mechanism.

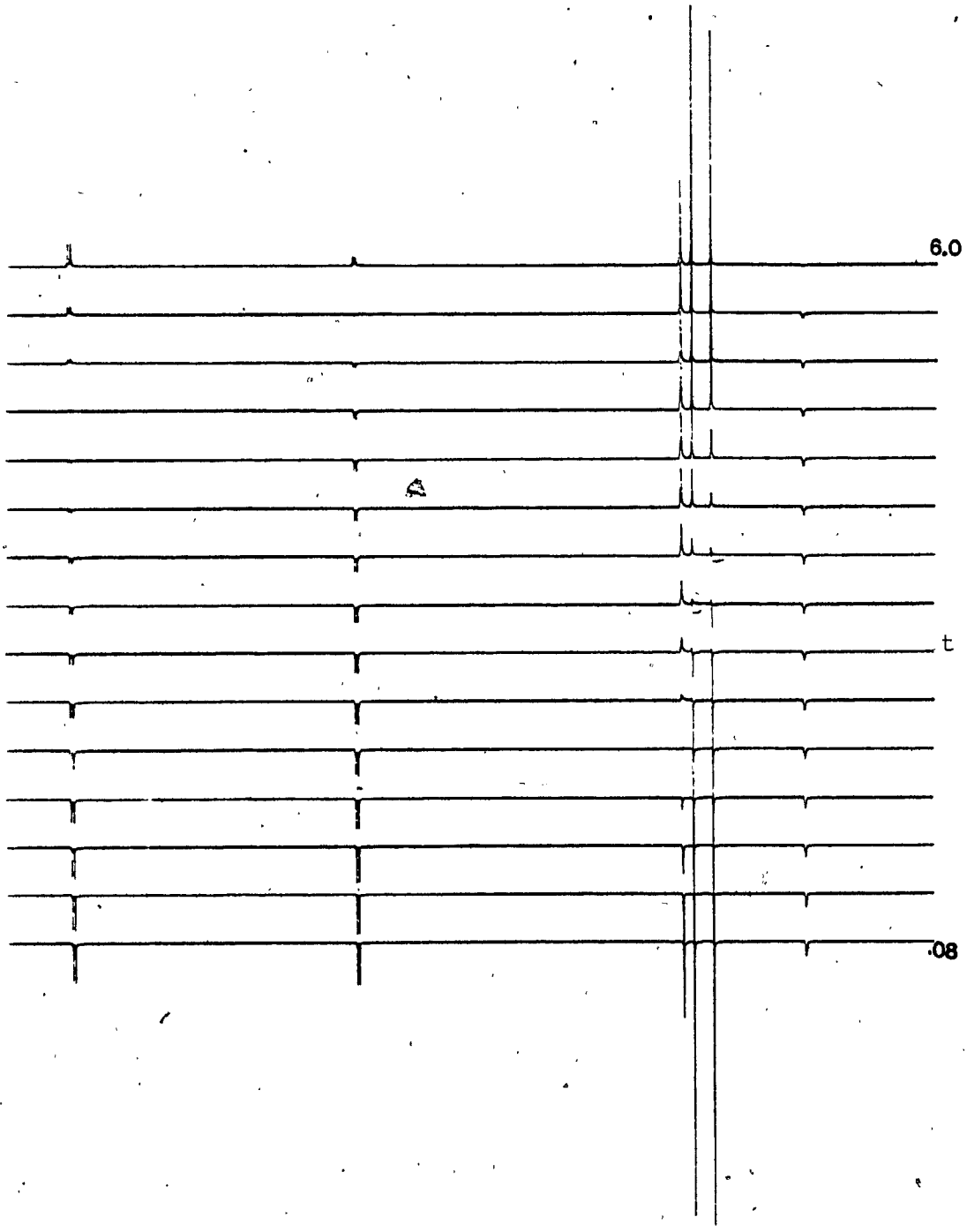


Figure 6.1 Stack plot displaying a selected series of partially relaxed spectra of 1,3-dimethyl uracil, taken for various delay times, t, in the inversion recovery method

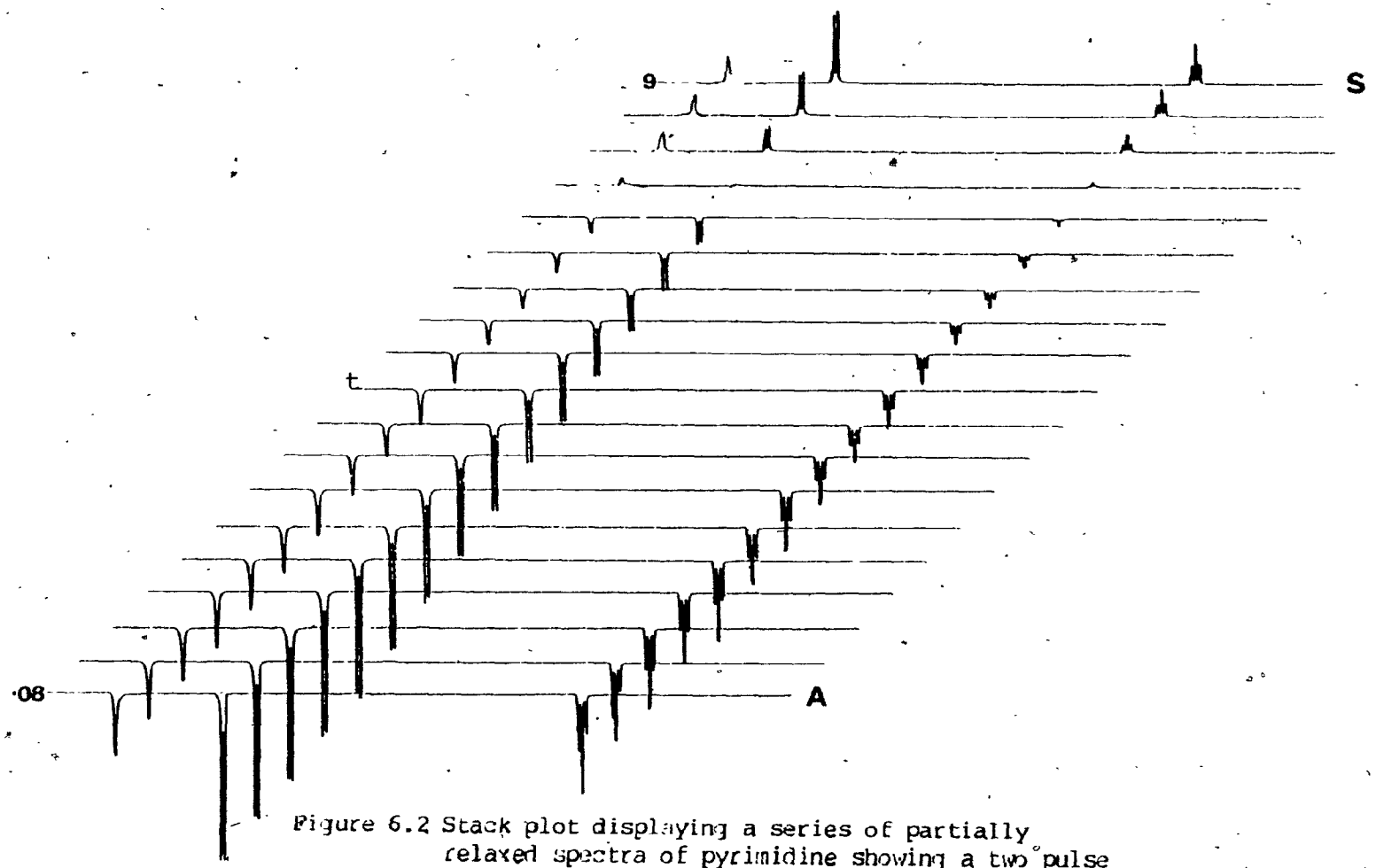


Figure 6.2 Stack plot displaying a series of partially relaxed spectra of pyrimidine showing a two pulse non-selective inversion recovery determination of the spin-lattice relaxation rates.

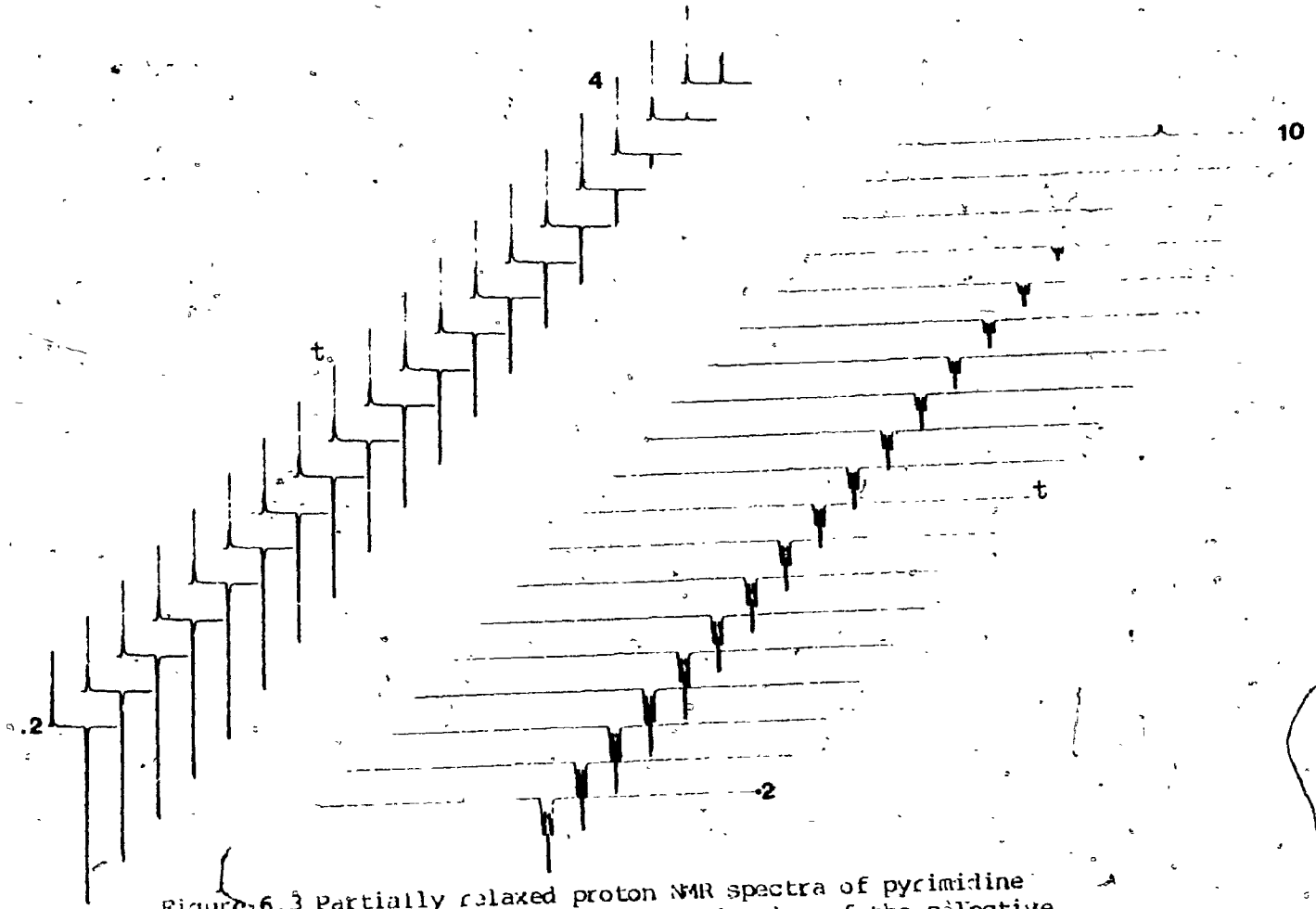


Figure 6.3 Partially relaxed proton NMR spectra of pyrimidine showing the selective determination of the selective relaxation rates of H-5 and H-4, H-6 resonances following perturbation with a selective 180° pulse and then by applying non-selective 90° pulse.

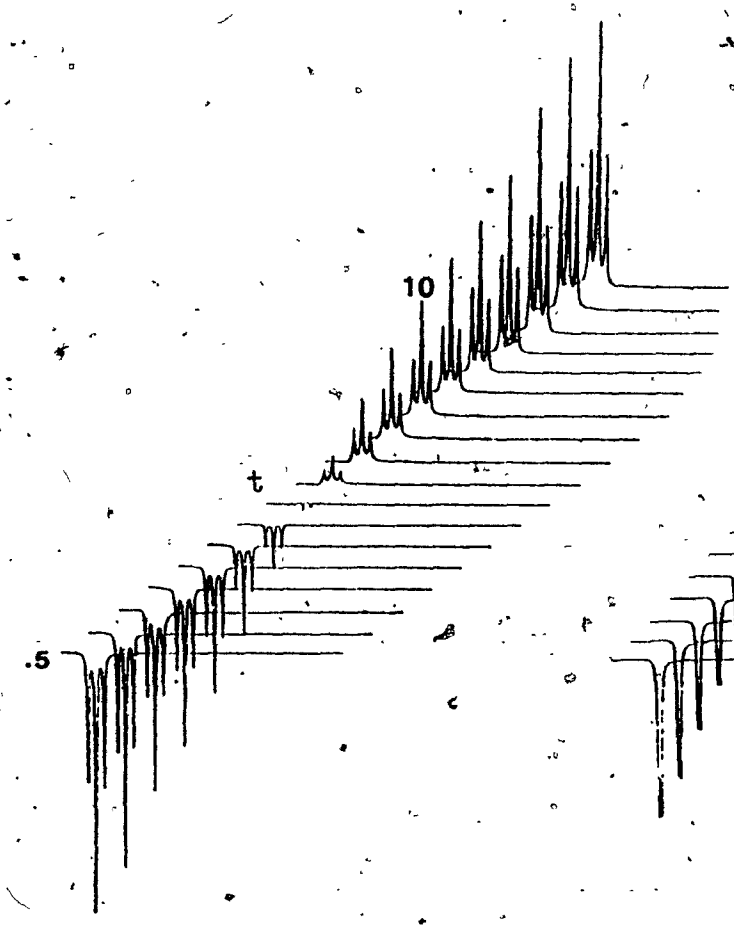


Figure 6.5 Partial 400 MHz proton NMR spectra of 2 pyrimidone showing the single selective determination of the spin-lattice relaxation rate of 5-H using a two pulse inversion recovery sequence.

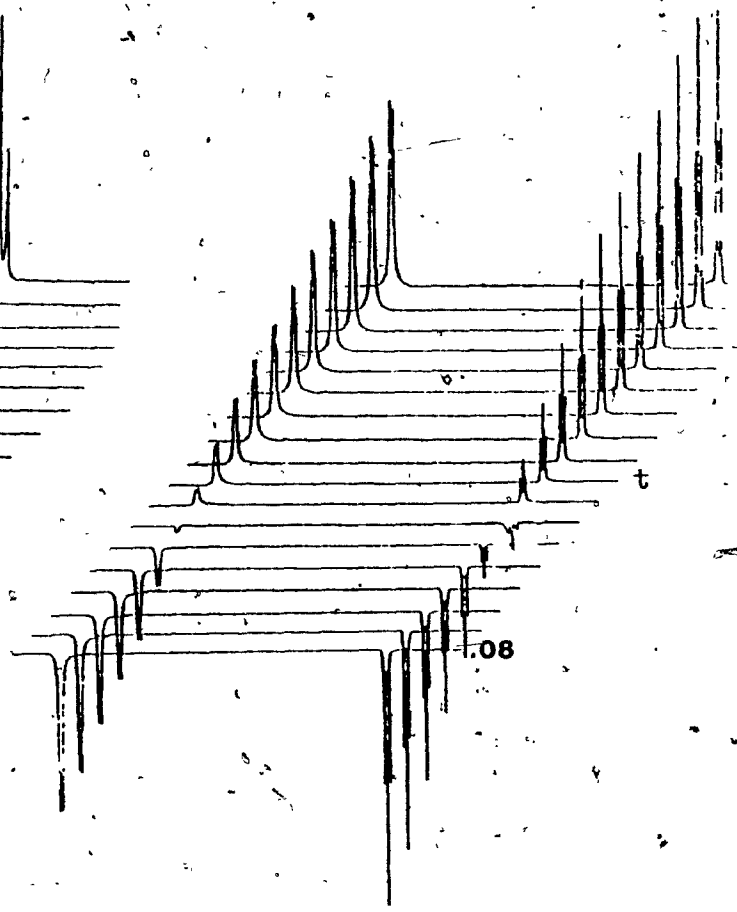


Figure 6.4 Partial 400 MHz proton NMR spectra of 2-pyrimidone showing a two pulse non-selective inversion recovery determination of the spin-lattice relaxation.

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