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Aromatic solvent induced shifts of trifluoromethyl pyrazoles

Manuel Constantine Bourlas

AROMATIC SOLVENT INDUCED SHIFTS OF TRIFLUOROMETHYL PYRAZOLES

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MANUEL CONSTANTINE BOURLAS

APPROVED:

James Worsham
W. Allan Powell
Wm. E. Trout
Richard A. Mateer
Richard W. Topham
Addison A. Campbell

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TABLE OF CONTENTS

To Maria and Kristin

ABSTRACT

Nuclear Magnetic Resonance (NMR) has been used to study the keto-enol equilibrium in a number of trifluoromethyl β-diketones as well as the dihydropyrazoles obtained when these β-diketones are reacted with thiosemicarbazide. The technique of Aromatic Solvent-Induced Shifts (ASIS) has been used to study the geometry of the collision complex and the strength of the association between solute and solvent. From the data presented, the stereochemistry of these pyrazoles has been determined and a reaction mechanism for their formation has been proposed.

ACKNOWLEDGMENTS

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I would like to thank Philip Morris, Inc. for being so understanding during the course of this work and also for allowing me to use their equipment.

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Preface

It is not the intention of this thesis to describe the physics and mathematics upon which nuclear magnetic resonance is based since the author has neither the expertise nor the background to do justice to these topics. Several excellent texts that have taken this approach have been written.[1-3] It suffices to say that once again, the physicist and the mathematician have provided the chemist with a tool with which to study organic reactions and molecular kinetics. The physicists and mathematicians have, within the past two decades, refined the instrumentation to suit the chemist's needs. In this way, the elucidation of complex organic structures has not only been made easier but certain nuclear magnetic resonance techniques have enabled the chemist to learn more about the stereochemistry of organic molecules. This thesis pertains to one of those techniques: the technique of Aromatic Solvent-Induced Shifts (ASIS).

The phenomenon of nuclear magnetic resonance was first observed in 1946 by two groups of workers in experiments which were conducted simultaneously but independently. Purcell's[4] group at Harvard University reported the resonance absorption of the protons in solid paraffin, while Block's[5] group at Stanford University reported the resonance absorption of protons in water.

Basically, nuclear magnetic resonance (NMR) is another form of absorption spectroscopy, just as is infrared or ultraviolet spectroscopy. Under certain conditions, a sample can absorb energy of radiowave frequency and when a plot is made of the peak intensities versus frequencies of absorption, the result is an NMR spectrum.

It is well known that all nuclei carry a charge and in a number of these nuclei, the charge "spins" on the nuclear axis generating a magnetic dipole. These nuclei such as ^{1}H, ^{19}F, ^{13}C, and ^{31}P may be likened to small bar magnets. When the above nuclei placed in a uniform, external magnetic field, these miniature magnets can align themselves in one of two directions: parallel with the applied field which is a low-energy, stable state; or anti-parallel with the applied field which is a high energy, unstable state. Not only is the alignment in a particular direction, but the axis of each spinning nucleus precesses about the axis of the external magnetic field, just as a gyroscope precesses under the influence of gravity.

Because it is easier for the protons to align themselves parallel with the external applied field, there are more of them in this low-energy state. If we apply and vary electromagnetic energy to the sample, at some point these nuclei will absorb energy and "flip" to the high-

energy state. The point at which this happens is when the frequency of the energy source matches the nuclei's frequency of precession. The energy source used is a secondary magnetic field applied at right angles to the nuclei's spin axis. When the nucleus "flips", the energy it has absorbed in the process is recorded as a peak by the NMR spectrometer.

Of course, nuclei in an organic molecule are not isolated but are acted on by neighboring atoms in ways that can change the magnitude of the field needed to "flip" them. If this were not so, then all protons in a molecule would absorb the same amount of energy and would appear as a single peak. Fortunately, the amount of energy a proton absorbs depends on its chemical and magnetic environment, and the energy absorbed determines its peak position in an NMR spectrum. The position, measured from a convenient reference compound, is termed the chemical shift.

The chemical shift concept can be made clearer if one keeps in mind that the spinning nucleus is surrounded by negatively charged electrons, some of which are involved in bond formation. These electrons and the applied magnetic field can interact, reducing the strength of the applied field at the nucleus. This "blocking" of the field is termed shielding. If, on the other hand,

neighboring atoms have the tendency to pull electrons away from the nucleus, then the nucleus becomes deshielded. Since the bonding electrons do not shield the nucleus from the applied magnetic field as well, the magnitude of the magnetic energy required to "flip" the nucleus is reduced. For example, a methyl group attached to oxygen will appear at a lower position in the spectrum than a methyl attached to a methylene group. There is a difference in absorption position because the oxygen tends to deshield the methyl protons more than the methylene group.

Not only does the chemical shift yield a wealth of information concerning the chemical and magnetic environment of the nucleus, but the area under each peak in the spectrum is proportional to the number of protons absorbing energy at that frequency. If areas under each peak in the spectrum are compared, the relative number of protons responsible for the absorption can be found. When this information is coupled with the chemical shift values, one can distinguish quite easily between methyl and methylene proton or between a methine proton and an aromatic one.

A third common NMR phenomenon is spin-spin coupling between nuclei. Coupling is produced by the interaction of one nucleus with another mainly via electron structure of the intervening bonds but in some cases by their interaction through space.

A set of protons can detect the alignment pattern of neighboring protons; that is, whether the neighbors are aligned parallel or anti-parallel to the magnetic field. The result is a perturbed arrangement of signals rather than one unperturbed signal. The number of peaks depends on the spin states of the neighboring set, i.e., the number of ways the protons in the neighboring set can align with the magnetic field. Consider the simplest case of two coupled protons such as would be found in a 2,5-disubstituted thiophene (Figure 1).

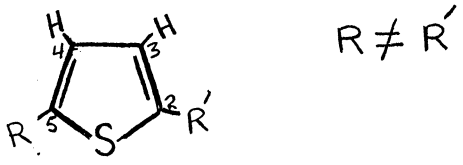


Figure 1. 2,5-Disubstituted Thiophene

This compound has two protons on adjacent carbon atoms, each in a different chemical environment since $R \neq R'$. Two signals are expected in the spectrum. In fact four lines are observed, in two pairs, as indicated in Figure 2.

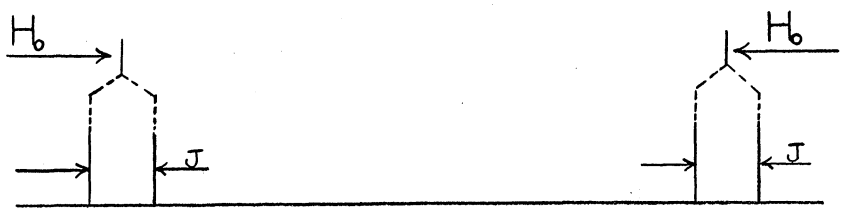


Figure 2. Proton Magnetic Resonance lines of a 2,5-disubstituted thiophene

Each pair shows the same spacing; this spacing is measured in cycles per second (c/s), and is known as the coupling constant J. The magnitude of J is characteristic of that particular situation and is dependent mostly on the number of intervening bonds and the dihedral angle between the two protons. A simple explanation of why two pairs are obtained is shown in Figure 3.

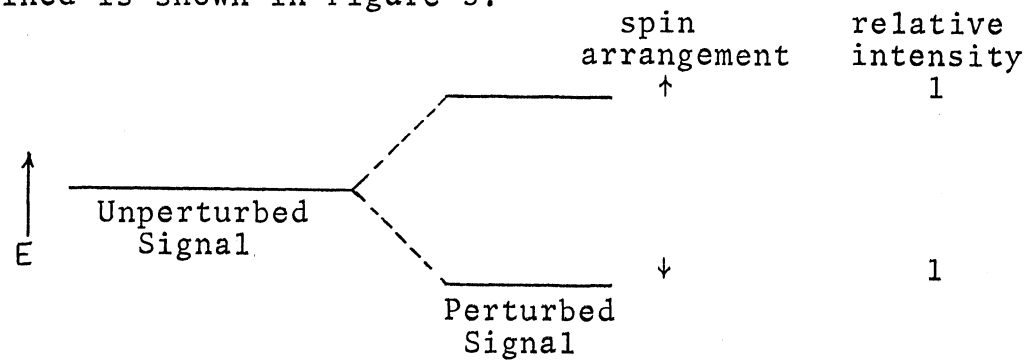


Figure 3. The splitting of the C-3 proton due to the two spin-states of the C-4 proton

The C-3 proton experiences not just the applied field but two modifications of the applied field, so that it comes to resonance at two positions in the swept spectrum. These two modifications of the field arise from the adjacent proton being at various times in its two different spin states. The applied field, therefore, experienced by the C-3 proton is augmented in some way by the C-4 proton being in one spin state (↑), and then diminished by the adjacent proton being in the opposite spin state (↓).

The spin states are equally probable, so that the spectral lines are of equal intensity. Furthermore, spin-coupling effects are mutual and in the same way the signal from the C-4 proton is split into a doublet by the C-3 proton.

A relatively more complicated situation is obtained in the spectrum of 1,1-dibromoethane. The spectrum is shown in Figure 4 while the energy diagram is described in Figure 5.

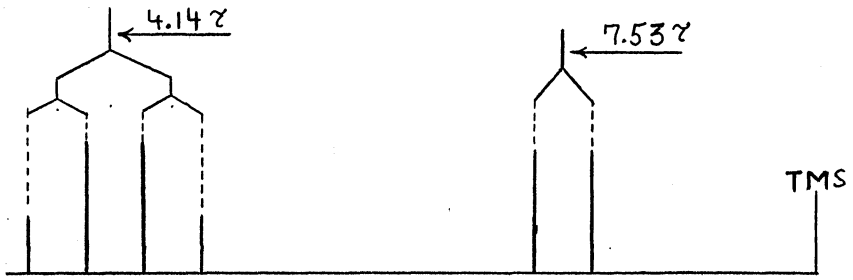


Figure 4. Proton magnetic resonance spectrum of 1,1-dibromoethane

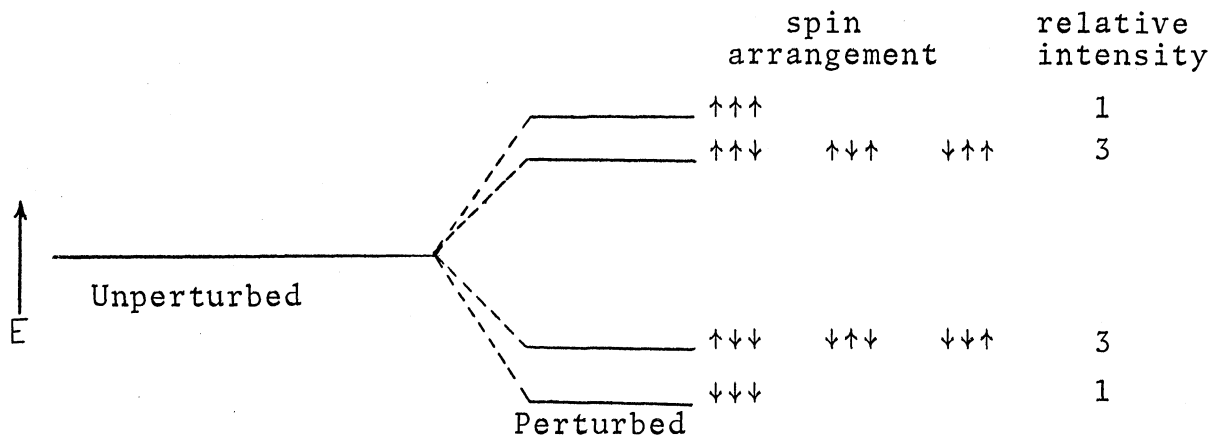


Figure 5. The splitting pattern of the methine proton due to the eight spin states of the protons of the methyl group

The three protons of the methyl group cause four modifications of the applied field each of which differs from that on an adjacent level by the effect of one change in spin orientation. Consequently, the methine proton, which experiences these field modifications, gives rise to four spectral lines as the field is swept. The lines are equally spaced by J (c/s), and this spacing, in turn, is equal to that in the methyl doublet signal.

In general, the number of lines in a multiplet is not due to the number of protons on the group giving rise to the multiplet signal, but to the number of protons on adjacent groups. The number of lines in a multiplet for equivalent nuclei will be $(2n\,I + 1)$, where n is the number of adjacent nuclei of spin I. For protons, where $I = 1/2$, this is the so-called (n + 1) rule.

I. INTRODUCTION

A. SOLVENT EFFECTS IN NUCLEAR MAGNETIC RESONANCE

Solvent effects may be defined in a general way as a consequence of intermolecular forces. Their relevance in nuclear magnetic resonance arises from the relatively high concentrations necessary, compared with other spectroscopic methods. Solvent effects were first observed by Bothner-By and Glick[6] and independently by Reeves and Schneider[7] in 1957. Since these initial observations were made, there has appeared a large number of publications dealing with the applications of solvent shifts to a wide variety of problems.

In a nuclear magnetic resonance experiment, the magnetic field at the nucleus (H_{local}) is measured. This nuclear magnetic field can be related to the applied magnetic field by the expression

$$H_{local} = (1-\sigma)H$$

where H is the applied magnetic field and σ is the screening constant. The total screening constant, σ_{total}, is composed of five contributors;[8]

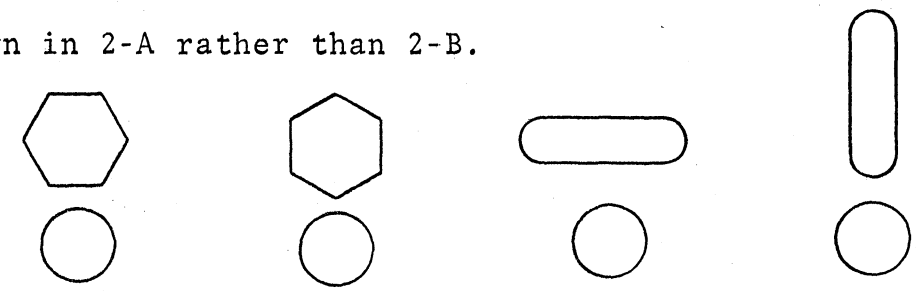
$$\sigma_{total} = \sigma_b + \sigma_w + \sigma_a + \sigma_e + \sigma_c$$

where σ_b refers to the bulk susceptibility of the medium, σ_w to Van der Waals interactions, σ_a to the anisotropy of the susceptibilities of the surrounding molecules, σ_e to the reaction field of the medium and σ_c to specific

solute-solvent interactions. The bulk magnetic susceptibility of the medium, σ_b, is zero if an internal reference is used when performing the NMR experiment. Van der Waals interactions, σ_w, tend to be negligible (0.1-0.2 ppm) unless large polarizable halogen atoms are present in the solvent. The magnetic anisotropy in the solvent molecules, σ_a, arises from the nonzero orientational averaging of solvent with respect to solute. The reaction field of the medium, σ_e, is induced when a polar molecule or a molecule containing polar groups is dissolved in a dielectric medium. The effect is usually to reduce the shielding around a proton in the solute. Experimental studies of the electric field effect indicate that σ_e may be as large as 1 ppm for polar molecules in solvents of high dielectric constant.[9] Specific solute-solvent interactions, σ_c, refers to the effect on chemical shift of a specific solute interacting with a particulate solvent. Aromatic solvents such as benzene and toluene greatly contribute to the magnitude of the total screening constant, σ_{total}, through σ_a and σ_c.

1. Magnetic Anisotropy in the Solvent Molecules (σ_a)

Buckingham and co-workers[10] have suggested that if specific solute-solvent interactions are absent, disc-like molecules, such as benzene, will adopt the configuration shown in 1-A rather than 1-B. This allows the benzene molecule to lie closer to the solute molecule In the same manner, rod-like solvents such as carbon disulfide will have, on the average, the configuration shown in 2-A rather than 2-B.



1-A 1-B 2-A 2-B

Aromatic rings, therefore, and groups such as C=C, C=O, C≡C, and C≡N will cause large effects. It is difficult to isolate this effect from others, but studies[10,11,12] have shown that aromatic solvents lead to positive σ_a's of about 0.8 ppm, while solvents containing triple bonds will have negative σ_a's of about 0.2-0.4 ppm. It is this large σ_a (diamagnetic shift, upfield direction) normally found for aromatic solvents, that has been exploited by the chemist.

Bhacca and Williams[13,14] have studied the chemical shifts induced by benzene in a number of steroidal ketones and acetates. They found that in the absence of polar functional groups there is a very slight effect on the C-18 and C-19 angular methyl groups in going from deuterochloroform to benzene solvent. However, the position of these same methyl resonances in the NMR spectra of a number of 5α-androstan-ketones are considerably different in going from the "inert" solvent $CDCl_3$ to the "active" solvent C_6H_6. In other words, solvent effects are selective in complex molecules containing a polar functional group. Systematic studies of the variation in chemical shifts of protons in well-known locations in large molecules have shown this selectivity as well as considerable regularity in solvent effects.[15] For example, a solvent shift can be denoted as

$$\Delta^{CDCl_3}_{C_6H_6} = \delta_{CDCl_3} - \delta_{C_6H_6}$$

where the δ's are defined as the chemical shift (in parts per million) downfield from tetramethylsilane. A positive value of Δ indicates a diamagnetic shift in the proton resonance on going from $CDCl_3$ to C_6H_6. It has been found that in molecules containing a C=O group, Δ is negative for protons located on the oxygen side of a plane through

the carbon atom of the carbonyl group perpendicular to the C=O axis, and positive on the other side of the plane.[14,15] This is shown in Figure 6.

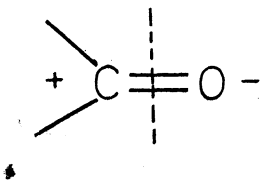


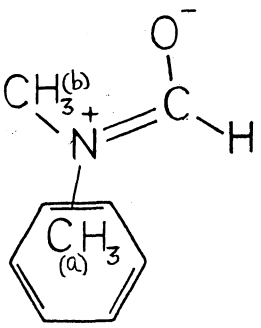
Figure 6. Effect of solvent change on chemical shifts of protons in a molecule containing a C=O group. Broken line indicates a plane perpendicular to the plane of the C=O group.

This result can be interpreted in terms of a complex or an association between the solute and aromatic solvent such that the π-electrons of the aromatic ring are near the slightly positively charged carbon atom of the C=O group, while at the same time remaining as far as possible from the negative oxygen.

2. Specific Solute-Solvent Interactions (σ_c)

The specific association term, σ_c, also predicts shifts due to anisotropy effects associated with specific interactions; however, it goes one step further in that σ_c includes the effect of geometrically associated solute-solvent orientation. In many cases, the solute-solvent collision complex is planar. For

example, the solvent shifts of the methyl groups of N,N-dimethylformamide[16] are consistent with a planar association between the benzene and the amide as shown in Figure 7.



$\Delta CH_{3\,(a)} = 1.08$ ppm

$\Delta CH_{3\,(b)} = 0.41$ ppm

Figure 7. Planar association of benzene and N,N-dimethyl formamide

The nitrogen atom, with its fractional positive charge, is situated close to the π-electron density of the aromatic ring with the negatively charged carbonyl oxygen as far away as possible from the center of the ring. Such an arrangement qualitatively explains the difference in the Δ chemical shifts (Δ Neat Benzene) between methyl groups (a) and (b). Other authors[17,18,19] have observed the planar association and indeed, have used it to study the chemical structure of molecules.

Naturally, not all benzene-solute collision complexes will be planar, since it is reasonable to assume that steric requirements would play an important role in the determination of the geometrical preferences of the interacting molecules. The solvent shifts observed[20]

for certain protons in 5α-androstan-11-one are more easily explained in terms of a non-planar arrangement such as in Figure 8.

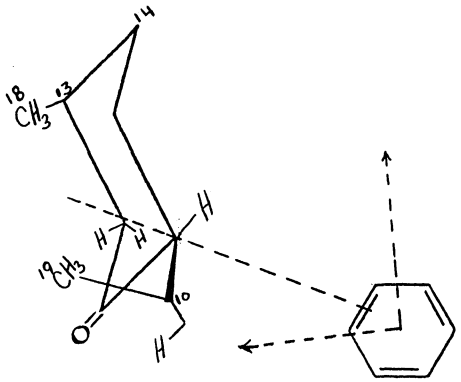


Figure 8. The non-planar association of benzene-5α-androstan-11-one.

Anderson[21] has determined that the solvent shifts of some 1,3-dioxans are highly dependent on the size of the axial substituent in the 5-position. A non-planar solute-solvent complex can account for the observed shifts. Similarly, solvent shifts of adamantyl halides,[22] steroidal ketones,[20] 3-dicarbonyl compounds[23] and anisoles[24] are best explained in terms of non-planar association.

In conclusion, it may be stated that solvent shift data indicate that a local dipole-induced dipole interaction exists between benzene and solute in such a way that the benzene ring avoids the negative end of the dipole and solvates electron deficient centers.

The stoichiometry of the interaction components involved in the benzene-solute collision complex has been assumed to be in a 1:1 ratio. This assumption is consistent with the observation that the magnitude of the solvent

shift at various concentrations of benzene in CCl_4 is approximately proportional to the mole fraction of benzene. These dilution studies do not exclude the co-occurrence, even to a small extent, of other solute-solvent combinations such as 2:1 or 1:2. Fort and Lindstrom[22] have examined a number of adamantyl halides in a variety of aromatic solvents and have concluded, through freezing point diagrams, that there is no evidence of compound formation. They suggest that the solute dipole causes a weak ordering of the solvent, geometrically, but not thermodynamically, equivalent to a 1:1 complex.

On the other hand, Stothers and co-workers[25] have found clear evidence, from variable-temperature NMR studies at various concentrations in deuterochloroform, that tricyclic aldehyde molecules such as 9-anthraldehyde associate with each other in solution in a 1:1 ratio. It seems; therefore, that in those cases where a specific stoichiometry is involved, the actual ratios (1:1, 2:1, 2:2, etc.), more than likely depend on the solutes and solvents involved.[26]

B. The Collision Complex

If the concept of a 1:1 transient collision complex is assumed, it can provide a useful working hypothesis for thermodynamic measurements of the strength

of the interaction. The reversible equilibrium reaction between solute and benzene may be written as

$$\text{BENZENE} + \text{SOLUTE} \rightleftarrows \text{COMPLEX}. \qquad (1)$$

If the equilibrium reaction has any significance, then the benzene-induced solvent shifts should be temperature dependent. This has been substantiated by a number of authors.[27,28,29,30] For the calculation of thermodynamic parameters; therefore, on the basis of an assumed 1:1 complex, Abraham[31] has suggested the following method. If, in a dilute solution (less than a 5% solution), a fraction p of the solute is in the complex form, then equation (2) holds, where K is the equilibrium constant for the equilibrium reaction (1), and ΔS and ΔH are the entropy of formation and heat of formation of the complex, respectively:

$$K = \frac{p}{1-p} = \exp\left(\frac{\Delta S}{R}\right) \exp\left(-\frac{\Delta H}{RT}\right) \qquad (2)$$

The fraction of solute molecules complexes, p, is given at any temperature, t by:

$$p = \frac{\delta_t - \delta_o}{\delta_c - \delta_o} \qquad (3)$$

where δ_t = the observed chemical shift at temperature t;
δ_o = the chemical shift of the uncomplexed solute; and
δ_c = the proton resonance in the pure complex.

If the position of the resonance in an "inert" solvent such as carbon tetrachloride or deuterochloroform is obtained to give δ_o, and this value is arbitrarily taken as zero, then equation (3) simplifies to:

$$p = \frac{\delta_t}{\delta_c} \qquad (4)$$

Estimates of the δ_c quantities can be made by measuring δ_t as a function of temperature, and extrapolating to 0°K. At this point, all of the solute molecules are assumed to be complexed and $\delta_t = \delta_o = \delta_c$. The equilibrium constant at any temperature is therefore, given by equation (2). The heat of formation, ΔH, is obtained by the usual manner of plotting log K versus 1/T which should yield a straight line with a slope of $\frac{\Delta H}{R}$ and intercept of $\Delta S/R$.

The significance of the thermodynamic parameters obtained in this manner has been questioned in view of the assumption of a 1:1 collision complex and the error involved in extrapolation for the determination of δ_c. However, the weak nature of the interaction is usefully demonstrated by such a technique.

II. DISCUSSION

APPLICATIONS OF AROMATIC SOLVENT-INDUCED SHIFTS (ASIS)

Since the studies of Bhacca and Williams[13] concerning the effects of benzene on steroidal ketones, there have been a number of publications concerning applications of ASIS. Saturated aliphatic ketones in particular have been the subject of many investigations,[32-35] and two important generalizations have been formulated from these studies. The first is the so-called "carbonyl plane rule" from which one can predict positive or negative shifts of protons depending on where the proton lies in relationship to the carbon-oxygen plant, Figure 6.

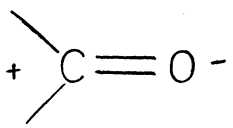
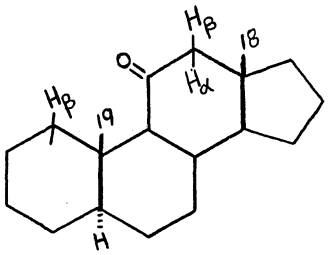


Figure 6. Effect of solvent change on chemical shifts of protons in a molecule containing a C=O group.

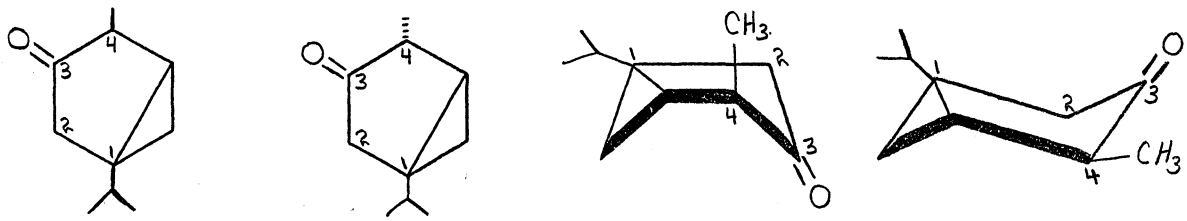
Thus in the case of 5α-androstan-11-one (Figure 9)



Proton	Δ $CDCl_3$ / C_6H_6 (ppm)
1β-H	-0.36
C-19	-0.14
12β-H	-0.02
12α-H	+0.34
C-18	+0.11

Figure 9. The effect of benzene on various protons in 5α-androstan-11-one

dissolved in benzene, the 1β-H and C-19 methyl group move downfield relative to their positions in deuterochloroform while the 12β-H is hardly affected and the 12α-H and C-18 methyl group move upfield. An example of practical application is cited in the conformation of the stereochemistry of α- and β-thujone.[36] Representing α-thujone (Figure 10) in its two possible conformations, it is



2 2-C 2-A 2-B

Figure 10. The chair and boat forms of α-thujone. β-thujone is also shown (2-C).

expected that in the boat form (Figure 2-A) the C-10 methyl group, will have a significant positive solvent shift whereas the same methyl group in the chair form (Figure 2-B) will have a negligible solvent shift. The β-isomer (Figure 2-C) will show the reverse of these trends in its boat and chair forms. Table I shows the observed shifts and clearly indicates that α- and β-thujone exist in the boat form.

Table I. Solvent Shifts of α- and β-thujone

Isomer	Solvent Shift ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$)				
	2α-H	2β-H	4α-H	4β-H	C-10-CH_3
α-thujone (2)	+0.07	+0.15	+0.03	--	+0.15
β-thujone (2-C)	+0.12	+0.25	--	+0.34	-0.01

Other studies have been made concerning the stereochemistry of ketones.[37,38]

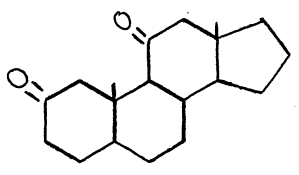
The second property of ASIS concerning ketones is the "additivity rule."[39] Benzene induced shifts incurred by steroidal di- and polyketones can be calculated as the sum of the separate shifts of the C-18 and C-19 methyl resonances due to the isolated carbonyl groups of the monoketones.

This phenomenon is best illustrated in Table II where the observed and calculated benzene induced shifts are listed for the C-18 and C-19 methyl groups.

Table II. Benzene Induced Shifts for Steroidal Ketones

$$\Delta = (\delta_{CDCl_3} - \delta_{C_6H_6})$$

Compound		$ASIS_{(OBS)}$	$ASIS_{(CAL)}$
I	C-19	0.02	0.02
	C-18	0.17	0.17
II	C-19	0.23	0.23
	C-18	0.20	0.21
III	C-19	0.49	0.49
	C-18	0.29	0.32
IV	C-19	0.45	0.45
	C-18	0.10	0.13
V	C-18	0.40	0.44



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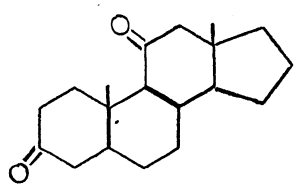
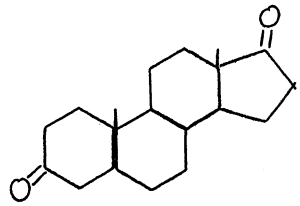


II



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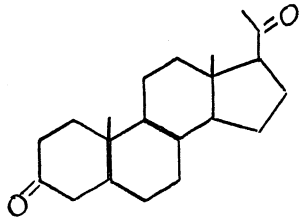
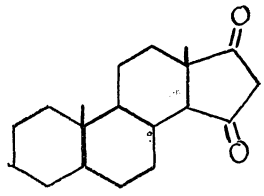


IV



V

Fitizan and Gramain[39] recognized the importance of the additivity rule and discovered that the additivity of ASIS exists regardless of the nature of the polar substituents introduced into the steroid frame. Both generalizations, the carbonyl phase rule and the additivity rule have been used extensively in the solution of stereochemical problems as well as in the identification of isomers.[40]

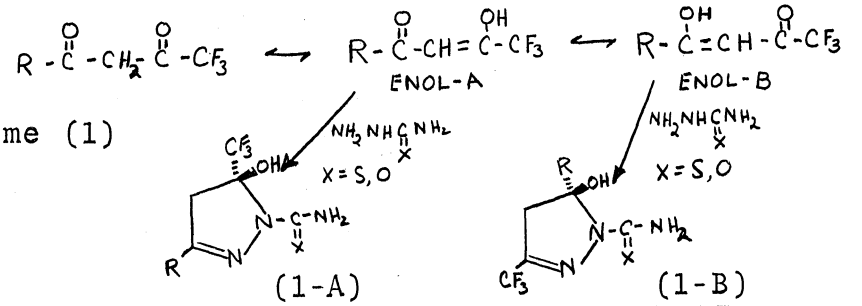
Applications of aromatic solvent-induced shifts have by no means, been limited to steroidal ketones. This class of compounds has been cited only because Bhacca and Williams are natural product chemists and all of their initial work was done on steroids.[41] ASIS have been applied to study N-methyl lactones,[42] bornane derivatives,[43] acetylated monosaccharides,[44] cyclic ethers and other heterocyclic compounds;[45] esters,[46] N-oxides,[47] amides,[48] and a number of other compounds. It is easily seen that as an NMR technique, solvent induced shifts have played a tremendous role in the simplification of complex NMR spectra and as an aid in solving stereochemical problems.

III. OBJECTIVES

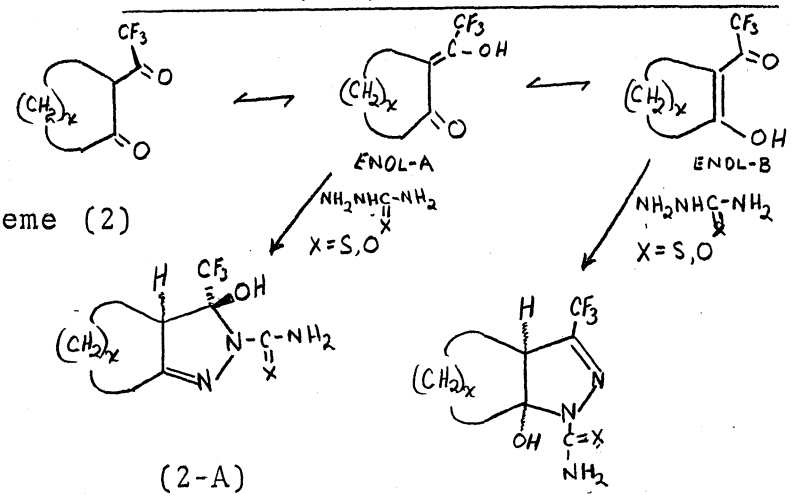
The objectives of this study are threefold: (1) To study the keto-enol equilibrium that exists in the trifluoromethyl β-diketones used to synthesize the pyrazoles, (2) To study the strength of the association between benzene and these pyrazoles, and (3) To determine if aromatic solvent-induced shifts can be used to define the stereochemistry in five of these compounds.

It has long been known that β-diketones undergo keto-enol conversion. Proton magnetic resonance provides a very fruitful method for investigating this tautomerism.[48-52] Reaction schemes I and II show that the direction of enolization will dictate what product will be formed when the diketone is reacted with thio- or semicarbazide.

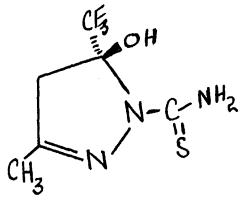
Scheme (1)



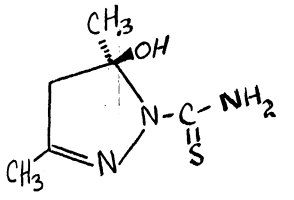
Scheme (2)



It is not possible, however, to distinguish between the two enol forms or their respective products either in the acyclic or cyclic case, by NMR techniques. The spectral position of the hydroxyl proton in compound (1) was compared to that in compound (2).



(1)



(2)

Solvent, temperature, and concentration being constant, the resonance of the hydroxyl proton in compound (1) is lower by 0.90 ppm's than its non-fluorinated counterpart. The chemical shifts for both compounds are shown in Table III.

Table III. Chemical Shifts of Methyl and Trifluoromethyl Pyrazoles in DMSO-d_6

Compound	δ_{NH_2}	δ_{CH_2}	$\delta_{CH_3(1)}$	$\delta_{CH_3(2)}$	$\delta_{(OH)}$
(1)	8.65-7.73	3.43	2.04	---	8.43
(2)	8.00-7.08	2.87	2.00	1.79	7.53

The difference in the chemical shifts is due to the inductive effect[53,54] of the CF_3 group as opposed to the donating power of the methyl group. Reducing the electron density about the hydroxyl proton results in its lower resonating frequency. A similar explanation may be given for the methyl and methylene groups. In this way, ENOL-A in both reaction schemes react with the carbazides to form products 1-A and 2-A. Salvador and Saucer[55] have shown that the trifluoromethyl group may be used to stabilize gem-diols, which normally lose water quite easily, and they may even be isolated and recrystallized. Intramolecular H-bonding increases the stability of these gem-diols. Both hydroxy compounds (1-A) and (2-A) are stabilized by the trifluoromethyl groups as well as through intramolecular hydrogen bonding.

Further evidence for the stabilization effect offered by the CF_3 group to the hydroxyl group has been given by mass spectrometry (MS). The most important primary fragmentation process for the trifluoromethyl dihydropyrazoles is the loss of 59 and 69 mass units from the parent ion. These losses were shown by high resolution MS to be CSNH and CF_3 respectively. The loss of both mass units are shown in Figure (11) and (12).

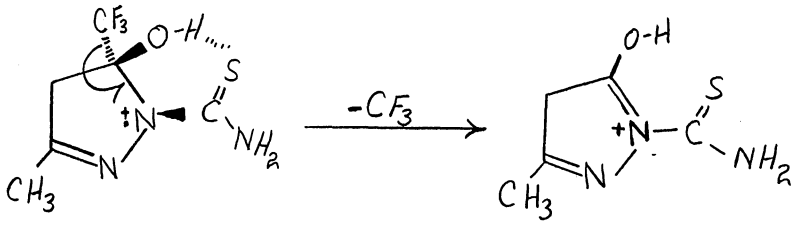


Figure (11)

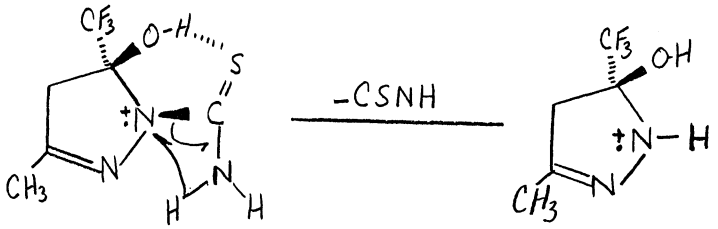


Figure (12)

The elimination of CSNH from the molecular ion can be explained by localization of the charge on the nitrogen atom followed by a cyclic decomposition with hydrogen transfer from the amino group. This mechanism would produce an odd electron ion at M-59. A metastable ion is present to confirm this loss to be from the parent ion.

All compounds show similar spectra and all contain a large molecular ion with the loss of both CSNH and CF_3 from the molecular ion to yield a stable even electron ion (Figure (13).

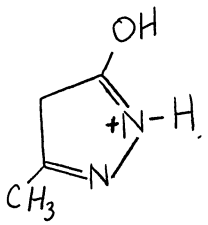
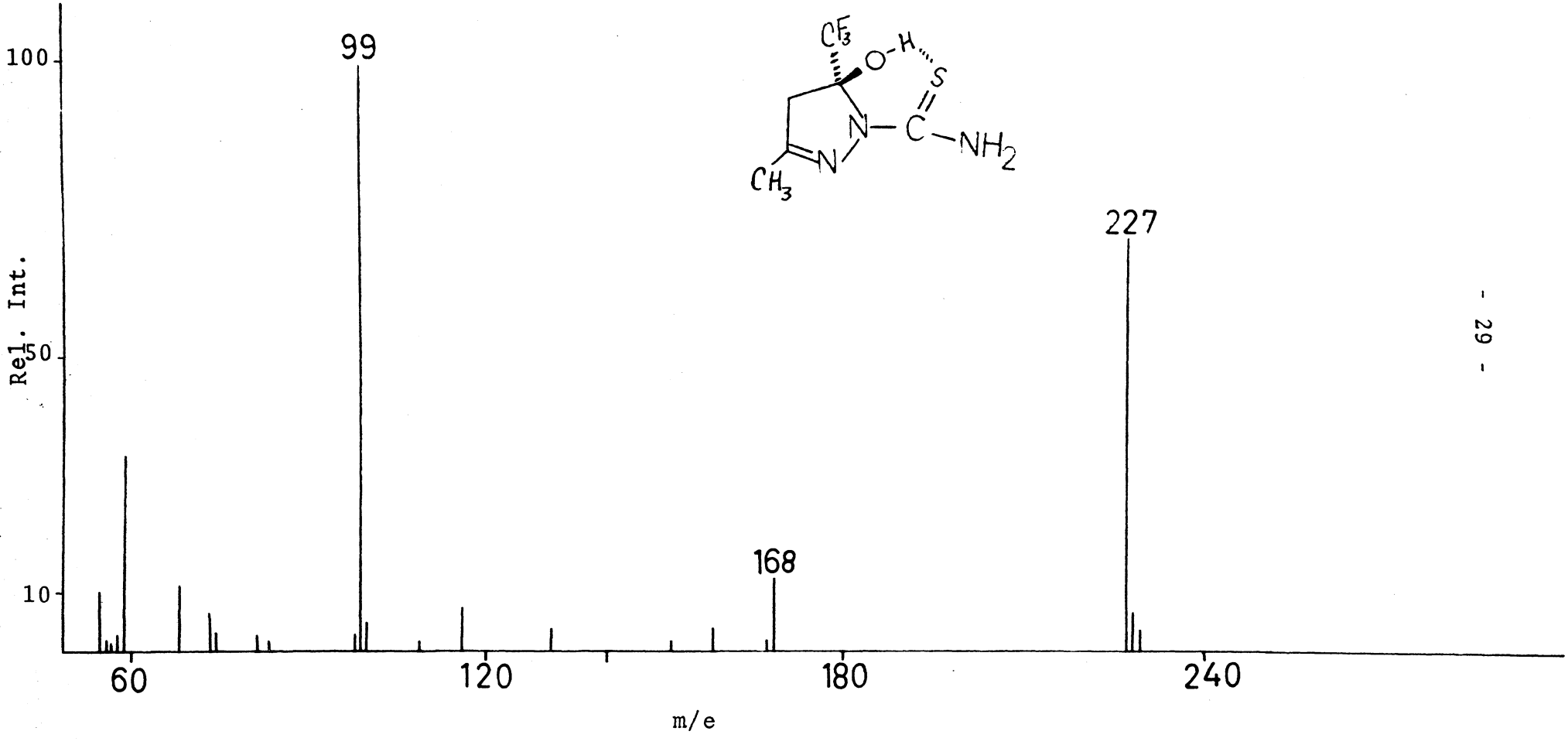
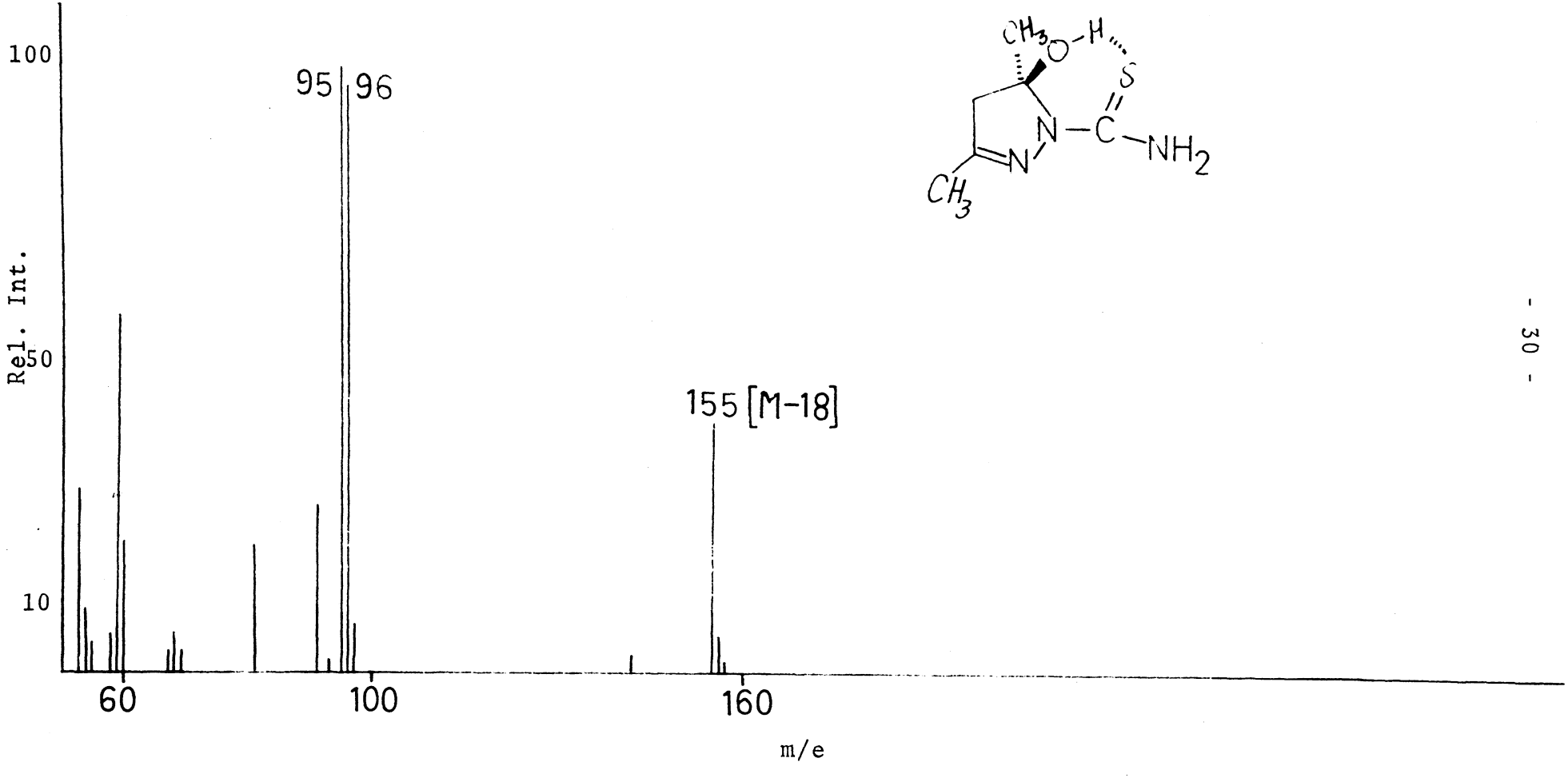


Figure (13)

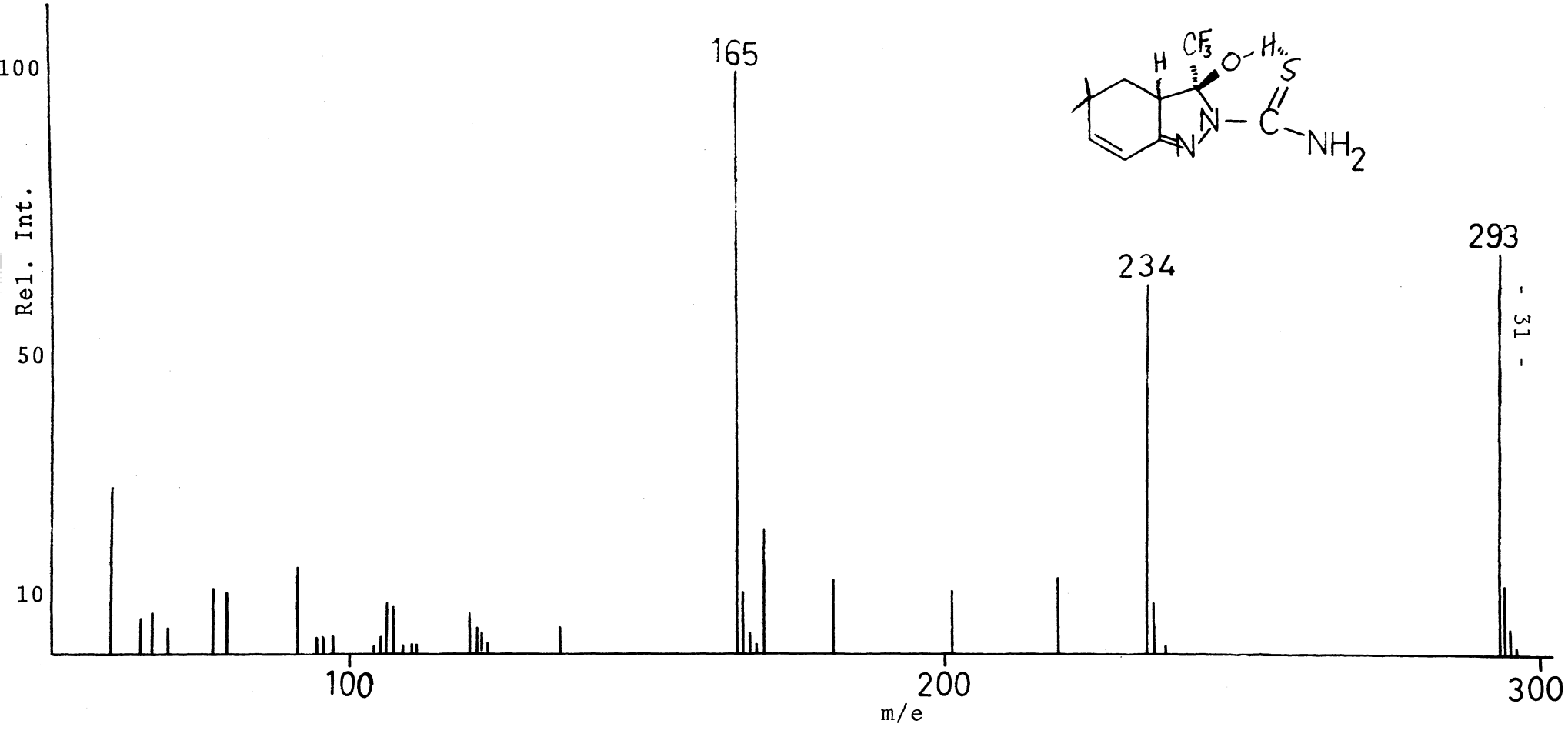
The fact that no (M-18) peak was observed in any of the trifluoromethyl pyrazoles is indicative of a highly stabilized hydroxyl group. A sample of a non-fluorinated pyrazole (Spectrum 2) was run under the same conditions and the dominant fragmentations involve the loss of a neutral molecule of water. This process (M-18) is so dominant that no parent ion is observed. The bar graphs for all of the pyrazoles run are shown in Spectra 1-6.



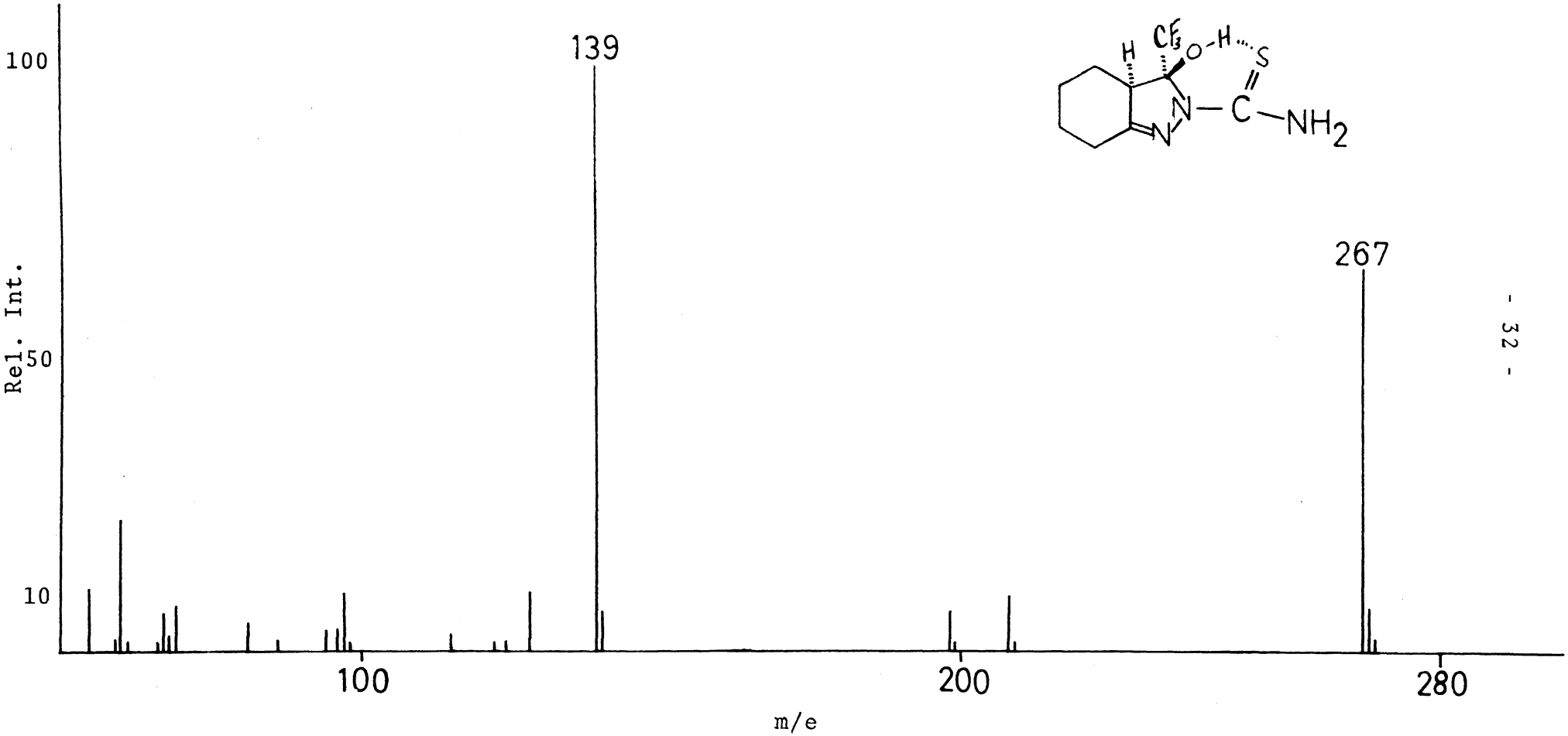
Spectrum 1. 3-Hydroxy-2-Thiocarbamoyl-3-Trifluoromethyl-3,4-Dihydropyrazole



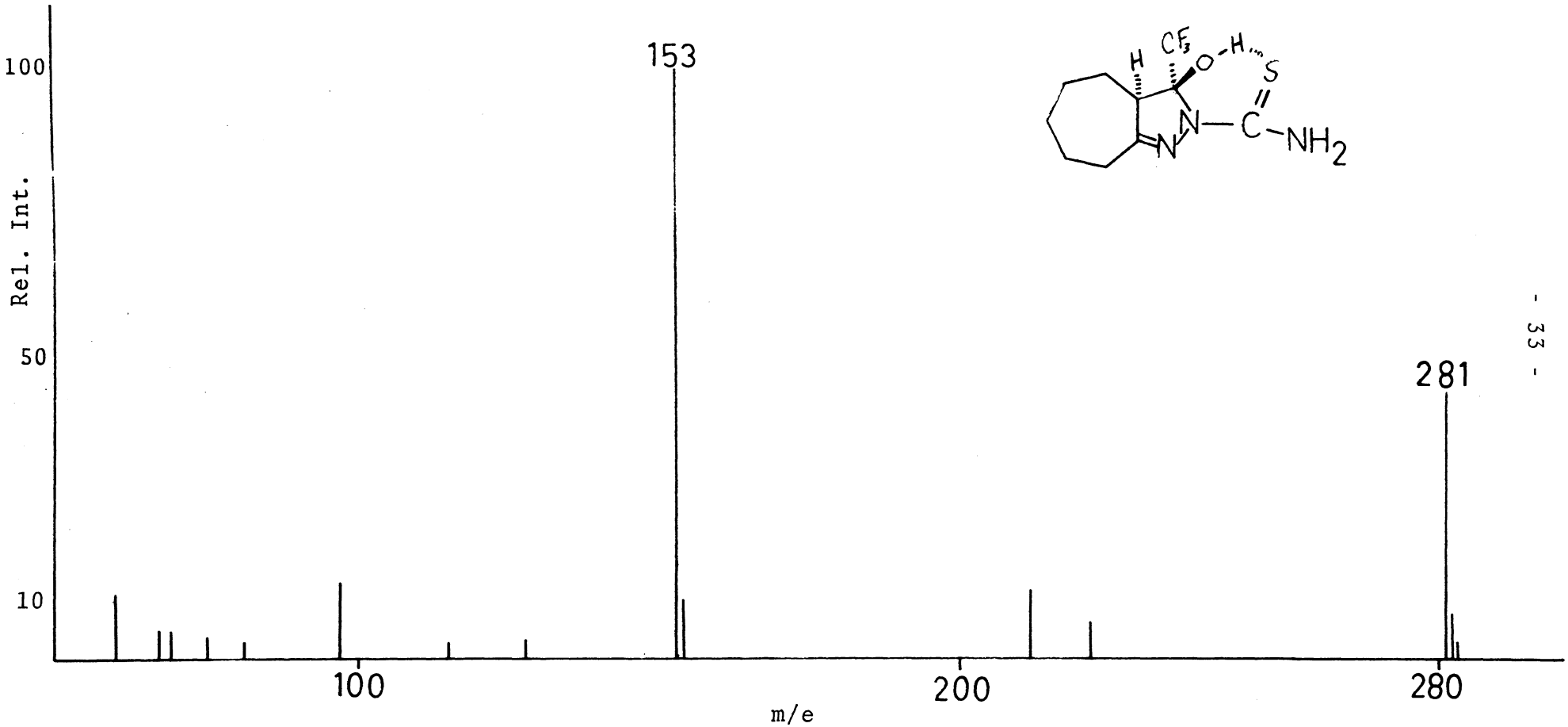
Spectrum 2. 3-Hydroxy-2-Thiocarbamoyl-3-Methyl-3,4-Dihydropyrazole



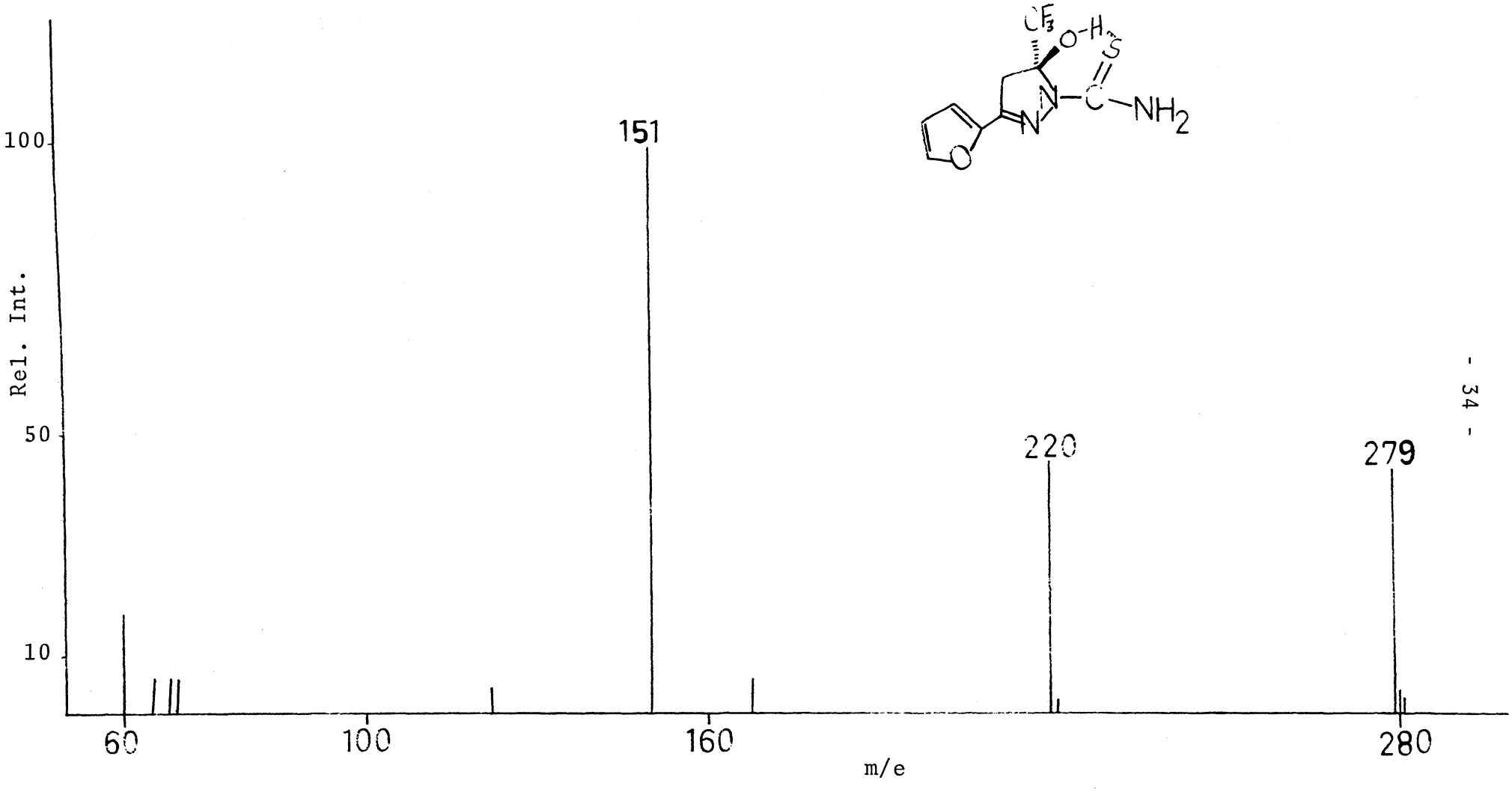
Spectrum 3. 5,5-Dimethyl-3-Hydroxy-2-Thiocarbamoyl-3-Trifluoromethyl-3,3a,4,5-Tetrahydroindazole



Spectrum 4. 3-Hydroxy-2-Thiocarbamoyl-3-Trifluoromethyl-3,3a,4,5,6,7-Hexahydroindazole



Spectrum 5. 3-Hydroxy-2-Thiocarbamoyl-3-Trifluoromethyl-3,3a,4,5,6,7,8-Heptahydrocycloheptapyrazole



Spectrum 6. 2',2-Furan-2-Thiocarbamoyl-3-Trifluoromethyl-3,4-Dihydropyrazole

IV. EXPERIMENTAL

All NMR spectra were determined using a Varian A60A spectrometer with a variable-temperature probe. Methanol was used to calibrate the instrument for all variable-temperature experiments. Ambient probe temperature was measured to be 37°C and all temperatures reported are good to ±1°C. All ^{13}C NMR spectra were determined using the Varian XL-100 equipped with a ^{13}C probe.

Solution concentrations employed were in the range of 2-4% w/v and resonance positions were all measured relative to tetramethylsilane (TMS). The benzene-d_6, toluene-d_8, $CDCl_3$ and CD_2Cl_2 were all purchased from Merck Sharp and Dohme, Montreal.

All compounds listed in Table I have been previously prepared by Secor[56] who made them available for this study. The 5-hydroxy-5-methyl dihydropyrazole was prepared by this writer in the following manner: Thiosemicarbazide (5.5×10^{-2} moles) was dissolved in 30 cc of a 50% acetic acid solution. To this is added 2.7×10^{-2} moles of acetylactone dissolved in 10 cc of methanol. The mixture is allowed to stand at room temperature for four hours and then refrigerated for two days. The crystals are filtered and dried. The NMR spectra indicates a mixture of the desired compound and the dehydrated compound. The mixture was dissolved in a minimum amount of hot 95%

ethanol and when cooled, only the hydrated product crystallized out leaving the dehydrated compound in solution. NMR and mass spectroscopy data confirm the structure. The yield of the reaction was 30%.

V. RESULTS

A. Induced Shifts

Table IV shows all of the trifluoropyrazoles studied and the change in the chemical shifts on passing from deuterochloroform to benzene solution ($\Delta^{CDCl_3}_{C_6D_6} = \delta_{CDCl_3} - \delta_{C_6D_6}$). Variable-temperature NMR studies were undertaken (in toluene-d_8)* to take advantage of the increased concentration of the complex at lower temperatures and the enhanced solvent shifts that result. Furthermore, the variation of the equilibrium constant with temperature for equation (2) would permit an

$$\text{AROMATIC SOLVENT} + \text{PYRAZOLE} \rightleftarrows \text{COMPLEX} \qquad \text{Equation (2)}$$

*Comparison of the C-18 and C-19 methyl resonances in toluene and toluene-d_8 (at the same probe temperature) indicate no significant secondary isotope effect is in operation.[57]

Table IV. BENZENE INDUCED CHEMICAL SHIFTS: $\Delta^{CDCl_3}_{C_6D_6} = [\delta CDCl_3 - \delta C_6D_6]$

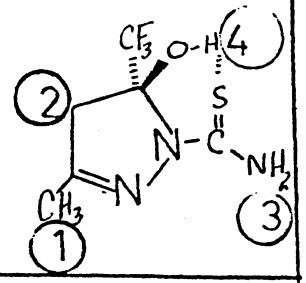
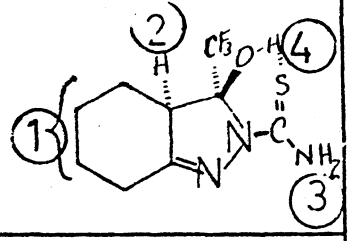
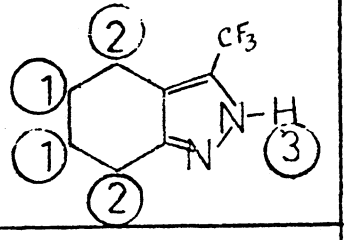
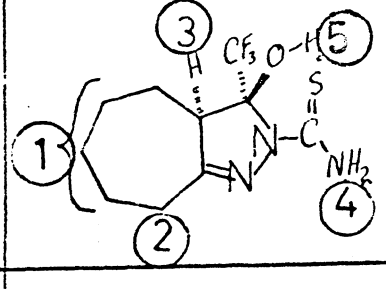
			H_1	H_2	H_3	H_4	H_5	H_6	H_7
1			0.87	0.63	0.70	-0.75			
2			0.43	0.35	0.70	-0.78			
3			0.50	0.19	-0.10				
4			0.55	0.57	0.20	1.10	-0.76		

Table IV. (Continued)

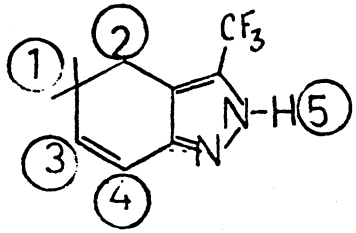
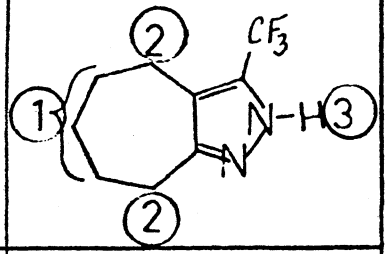
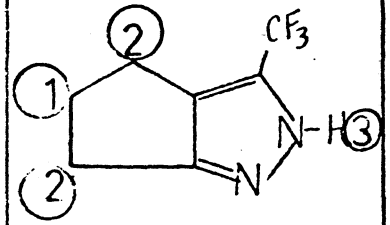
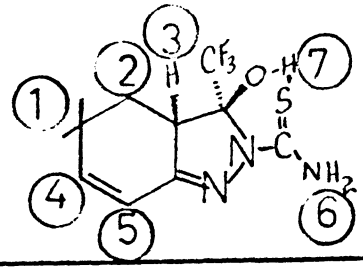
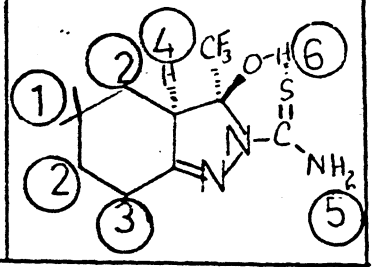
			H_1	H_2	H_3	H_4	H_5	H_6	H_7
5			0.28	0.17	0.34	0.12	0.87		
6			0.28	0.15	-0.45				
7			0.73	0.15	-0.30				
8			0.55	0.20	0.10	0.62	0.29	0.30	-0.69

Table IV. (Continued)

			H_1	H_2	H_3	H_4	H_5	H_6	H_7	
9			0.50	0.50	0.63	0.16	0.85	-0.70		

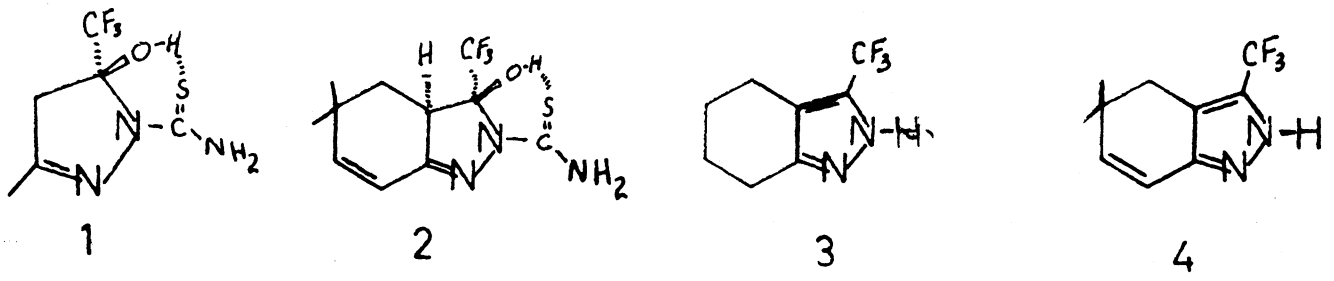
evaluation of the enthalpy of formation of the complex on the basis of an assumed 1:1 complex. It is unlikely that the complex is other than a 1:1 complex since a plot of the chemical shift of a variety of pyrazoles versus the mole fraction of toluene-d_8 is linear - (Graphs 1 and 2). The change in chemical shifts on passing from the inactive to the active solvent as the temperature is varied for pyrazoles 1,2,3,5 and 8 (Table IV) are shown in Graphs 3-8. Two important observations are made regarding Graphs 1-8.

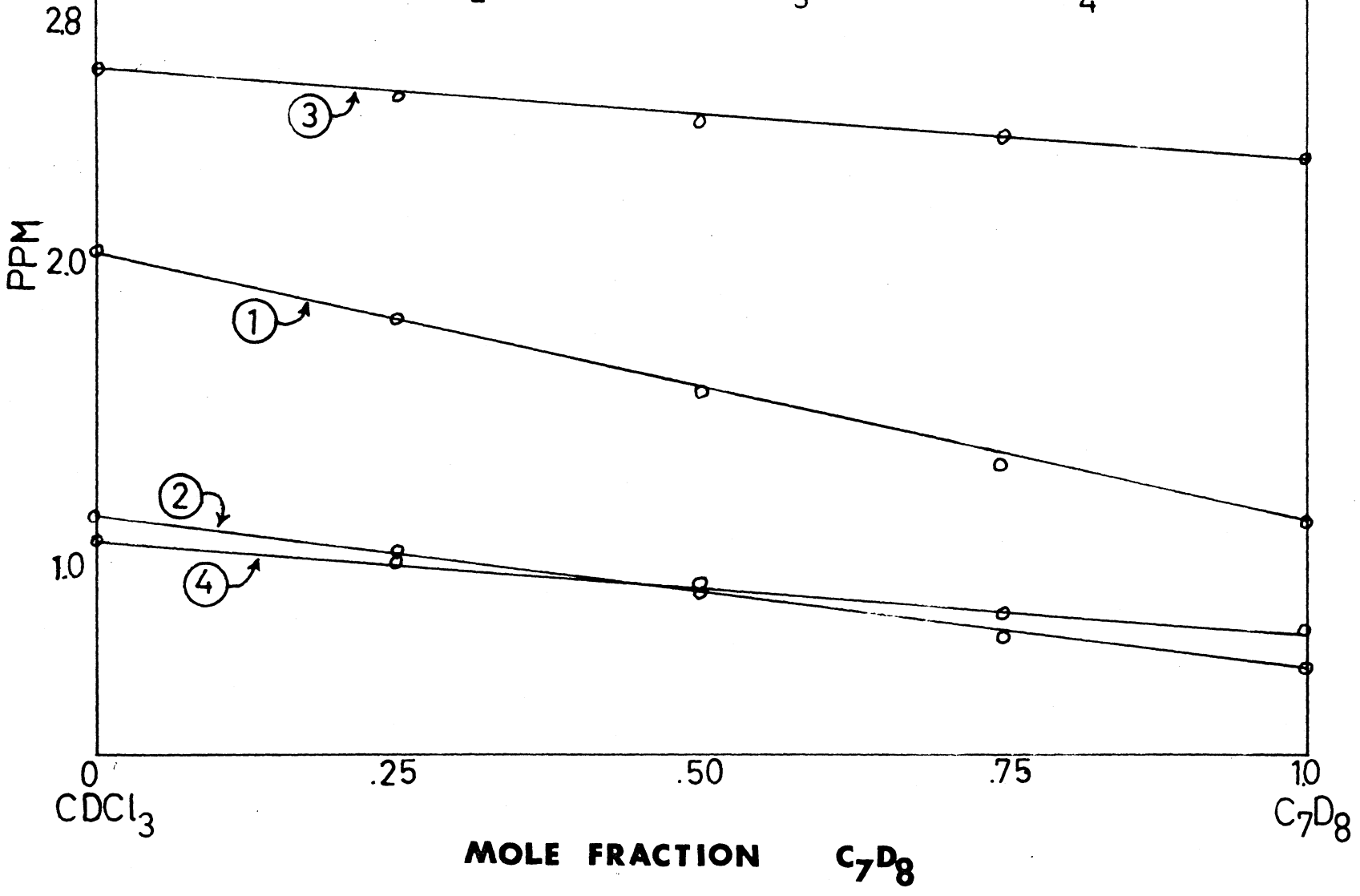
1. The hydroxyl protons have a negative $\Delta\ \delta$, while all other protons have a positive $\Delta\ \delta$.

2. The proton least affected by the solvent change or by the variation in temperature is the methine proton in compounds 2,4,8 and 9 - (Table IV).

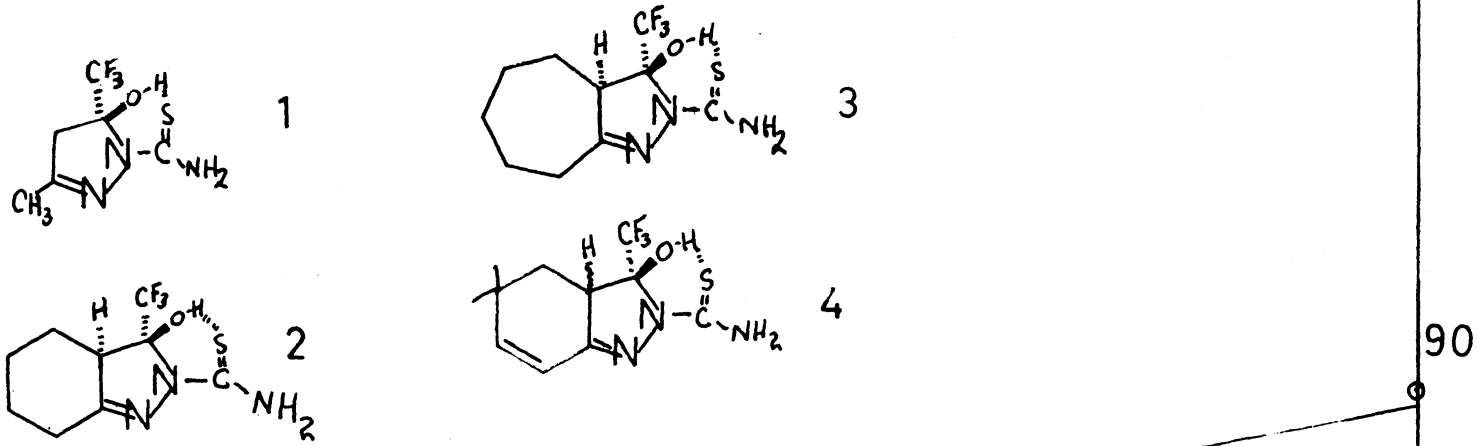
The paramagnetic induced-shift of the hydroxyl proton has been observed by Demarco and Spangle[58] and is attributed to the geometry of the collision complex. The induced-shifts in all protons are definitely due to the aromatic solvent and not to the differences in the dielectric constants of $CDCl_3$ and toluene-d_8. This is shown in Table V and Graph 9.

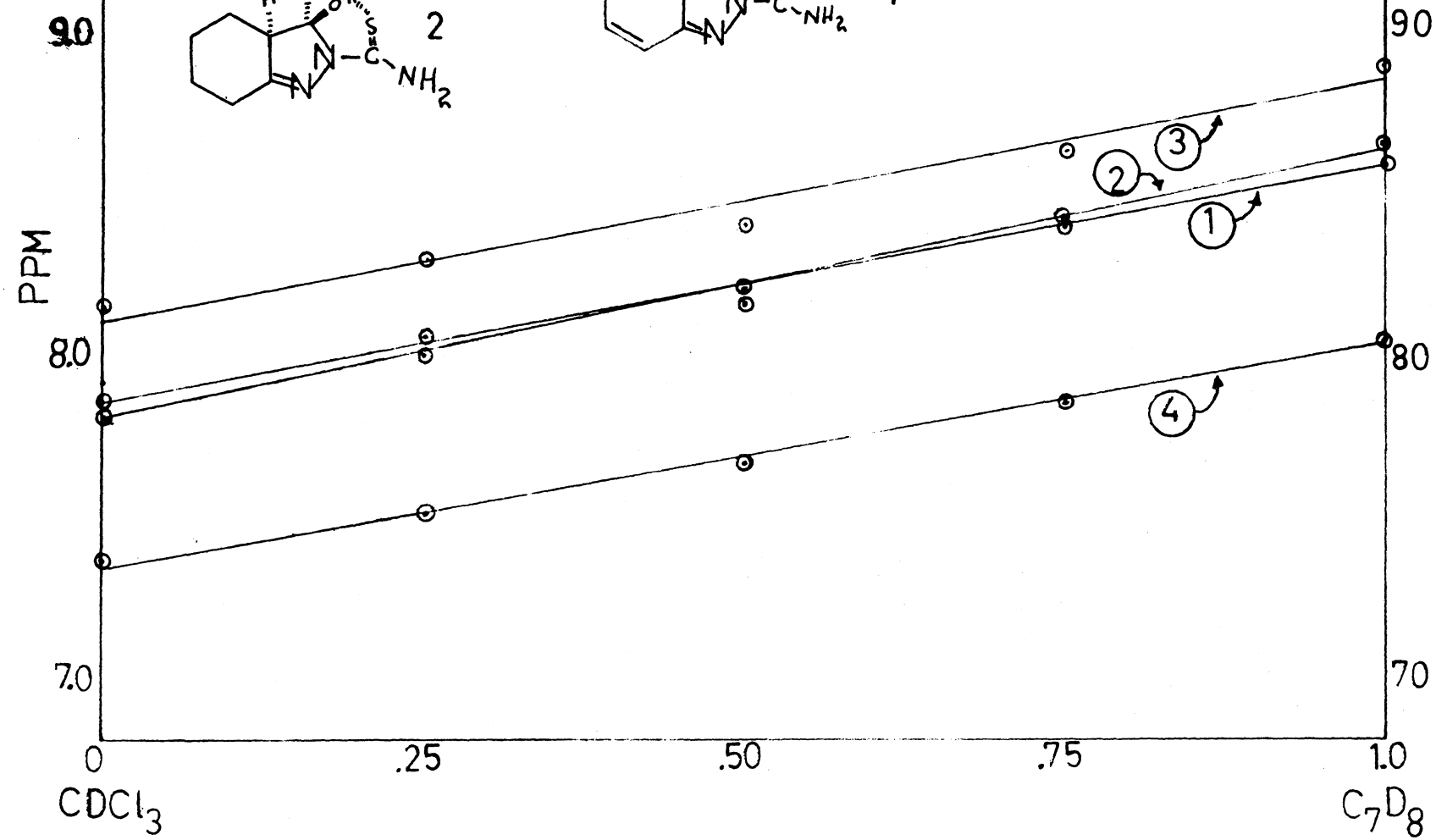
Graph 1. Chemical Shift vs. Mole Fraction of Toluene-d_8



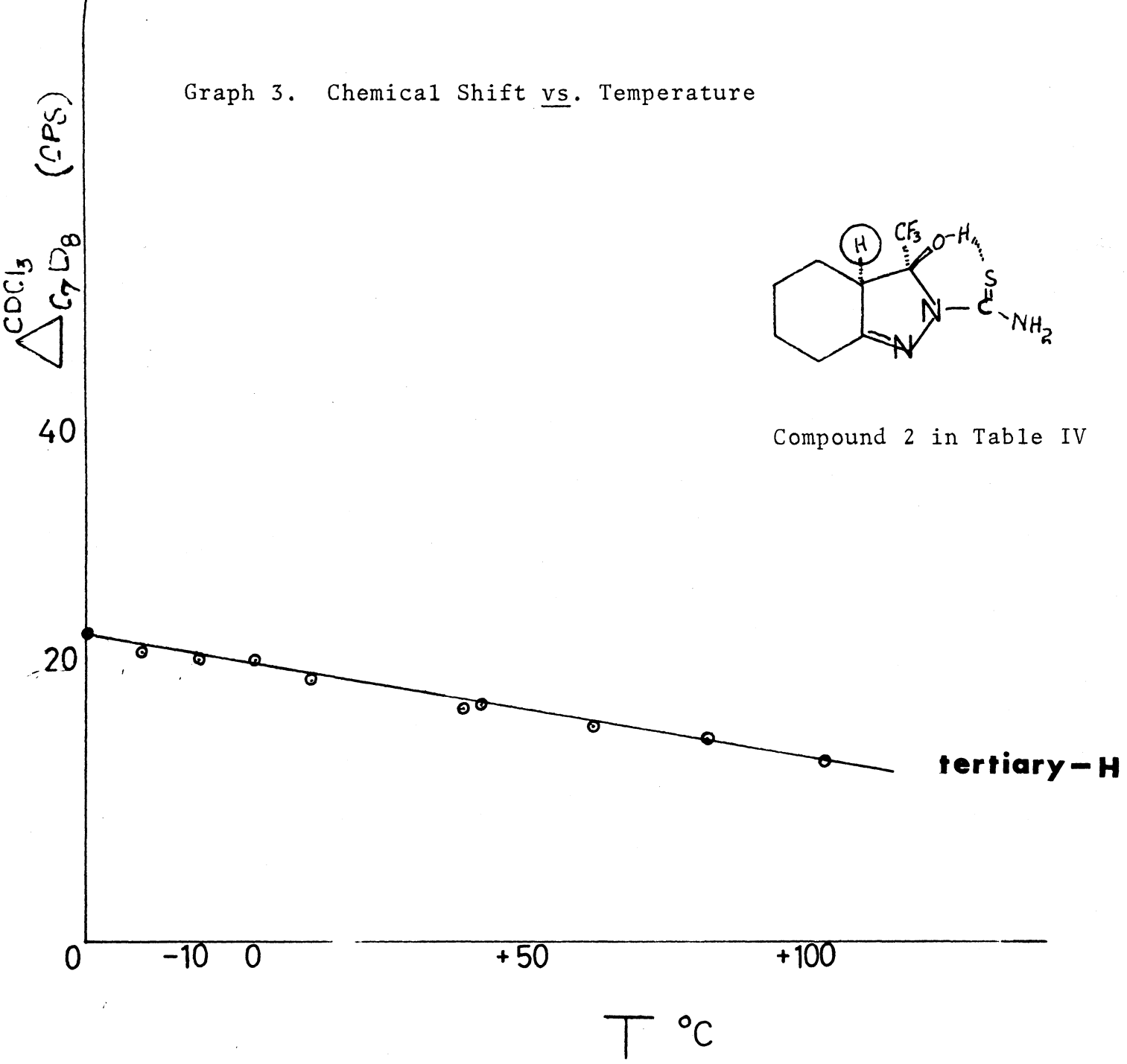


Graph 2. Chemical Shift vs. Mole Fraction of Toluene-d_8



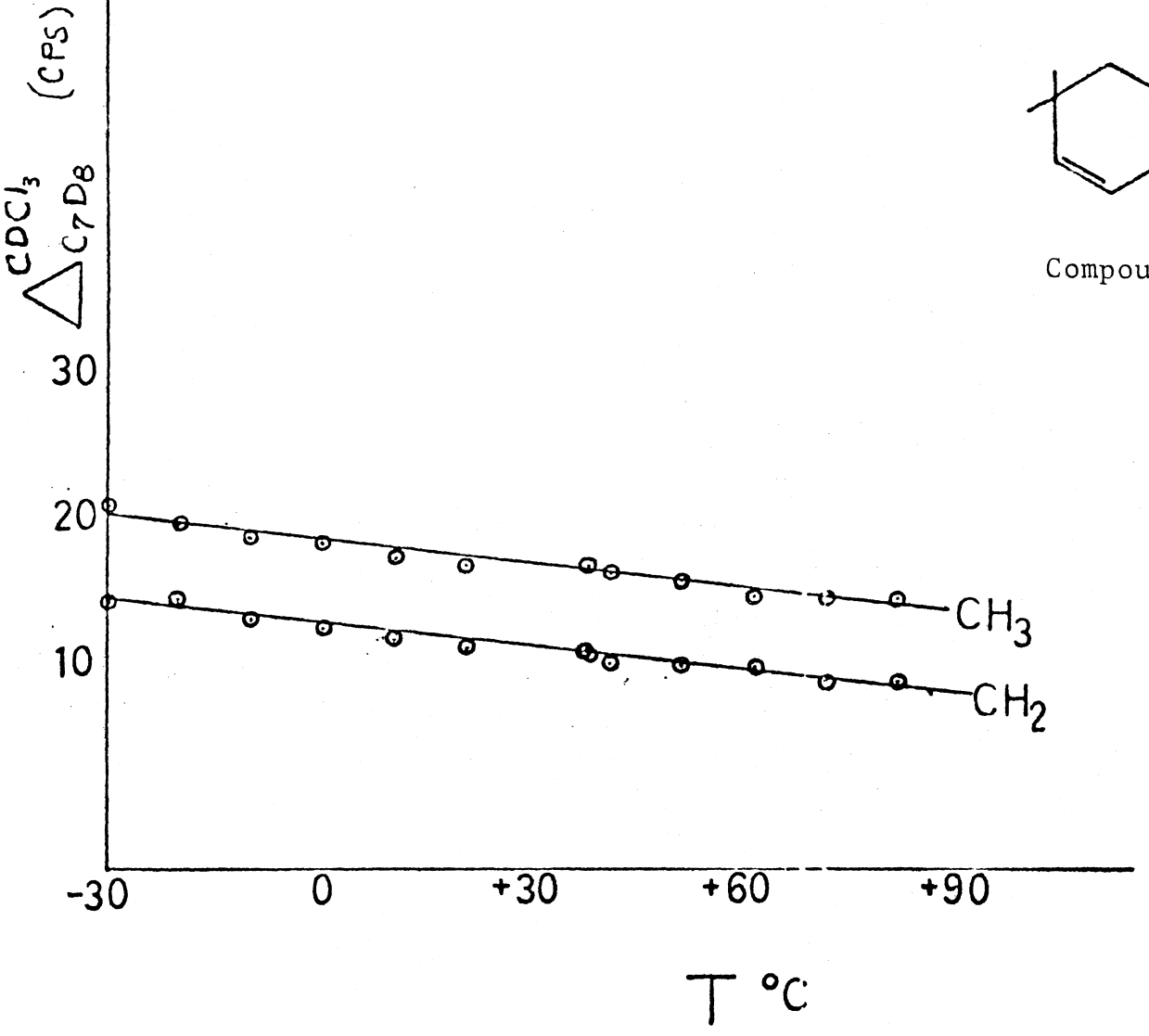


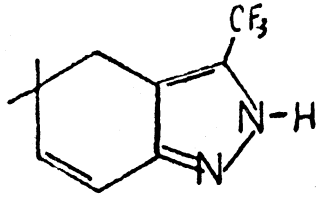
Graph 3. Chemical Shift vs. Temperature



Compound 2 in Table IV

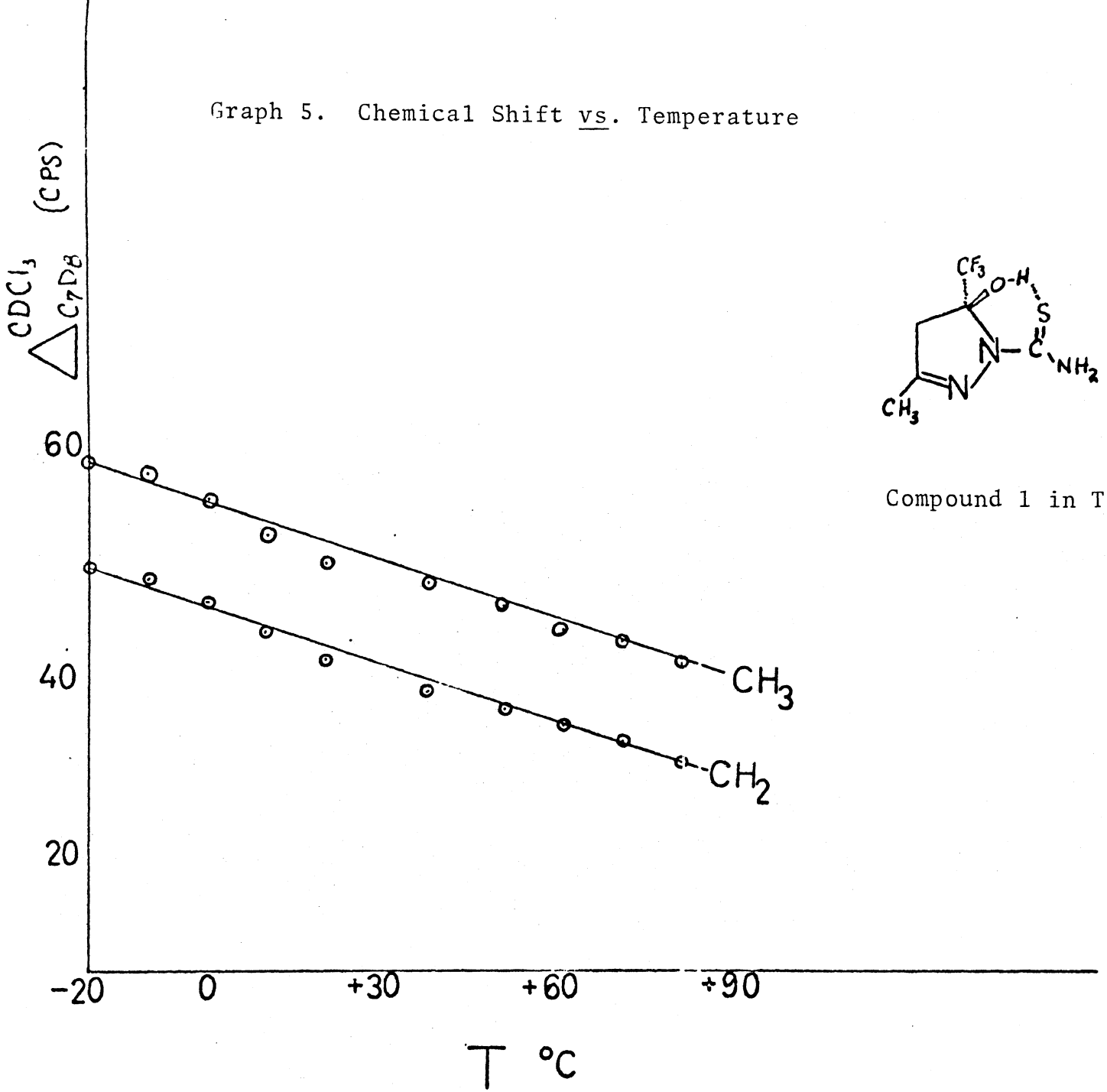
Graph 4. Chemical Shift vs. Temperature





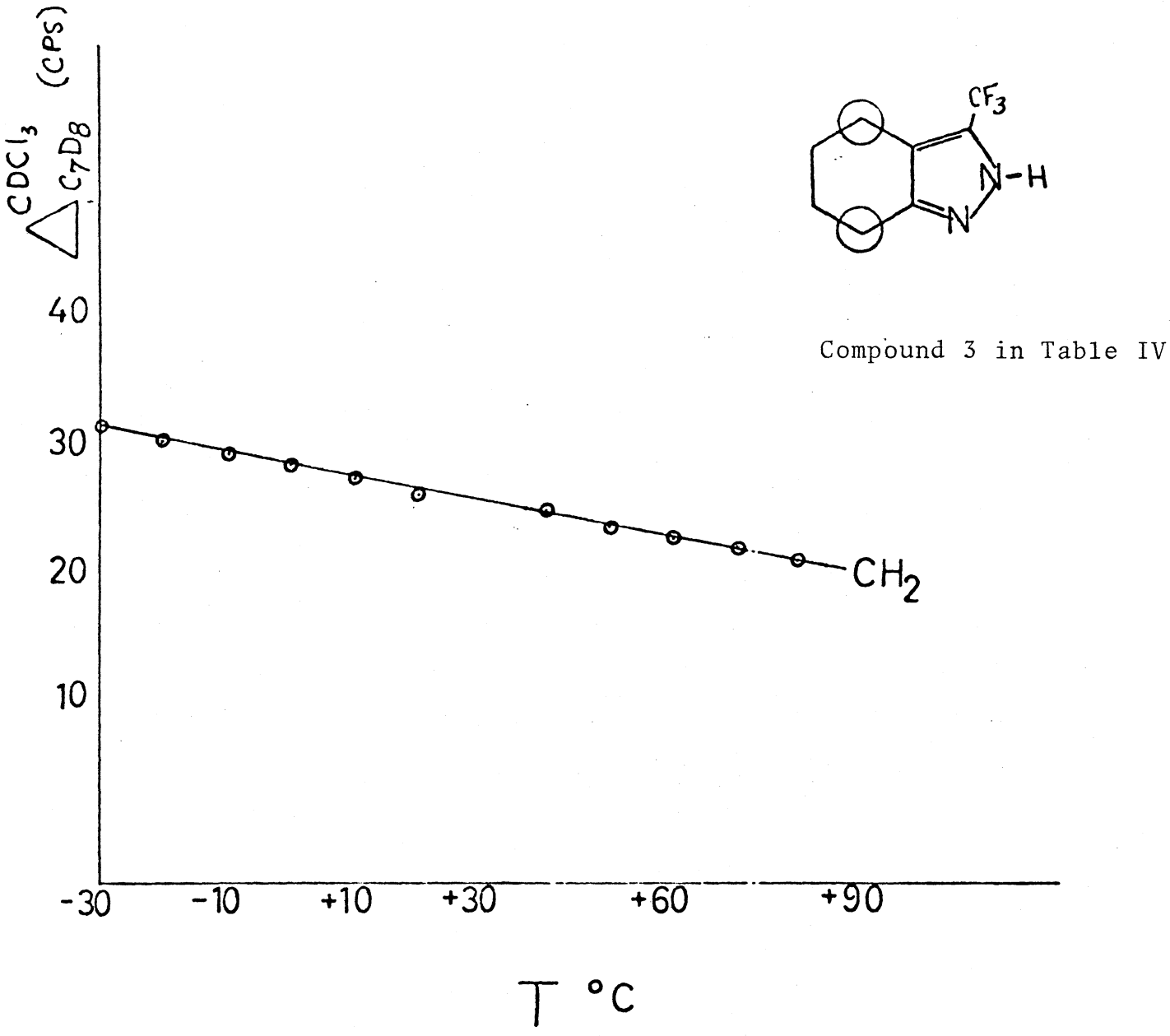
Compound 5 in Table IV

Graph 5. Chemical Shift vs. Temperature



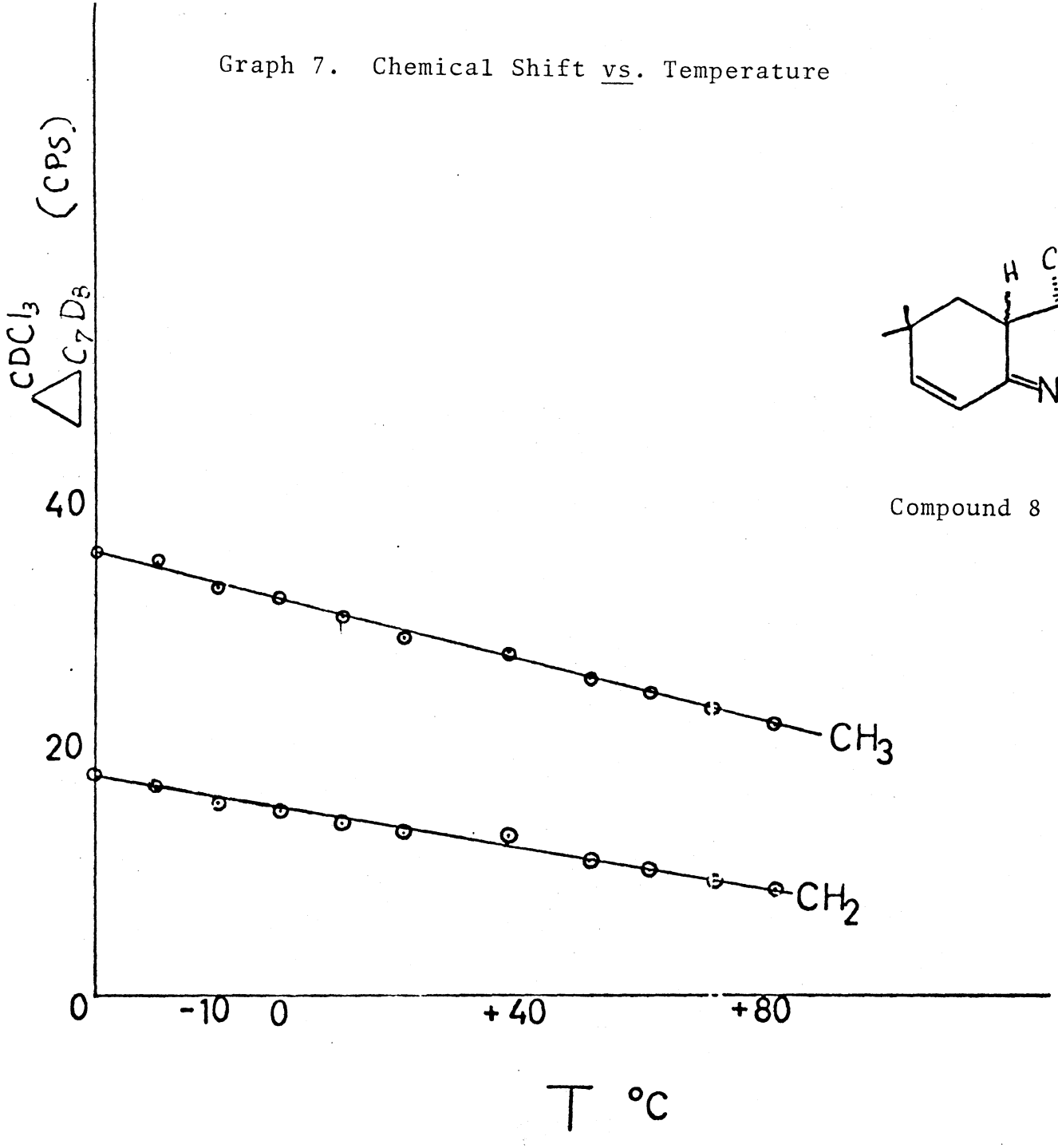
Compound 1 in Table IV

Graph 6. Chemical Shift vs. Temperature



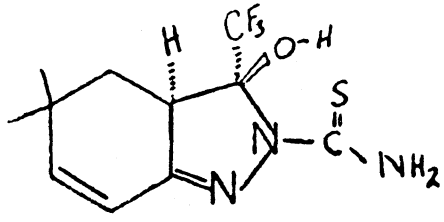
Compound 3 in Table IV

Graph 7. Chemical Shift vs. Temperature



Compound 8 in Table IV

Graph 8. Chemical Shift vs. Temperature

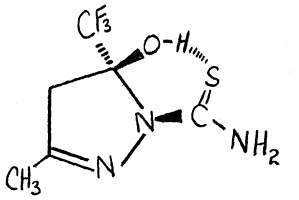


Compound 8 in Table IV

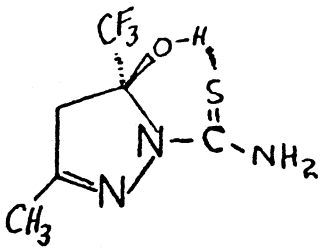
Table V. Induced Shift* Due to Change in Solvent System

Solvent	ε	$\frac{\varepsilon-1}{\varepsilon+1}$	$CH_2(\delta)$	$CH_2(\delta)$	$OH(\delta)$
Benzene	2.26	.39	1.18	2.65	8.60
CS_2	2.64	.45	2.09	3.21	7.68
$CDCl_3$	4.55	.64	2.05	3.28	7.85
CH_2Cl_3	9.10	.80	2.06	3.31	7.94
Pyridine	12.30	.85	1.88	3.42	--
Acetone	19.80	.90	2.08	3.42	8.28
CH_3CN	35.10	.94	2.03	3.38	8.13

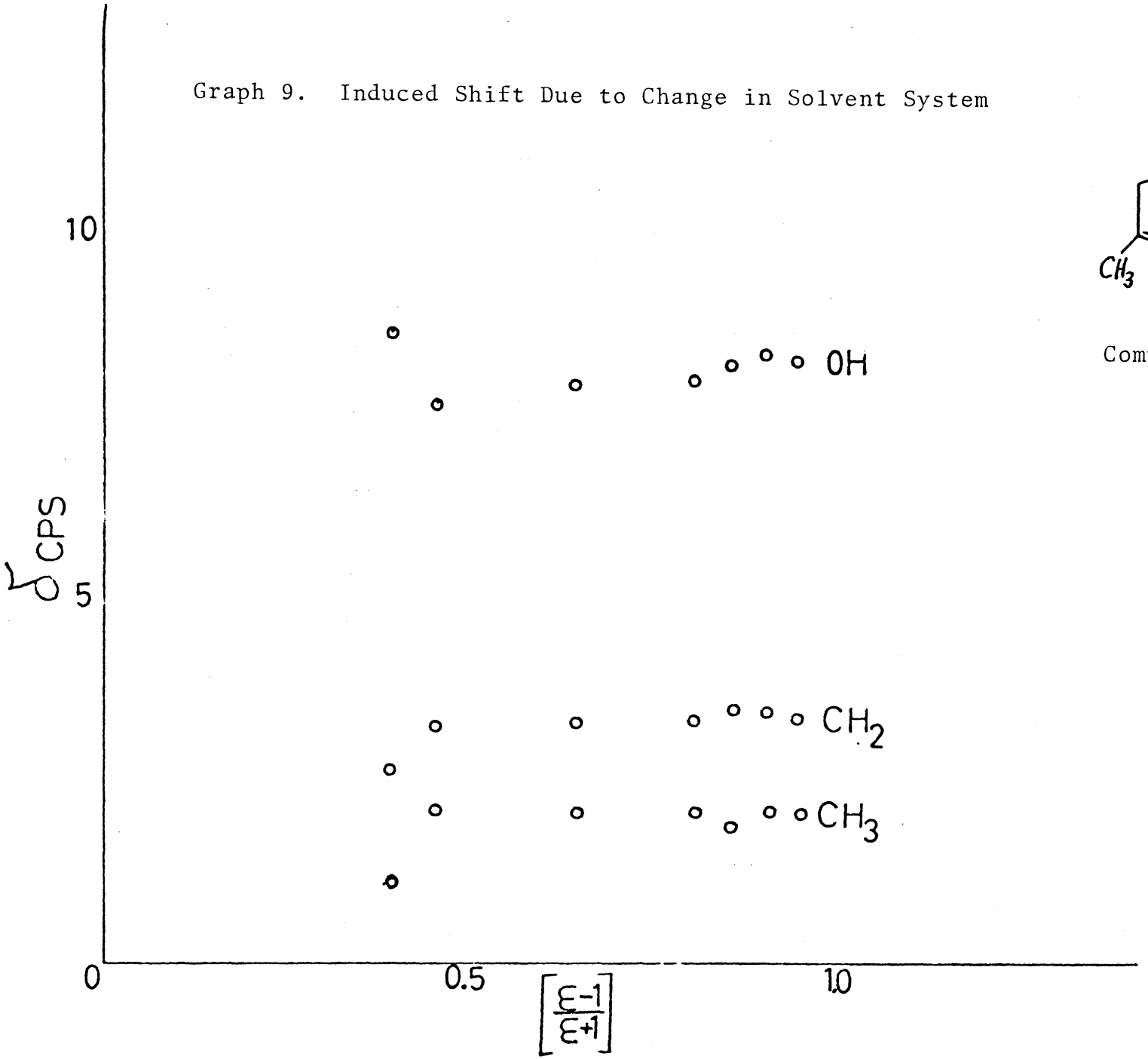
* Compound investigated.



Graph 9. Induced Shift Due to Change in Solvent System



Compound 1 in Table IV

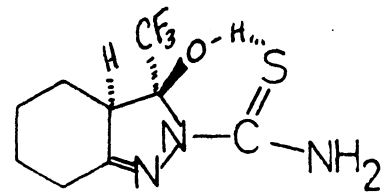


It is observed that the plot of chemical shift (δ) versus $(\varepsilon-1)/(\varepsilon+1)$ yields a zero slope from CS_2 to CH_3CN.

Furthermore, infrared spectroscopy shows strong intramolecular hydrogen bonding between the hydroxyl proton and the sulfur electrons. This interaction has been confirmed by Krueger[59] in a very elegant study on the intramolecular hydrogen bonding in o-aminophenols and o-aminothiophenols. Further evidence of -OH---S bonding is seen in Spectra 7 which is a low-temperature study of compound 2 (Table IV) in CD_2Cl_2. If -OH---N bonding predominated, the two protons on the amide nitrogen would have the same chemical shift at low temperature, since each proton would be fixed in space and have the same environment.

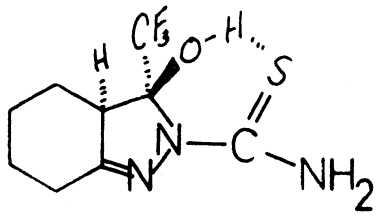
It has been shown that benzene solvent molecules can form a stereospecific complex with the polar groups of a solute molecule. Complex formation allows for valuable stereochemical and structural conclusions to be made from the solvent shift data. Compounds 2,4,8 and 9 in Table IV may exist in two isomeric forms. Figure (14) shows the methine proton <u>trans</u> to the hydroxyl group while Figure (15) indicates the relationship to be <u>cis</u>.

Spectrum 7. NMR Spectrum at $^{+}10°$ Centigrade

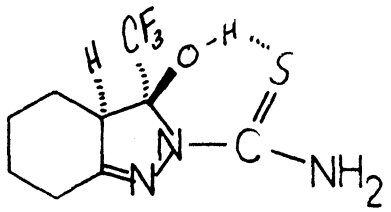


Compound 2 in Table IV

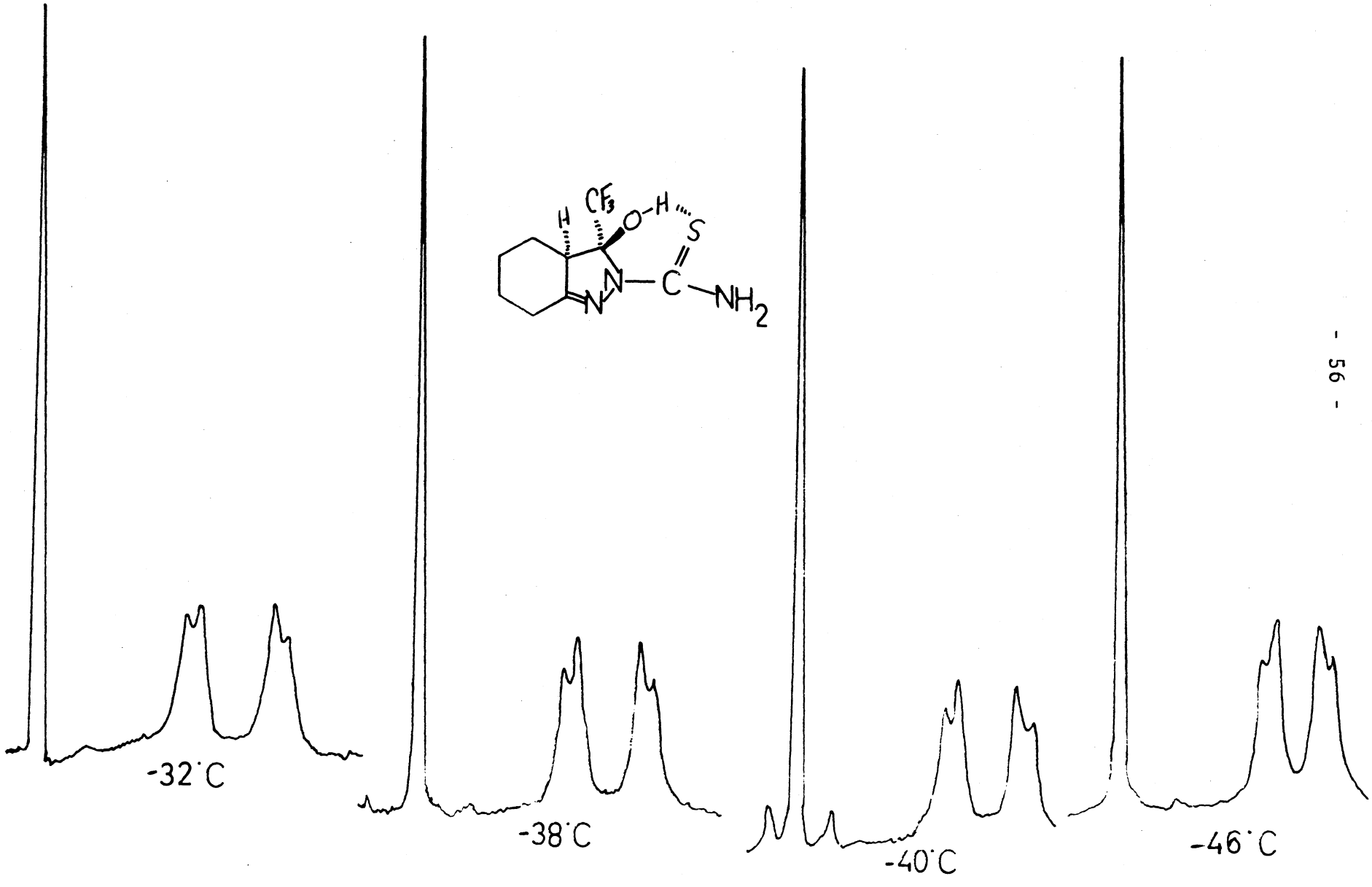
Spectrum 7. NMR Spectrum at 0° Centigrade



Spectrum 7. NMR Spectrum at -20° Centigrade



Spectrum 7. NMR Spectrum at -32°, -38°, -40° and -46° Centigrade



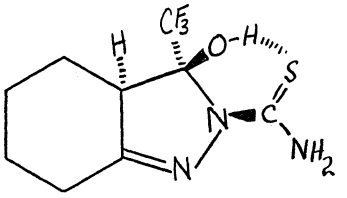


Figure (14)

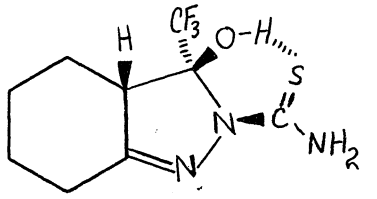


Figure (15)

Figure (16) shows the relationship between the aromatic system and the polar sites in the pyrazole derivative.

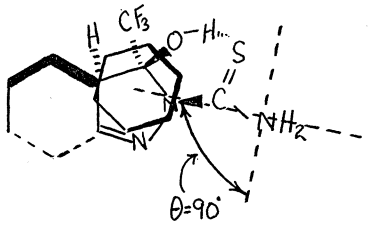
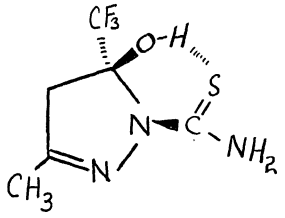
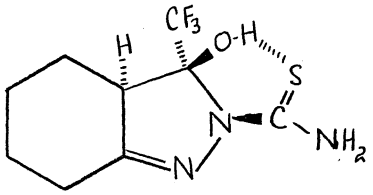


Figure (16)

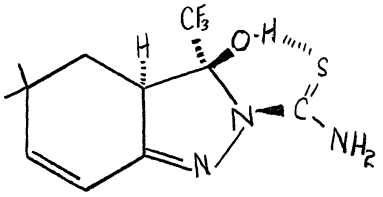
Steric requirements will dictate the "tightness" of the collision complex and explain why the methyl and methylene groups in compound (1) have a much greater diamagnetic shift than the methyl and methylene protons in compounds 2, 8 and 9. (Table IV)



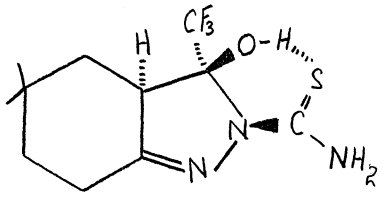
Compound 1



Compound 2



Compound 8

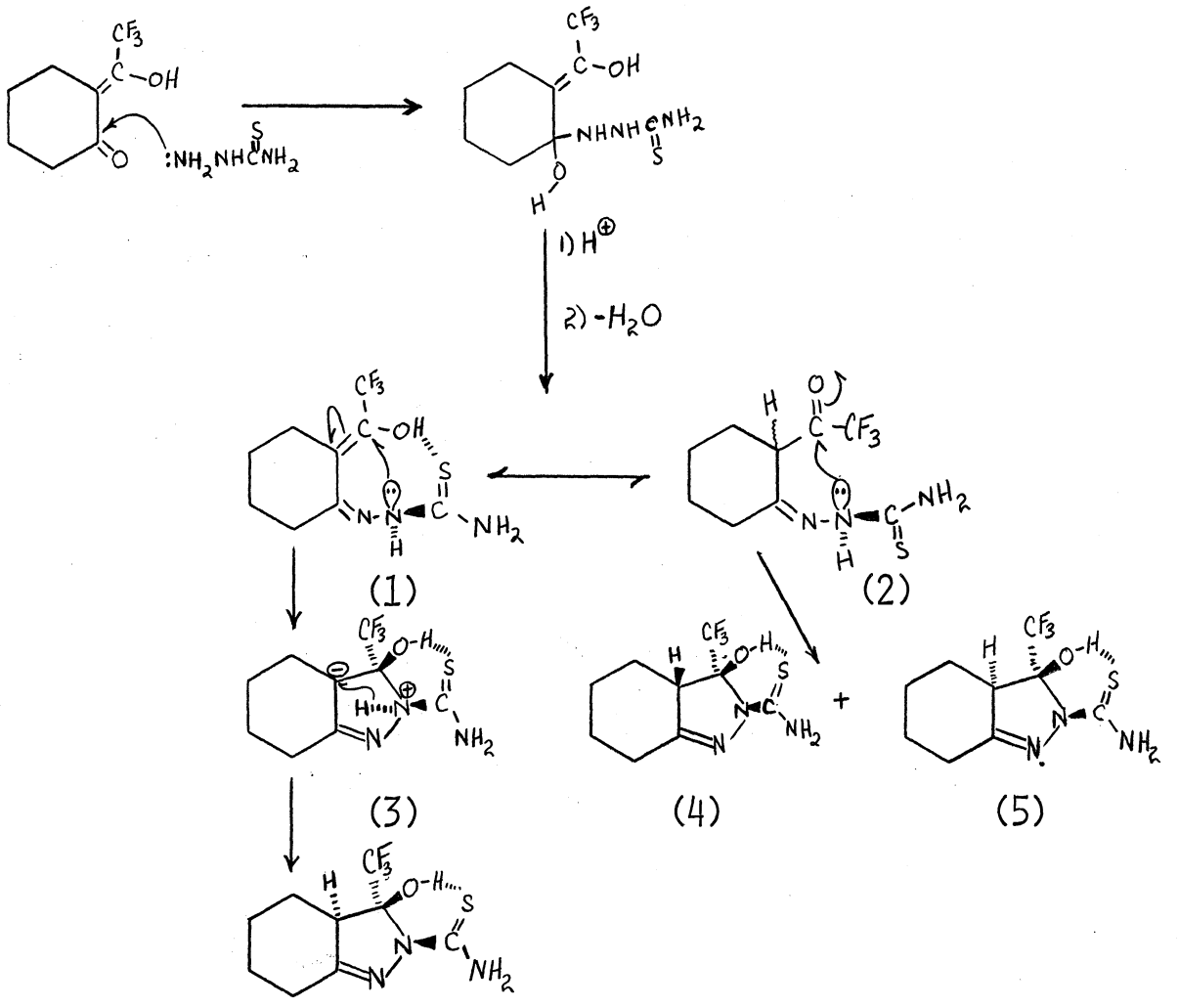


Compound 9

The methine proton must be trans to the hydroxyl group, since it is the least affected by the change in solvent system--thus being further away from the plane of the phenyl ring. The geometry of the collision complex also accounts for the upfield shifts of all of the other protons and in particular explains the very large diamagnetic shifts of the $-NH_2$ protons.

B. Stereochemistry of Trifluoropyrazoles

By knowing the stereochemistry of these compounds, it is possible to postulate a reaction mechanism for the cyclization step in the synthesis. Reaction Scheme III shows the initial attack of the carbazide on the carbonyl carbon* and subsequent protonation of the hydroxyl group to lose water and form thiosemicarbazone (1).



Reaction Scheme III.

The thiosemicarbazone also exists in the keto state (2) but the equilibrium will more than likely favor the enol form since it will be stabilized by conjugation as well as intramolecular H-bonding. Model inspection shows that cyclization may take place via the formation of the carbanion (3) which may be protonated by the proton leaving the positive nitrogen as shown in (3), via a backside attack. If cyclization occurred in the keto form (2), then two isomers may be expected (4 and 5), and is indeed what is observed in the ^{13}C NMR spectra of compound (8) of Table IV. The ^{13}C spectra of all other compounds showed one pure compound. The possibility that conformational effects were responsible for what was observed was considered, however, temperature studies clearly indicated that two isomers do indeed exist. The results are shown in Spectra 8. The possibility exists that the internal double bond affects the keto-enol equilibrium in favor of the keto form.

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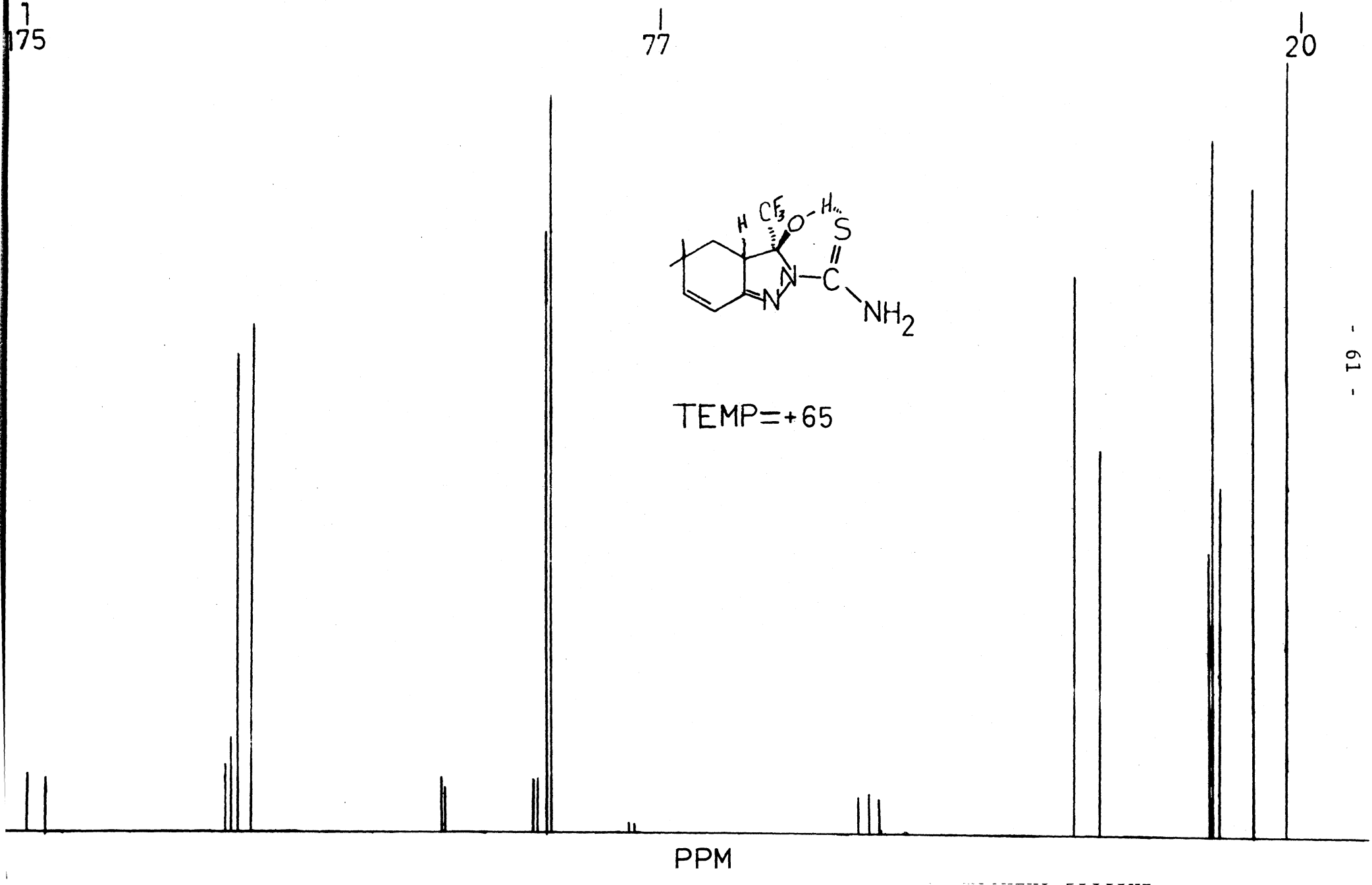
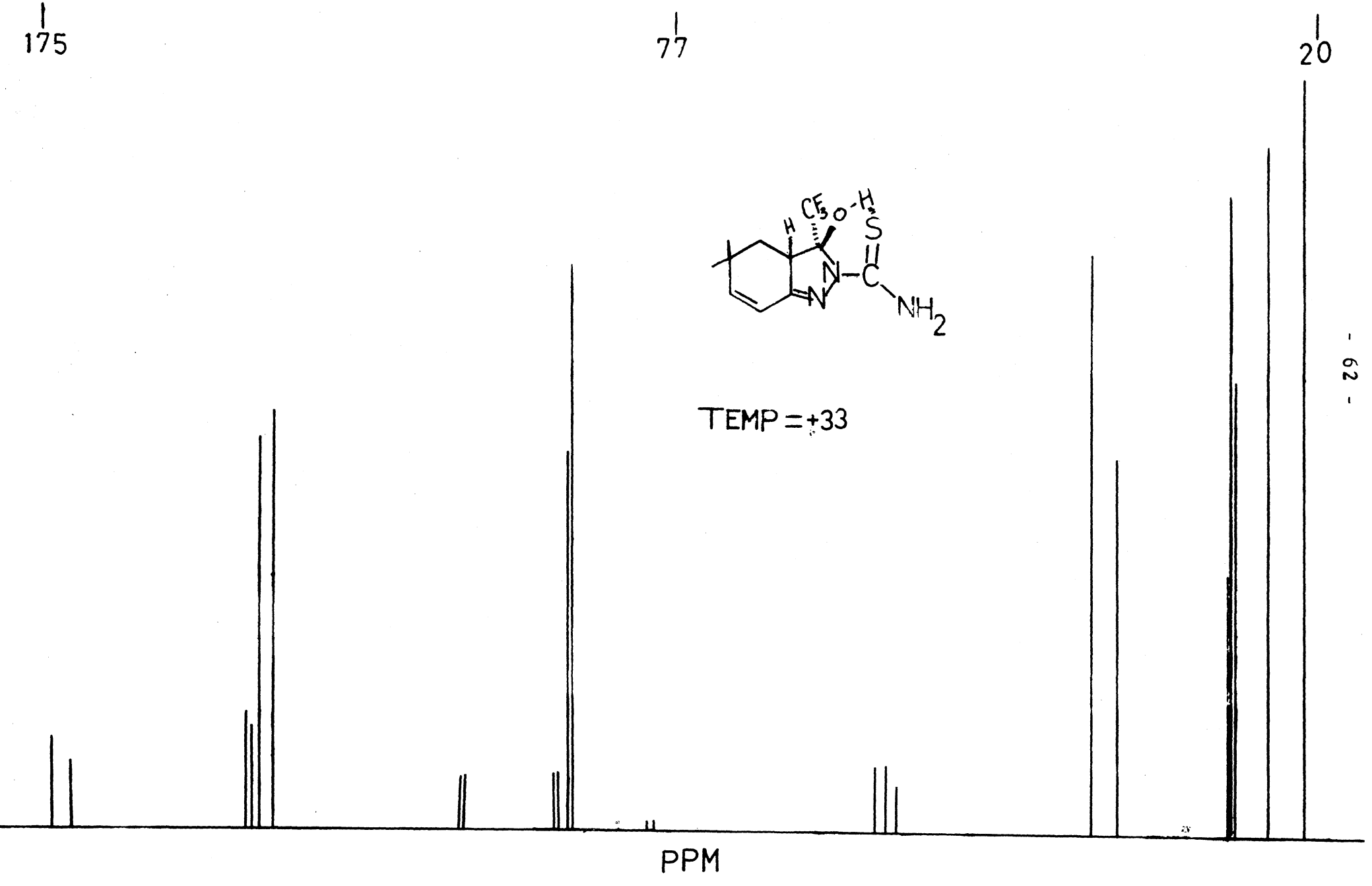
* That the initial attack is on the carbonyl carbon has been verified by Secor.[60]

Spectrum 8. ^{13}C NMR Spectrum of Compound 8 at +65° Centigrade



Spectrum 8. ^{13}C NMR Spectrum of Compound 8 at +33° Centigrade

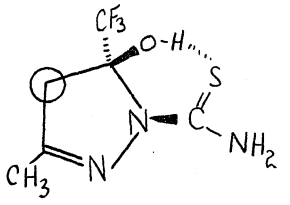


C. Strength of Collision Complex

The strength of the association between solvent and the polar solute molecules has been measured in the manner suggested by Abraham.[31] Tables VI-X show the data obtained at various temperatures while the accompanying graphs (Graphs 10-14) show the linear regression plots needed to obtain the heat of formation of each collision complex. Table XI is a summary of all of the parameters measured as well as the calculated enthalpy and entropy of formation. For one and two polar sites in the solute molecule, the range reported for the enthalpy of formation is -0.9 to -1.7 K cal $mole^{-1}$ while the entropy has a range of -3.5 to -4.4 e.u. All of the heats of formation are within reported limits while three of the entropy measurements are outside previously measured limits. The fact that multiple sites are present may account for this discrepancy. Nevertheless, the associations are seen to be extremely weak and slightly exothermic.

Table VI. DATA OBTAINED FOR STRENGTH OF SOLUTE-SOLVENT ASSOCIATION

(°K)	δ_{t*} (cps)	P	K_{eq}
253	147.0	.540	1.176
263	148.5	.524	1.101
273	150.5	.502	1.009
283	153.0	.475	0.906
293	155.5	.448	0.812
310	158.0	.421	0.727
323	159.5	.405	0.680
333	161.0	.388	0.635
343	162.0	.378	0.607
353	164.0	.356	0.553



* Calculations based on chemical shift of methylene protons

δ_o = 3.28 ppm

δ_c = 1.74 ppm

Equation of Line: y = 0.292905x-1.07851
Std. Err. of Slope: 0.006924
Correlation Coeff.: 0.997772

.10

\+

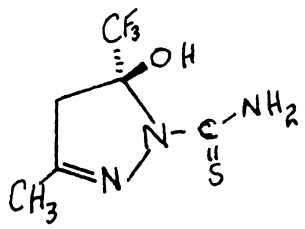
0

\-

Log_{10} K

.10

.20

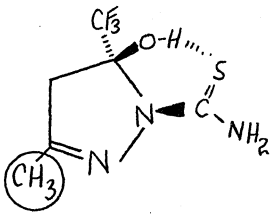


3.0 3.4 4.0

$\frac{1}{T} \times 10^3$

Table VII. DATA OBTAINED FOR STRENGTH OF SOLUTE-SOLVENT ASSOCIATION

(°K)	δ_{t^*} (cps)	P	K_{eq}
253	65.0	.574	1.346
263	66.0	.564	1.293
273	68.0	.544	1.194
283	71.0	.514	1.059
293	73.5	.489	.959
310	75.0	.474	.904
323	77.0	.455	.835
333	79.0	.435	.771
343	80.0	.425	.740
353	82.0	.406	.682



*Calculations based on chemical shift of methyl protons

δ_o = 2.05 ppm

δ_c = .365 ppm

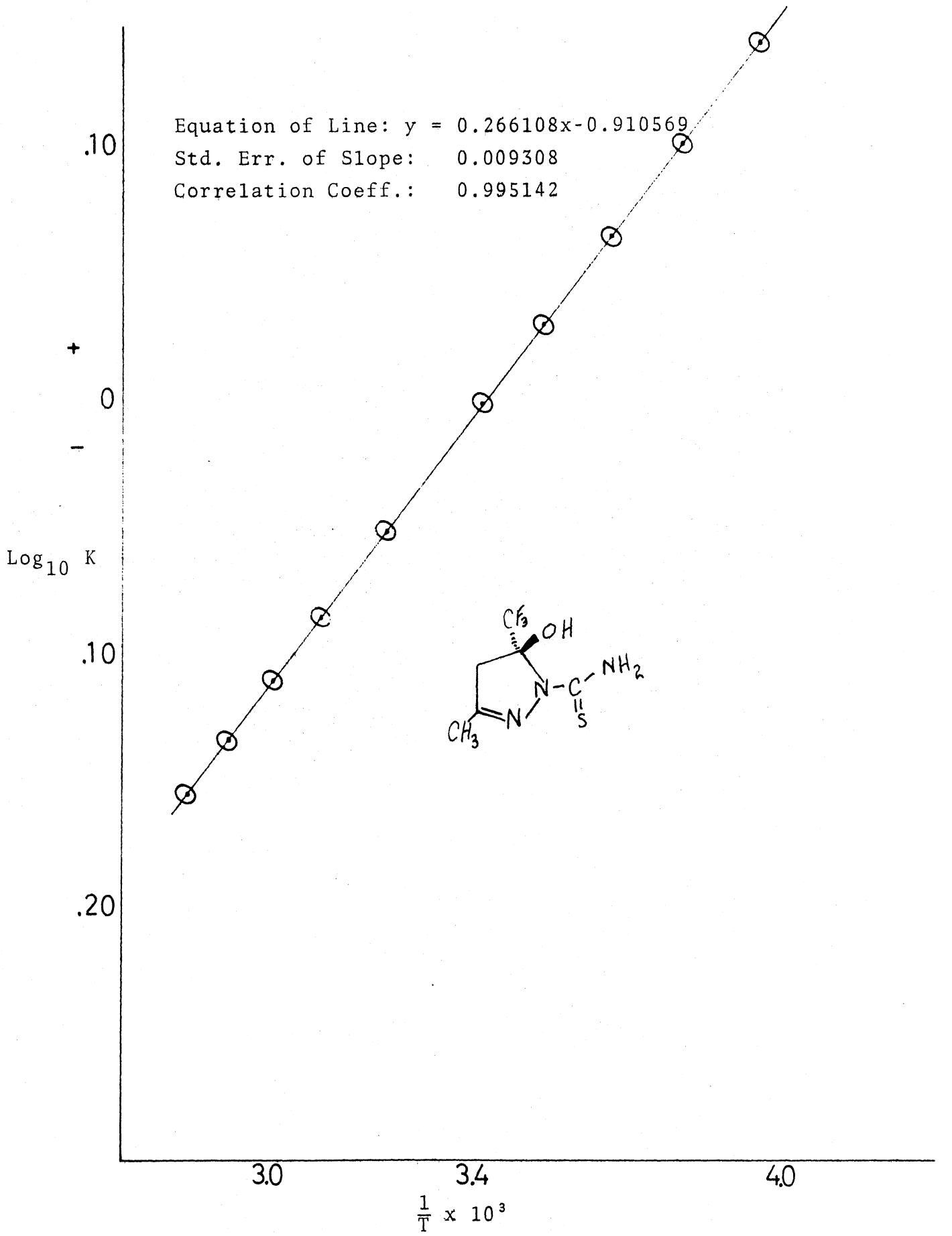
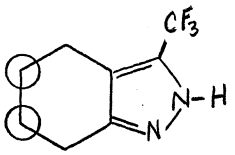

Equation of Line: y = 0.266108x-0.910569
Std. Err. of Slope: 0.009308
Correlation Coeff.: 0.995142
.10
+
0
−
.10
.20
Log10 K
3.0
3.4
4.0
1/T x 10³
CF3
OH
NH2
N
C
S
N
CH3

Table VIII. DATA OBTAINED FOR STRENGTH OF SOLUTE-SOLVENT ASSOCIATION

(°K)	δ_{t*} (cps)	P	K_{eq}
243	76.5	.581	1.384
253	78.0	.553	1.237
263	79.0	.535	1.148
273	80.0	.516	1.067
283	81.0	.498	0.991
293	82.1	.477	0.913
310	83.1	.459	0.848
313	83.2	.457	0.842
323	84.8	.428	0.747
333	85.5	.415	0.709
343	86.5	.396	0.656



*Calculations based on methylene chemical shift

δ_o = 1.80 ppm

δ_c = .896 ppm

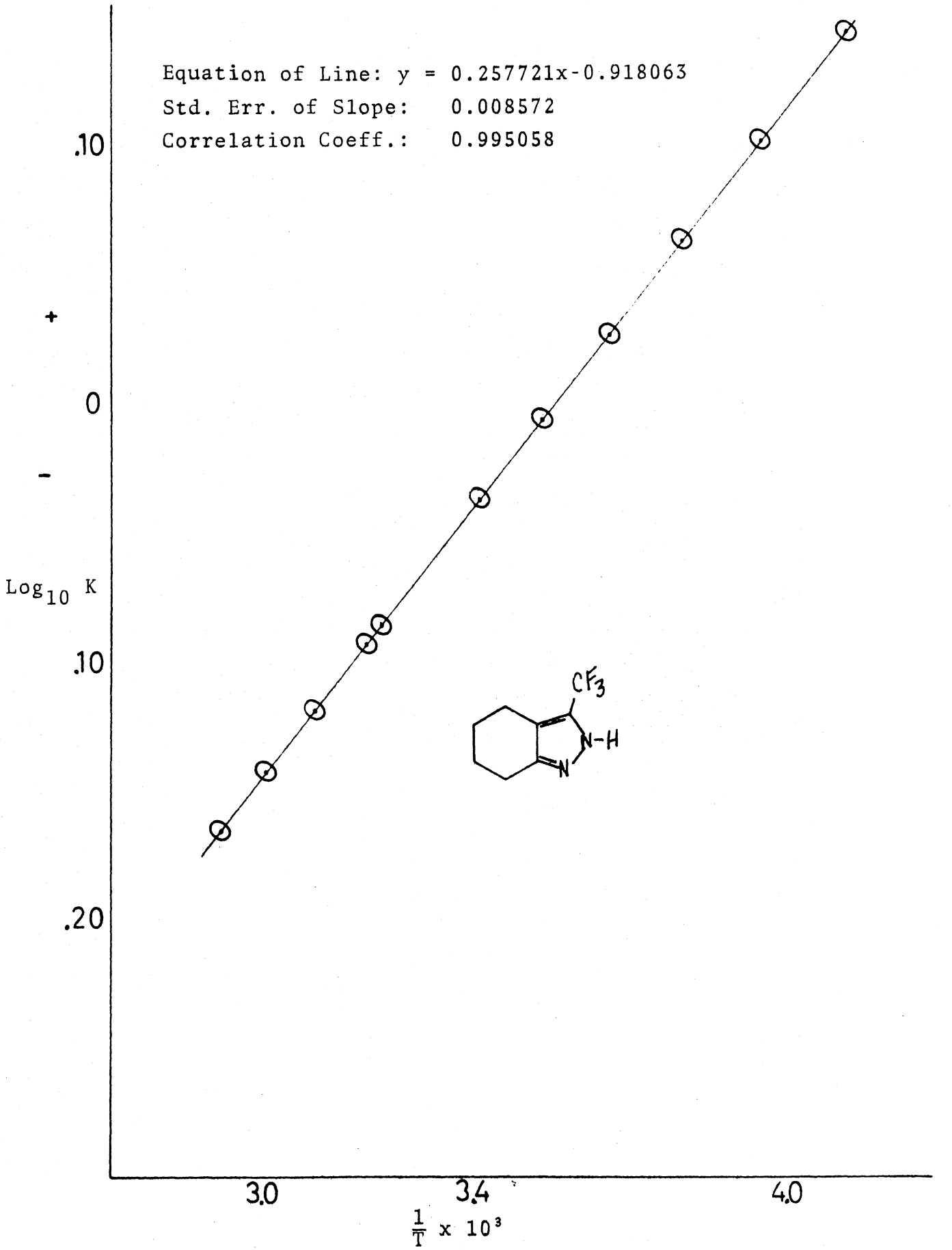
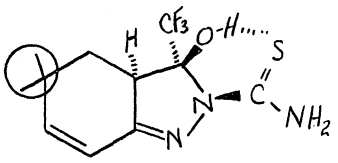

Equation of Line: y = 0.257721x-0.918063
Std. Err. of Slope: 0.008572
Correlation Coeff.: 0.995058
.10
+
0
-
Log10 K
.10
.20
CF3
N-H
N
3.0
3.4
4.0
1/T x 10³

Table IX. DATA OBTAINED FOR STRENGTH OF SOLUTE-SOLVENT ASSOCIATION

(°K)	δ_{t^*} (cps)	P	K_{eq}
243	33.0	.554	1.196
253	35.0	.515	1.064
263	37.0	.486	.946
273	38.1	.470	.887
283	39.2	.454	.831
293	41.0	.428	.747
310	42.2	.410	.695
323	44.5	.376	.603
333	45.5	.362	.567
343	47.0	.339	.514
353	48.0	.325	.482



* Calculations based on chemical shift of methyl groups

δ_o = 1.17 ppm

δ_c = 0.032 ppm

Equation of Line: y = 0.322981-1.241314
Std. Err. of Slope: 0.015190
Correlation Coeff.: 0.990192

.10

+

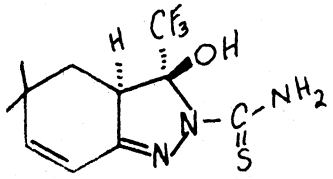
0

−

Log_{10} K

.10

.20

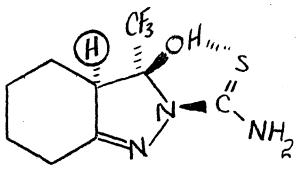


3.0 3.4 4.0

$\frac{1}{T} \times 10^3$

Table X. DATA OBTAINED FOR STRENGTH OF SOLUTE-SOLVENT ASSOCIATION

(°K)	δ_{t*} (cps)	P	K_{eq}
243	170.0	.528	1.120
253	171.5	.492	.970
273	172.3	.473	.898
283	174.0	.432	.762
310	176.5	.372	.593
313	176.0	.384	.624
333	178.0	.336	.506
353	179.0	.312	.454
373	181.0	.264	.359

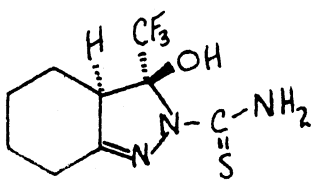


*Calculations based on chemical shift of methine proton

δ_o = 3.20 ppm

δ_c = 2.51 ppm

Equation of Line: y = 0.327632x-1.282151
Std. Err. of Slope: 0.019136
Correlation Coeff.: 0.988270



.10

\+

0

\-

Log_{10} K

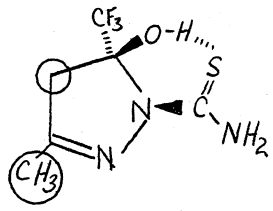
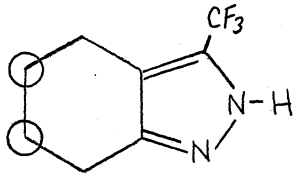
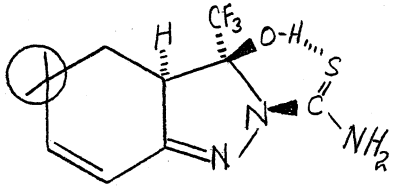
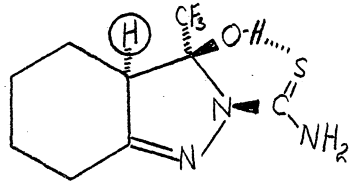
.10

.20

3.0 3.4 4.0

$\frac{1}{T} \times 10^3$

Table XI. SUMMARY OF DATA PRESENTED IN TABLES VI-X AND GRAPHS 10-14

Compound	δ_o (ppm)	δ_c (ppm)	ΔH (K Cal/Mole)	ΔS (e.u.)
	3.28 (1)	1.74	-1.34 ± 0.03	-4.94
	2.05 (2)	0.36	-1.22 ± 0.04	-4.17
	1.80 (3)	0.89	-1.18 ± 0.04	-4.20
	1.17 (4)	0.03	-1.48 ± 0.07	-5.68
	3.20 (5)	2.51	-1.50 ± 0.09	-5.87

(1) Based on the induced shift of the methylene protons
(2) Based on the induced shift of the methyl protons
(3) Based on the induced shift of methylene protons circled
(4) Based on the induced shift of methyl protons
(5) Based on the induced shift of methine protons

VI. SUMMARY

Aromatic Solvent Induced Shifts (ASIS) of some trifluoromethyl pyrazoles have been accomplished. The strength of the solute-solvent association has been measured and a reaction mechanism for pyrazole formation proposed.

The reaction mechanism (as is shown in Reaction Scheme III) involves an initial nucleophilic attack on the β-diketone by thiosemicarbazide to form the thiosemicarbazone and a second nucleophilic attack to form the pyrazole.

The cyclization step is seen to involve a backside attack by a proton, thus fixing the stereochemistry of the product.

The strength of the solute-solvent interaction has been measured in the manner suggested by Abraham[31] and is seen to be a weak association.

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BIOGRAPHY

The author was born July 1, 1943, in Greece. He attended primary and secondary public school in Canton, Ohio, graduating from Lehman High School in 1962. He attended Muskingum College, New Concord, Ohio and received a B. S. degree in 1966 with a major in Chemistry. He attended the University of Maine for one year (1966-67) and then taught school for two years. He joined Philip Morris, Inc. in 1969 and entered the Graduate School of the University of Richmond in 1970.