

AN ABSTRACT OF THE THESIS OF

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Behavior in Phenylsulfonylacetone and Acetohydroxamic Acid

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Abstract approved

The compound phenylsulfonylacetone was prepared, using a method slightly different than that given in the literature, so that an investigation could be made of the characteristics of the sulfonyl group and its influence on adjacent methylene protons. Measured portions of the sulfone were dissolved in methanol, nitrobenzene, and carbon tetrachloride, and the resulting solutions were analyzed on a Varian Model A-60 high-resolution nuclear magnetic resonance spectrometer. It was found that no signals in any of the resulting spectra could be attributed to an -OH proton of an enol tautomer. Intramolecular hydrogen bonding was therefore absent in the sulfone.

A spectrum was obtained for a methanolic solution of the sulfone to which sodium methoxide had been added in small, successive portions. Results indicated that exchange between the sulfone and the methoxide ion was occurring but that neutralization was

complete upon the addition of a sufficient amount of base.

An attempt was made to prepare a 1:1 molecular complex between the sulfone and diethylamine, but no complex of a specific composition could be obtained. Benzene and chloroform solutions of stoichiometric mixtures of the amine and sulfone, when analyzed by n. m. r. methods, were observed to undergo an exchange of some sort between the amine proton and those of the methylene group in the sulfone. Whether or not an enol form of the sulfone participated in the exchange could not be definitely determined because temperature-dependent studies to resolve the nature of a broad peak in the spectrum could not be performed. However, a plausible exchange mechanism has been postulated that accounts for the equivalence of the three protons involved by assuming a short-lived, intermediate state with labile hydrogen bonds that exists between hydrogen-bonded keto and enol forms.

Acetohydroxamic acid was prepared by methods similar to those in the literature, and a study was undertaken to see if tautomerism could be observed in the compound. N. m. r. spectra were taken for acetone and diglyme solutions of the acid, and no signals were observed that could account for the existence of any substantial amount of an enol form.

NUCLEAR MAGNETIC RESONANCE INVESTIGATION
OF ACIDIC PROTON BEHAVIOR IN
PHENYLSULFONYLACETONE AND ACETOHYDROXAMIC ACID

by

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NUCLEAR MAGNETIC RESONANCE INVESTIGATION
OF ACIDIC PROTON BEHAVIOR IN
PHENYLSULFONYLACETONE AND ACETOHYDROXAMIC ACID

Introduction: The field of high-resolution nuclear magnetic resonance spectroscopy has expanded with celerity in recent years, and its growth may be attributed to the successful utilization of the techniques of this area in the investigation of molecular structure, tautomerism, hydrogen bonding, isomerism, reaction rates, and chemical equilibria. The application of this spectroscopic analytic method to these several important subjects of concern is particularly valuable, but the lack of complicated apparatus and preliminary preparation that is often necessary in many analytic procedures underscores the usefulness of nuclear magnetic resonance techniques.

NMR Theory: Magnetic moments are a characteristic of some atomic nuclei, and under certain conditions these nuclei can absorb energy from an oscillating magnetic field in the radio-frequency range to produce nuclear magnetic resonance spectra. A resultant magnetic moment arises when the magnetic moments of the individual nuclei, upon placement in a magnetic field of constant strength, become oriented in the direction of the field. This resultant moment then precesses about the direction of the field.

A small coil connected to a radio frequency signal generator causes a small alternating magnetic field to be introduced at right angles to the original field, and this small alternating field rotates

about the direction of the original field at the applied radio frequency. The alternating field causes a tilting of the direction of the nuclear magnetic moment away from the original field, and the tilting increases as the radio frequency nears the frequency of precession of the nuclear moment about the direction of the original field.

Transitions induced between nuclear spin states which correspond to a change of orientation in the field by the magnetic nuclei occur at the resonant frequency, which is the frequency at which the applied radio frequency equals the precession frequency. The radio frequency voltage drop caused by the absorption of energy occurring in this process can be detected and recorded. The spectrometer employed in the research later described was a 60 Mc/sec high-resolution spectrometer of the cross-coil type manufactured by Varian Associates; it was designed to obtain spectra only for protons.

Chemical Shift: Although the manual operations involved in operating the A-60 spectrometer are relatively simple, the analysis of spectral data obtained from it is not always such an uncomplicated task. The chemical shift is one of the more important factors to be analyzed after having obtained spectral data. The chemical shift is observed when a signal for a proton is displaced on account of a variation in the screening constant for that particular hydrogen atom. Various protons within a molecule exist in different environments and are affected by the surrounding electrons. When molecules are subjected to a

magnetic field, moments are produced by the orbital motion of their electrons that create a second magnetic field acting on the nuclei. The screening constant, σ , is dependent on the electronic environment and is related to the second magnetic field by $H_{\text{local}} = H_0(1 - \sigma)$, where H_{local} represents the secondary magnetic field acting on the nucleus and H_0 is the applied field (19, p. 8). If protons, for example, are examined in differing environments, the screening constant will assume various values, displacing the signal for a proton in a certain locality.

Analysis of the chemical shifts for protons in a particular molecule, then, will aid in establishing the structure of the molecule. The chemical shift, δ , is given by $\delta = \frac{H - H_R}{H_R}$ and is expressed in ppm.

H corresponds to the resonant field of a signal measured at a fixed frequency, and H_R is the resonant field for a second proton signal that is selected as a reference (19, p. 87). With reference to some standard, if the electron density around a proton is decreased, the signal for that proton will shift down field or to the left on a spectrum. Likewise, if the electron density is increased, the signal will shift up field or to the right.

Signal Intensity: A second factor to be investigated in the analysis of spectra is the signal intensity. From the signal intensity may be directly ascertained the relative number of protons that give rise to

the signal if a reasonably good separation between the different signals in the spectrum occurs. To determine the signal intensity requires an estimation to be made of either the peak height or the area under the peak. Determination of the area under the peak is generally more accurate, especially when signals are not of the same width.

Spin-spin Coupling: The phenomenon of spin-spin coupling occurs when fine structure is noticed in the spectra of molecules containing two or more different sets of equivalent nuclei. Through the bonding electrons, a spin-spin interaction results between non-equivalent nuclei that creates a fine structure by splitting the primary resonance signals of equivalent nuclei into further components.

For example, in the $-\text{CH}_2\text{CH}_3$ group, there are two sets of equivalent nuclei. The signal for the methyl protons will be split due to interaction with the methylene protons, and a triplet structure will arise because each of the methylene protons has two spin states. Likewise, the methylene signal will be split by interaction with the equivalent methyl protons, and since there are four spin components for the methyl protons, it will appear as a quartet.

Generally, then, the signal for a particular set of n_A equivalent nuclei of type A interacting with n_X equivalent nuclei of type B will have $2n_X I_X + 1$ components; the X signal will show $2n_A I_A + 1$ parts (19, p. 94). I is the nuclear spin.

The ratio of the corresponding binomial coefficients determines the relative intensities of each group of signals. Two equivalent nuclei would produce a triplet structure in the resonance signal of a nucleus in juxtaposition with which they interact, and relative intensities of the peaks would be in the ratio of 1:2:1. A quintet would appear as the resonance signal for a nearby nucleus when four equivalent nuclei interact; 1:4:6:4:1 would be the relative peak heights. These predictions for fine structure of resonance signals can be applied only when the value of the chemical shift is large compared with the spin coupling constant.

Factors Affecting Spectrum: A number of factors affect the nature of the n. m. r. spectrum, such as solvent effects, sample viscosity, and mechanical spinning of the sample. Careful consideration of these influences is requisite before a reasonable interpretation of the spectrum can be made. In fact, some of these factors must be taken into account long before the analysis is performed, so that experimental conditions may be adjusted to eliminate as much as possible any undesirable or deleterious effects that will produce a spectrum not easily explicable.

Solvent Effects--Bulk Diamagnetic Susceptibility: One factor, the nature of the solvent employed in n. m. r. experiments, sometimes exerts a profound influence on the type of spectrum that results. The bulk diamagnetic susceptibility of the solvent is a property for

which allowance must be made when calculations of the chemical shift for a particular signal in the spectrum are being carried out. This effect results from an induced magnetism in the region between the sample boundary and some arbitrarily defined sphere, at the center of which is a nucleus. Not only must the susceptibility of the solvent be taken into account, but that of the solute and of the reference compound need to be included in the calculations of the chemical shift.

Susceptibility corrections need only be applied when an external reference is employed. When the reference compound is in solution in the sample (internal standard), no correction is necessary because the susceptibilities are the same. Because small chemical shifts are observed in proton resonance spectra, this correction becomes significant.

Susceptibilities vary with temperature because thermal expansion results upon a temperature rise; it is important to be reminded of this when spectra have been taken over an appreciable temperature range.

Anomalous Aromatic Solvent Effects: An interesting solvent effect is noticed in the case of aromatic solvents, for example, benzene. Unusual diamagnetic susceptibilities are a characteristic property of them. A circulating current is induced in an aromatic ring subjected to a magnetic field, and therefore a secondary magnetic field results from the circulating current. The secondary field

acts on a nearby solute proton, causing it to undergo a resonance signal shift. The extent of the shift depends on concentration because the distance of approach of solvent or solute molecules determines how effective the secondary field is. Thus, benzene and other aromatic solvents are responsible for anomalous shifts in proton resonance signals.

Hydrogen Bonding: A second way in which solvent behavior contributes to the structure of the spectrum is to create chemical shifts that can be accounted for by ascribing them to intermolecular interactions between solute and solvent molecules or among solute molecules themselves. Hydrogen bonding between the solute and solvent is one of these molecular interactions that has been a phenomenon of much interest to chemists. The degree of intermolecular hydrogen bonding between solute and solvent, if any, in a sample is dependent upon the solvent, and the extent of such can be approximated from spectral data.

A hydrogen atom experiences a change in its electronic environment when a hydrogen bond is formed because it is drawn away from the atom to which it is attached. The resultant change in magnetic shielding between the associated and non-associated states alters the nature of the proton signal in the spectrum so that it is seen at a frequency representing an average of the shielding for the two states. Because temperature changes will affect the proportion of molecules

existing in the associated and non-associated forms, signals will shift correspondingly.

Indeed, hydrogen bonding has been investigated in compounds by measuring the chemical shift of a proton signal at varying temperatures. Arnold and Packard noted that the OH proton signal for ethanol shifted to high field by approximately 1.6 ppm when the temperature was raised from 160 to 350°K (3).

Proton Exchange: Proton exchange may occur in systems where the molecules are associated by hydrogen bonds that are relatively strong, and the rate of exchange, which is temperature-dependent, may be measured by proton magnetic resonance methods. Raising the temperature of a system has the effect of increasing the rate of exchange. If exchange takes place slow enough so that the lifetimes of the states exceed the critical value given by $\tau\Delta\nu \approx \frac{1}{2\pi}$ (τ is the smallest time for which two individual states are distinguishable, and $\Delta\nu$ is the separation of the corresponding resonance signals), two signals will arise in the spectrum, but when the rate increases as a result of higher temperatures, the two signals are observed to coalesce into a single peak (19, p. 100).

An interesting observation of this effect was made by Schneider and Reeves when they studied the proton exchange rate as a function of temperatures of a 2:1 molar ratio of ethanol and water (24, p. 860-861). As they increased temperature, they noted a gradual coalescence of the

OH-group signals and a corresponding shift to high field because the dissociation of hydrogen bonds became greater with higher temperature.

Choice of Solvents: The choice of solvents to be used in n. m. r. investigations is a matter of no little concern, for it is important to select a solvent which will not produce a spectrum of its own that interferes with the resonance signals of the sample. Obviously, if peaks attributable to the solvent obscure sample signals, then it becomes impossible to completely and correctly interpret the spectrum for the sample. For example, when water is the solvent or is present in the solvent as an impurity, a characteristic broad signal is obtained which can blot out a large portion of the spectrum. Signals for protons bonded to a nitrogen atom often appear as broad peaks; therefore, sagacity would dictate the use of a non-aqueous, anhydrous solvent to eliminate the possibility of a broad water signal interfering with or being mistaken for the nitrogen proton signal.

Solubility Considerations: Solvents should be selected so that maximum solubility of the sample can be achieved, for it is desirable to have solutions of about ten mole percent to analyze if possible. Considerable difficulty is frequently encountered in the choice of solvents because a particular solvent may possess the appropriate properties for dissolving a compound sufficiently, yet may be one that produces an interfering spectrum.

Viscosity Effects: Sometimes samples possess high viscosity,

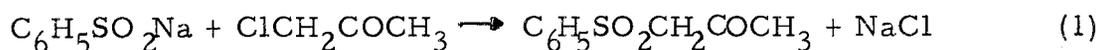
which will cause broadening of the signal; this effect may be diminished by diluting with the solvent or by raising the temperature of the sample. Elevating the temperature, however, is not a plausible solution to the problem if the sample decomposes at higher temperatures.

Sample Spinning: Mechanical spinning of the sample produces the effect of improving the homogeneity of the applied magnetic field. If the field varies by some quantity and a certain molecule is subjected to the range of variation of the field during a given time interval, then as the time interval is decreased, a nucleus in the molecule acts as if it were being affected by the average value of the field. When t , the time interval, becomes approximately equal to $\frac{1}{\gamma \Delta H}$ (γ is a constant and ΔH is the field variation), this behavior becomes appreciable (19, p. 69).

Now that some essential features of nuclear magnetic resonance spectra have been discussed, a presentation of theoretical and experimental data pertinent to the subject of this thesis will be given. Then it will become more clear how n. m. r. has been applied in the investigation of some properties of phenylsulfonylacetone and acetohydroxamic acid.

PREPARATION OF PHENYLSULFONYLACETONE

Preparative Procedure: The preparation of phenylsulfonylacetone according to the reaction given below



was a more challenging task than was anticipated, and it became necessary to prepare several yields. Thus, a good opportunity was provided to devise improvements upon the method described in the literature (16, p. 403-404). Difficulty was encountered obtaining satisfactory yields of the sulfone because sizable loss was sustained during recrystallization steps; therefore, repetition of the preparative procedure was necessitated.

Reagent grade chloro-2-propanone, benzenesulfinic acid sodium salt, and 95% ethanol were the reagents needed initially. Although different quantities of reagents were used each time the synthesis was performed, the sodium salt and the chloro-2-propanone were always mixed in stoichiometric amounts. The sodium salt was first mixed with the ethanol in a round bottom flask, and the chloro-2-propanone was added in portions at intervals during reflux. Reflux was allowed to continue for at least two hours, or longer if the reaction was not complete.

Upon termination of reflux, the ethanol was removed by distillation. A dark brown liquid, containing the product, remained upon completion of the distillation, and after standing for several hours, it solidified and added to the already solid sodium chloride and any unreacted reagents or solid impurities present as a result of side reactions. Distilled water was used to remove the hardened mass of reaction products from the flask. The first time the sulfone was prepared, the solid products were washed with an approximate 1M sodium chloride solution and pressed on filter paper to remove some of the oily impurities as the procedure from the literature directed, but in succeeding preparations, these steps were omitted because they were inefficient and accomplished nothing particularly helpful in the recovery scheme.

From an aqueous mixture of the solid products, then, the sulfone was extracted by shaking three times with separate portions of U. S. P. grade diethyl ether. As the sulfone and oily impurities were extracted into the ether layer, the hard, solid sodium chloride dissolved slowly in the aqueous layer. The three ether extracts were combined and evaporated to dryness on a water bath.

Purification: Using the technique suggested in the literature for purification of the sulfone obtained after evaporation of the extract proved to be a time-consuming and unprofitable operation, resulting in substantial loss of product. Recrystallization from alcohol and then

hot water, using charcoal to absorb impurities, was the recommended technique. Recrystallization from hot water, using Nuchar, was employed for the first two times the sulfone was prepared. The main difficulty experienced was that the Nuchar failed to absorb all of the oily impurities, apparently because a small amount of the oils was just soluble enough in the hot water to run through the filter in the Buchner funnel and contaminate the filtrate containing the product.

Numerous successive recrystallizations became necessary in order to reduce the amount of contaminating oils to a degree of purity such that a melting point of 57°C for the sulfone could be obtained for the first yield. Losses were sustained during each of the recrystallizations due to slight solubility of the sulfone in cold water, and it was found that a large quantity of the product was lost because it was adsorbed along with the oils by the Nuchar. This was substantiated when good yields of sulfone were obtained simply by reheating with additional water the filter paper and Nuchar residues from the successive recrystallizations first performed and filtering and cooling as before. Some sulfone was also obtained by evaporating the filtrates and recrystallizing again with substantially less water to reduce solubility losses.

Even after so many recrystallizations, a melting point of 57°C for the sulfone could not be achieved for the second yield that was prepared, so, in order to proceed with greater celerity and to obtain larger and more pure yields, an attempt was made to discover an

improved method of purification. Using the impure sulfone of the second yield, small amounts were added to hexane, benzene, and a hexane and benzene mixture, but these solvents were found unsatisfactory for recrystallization purposes. Success was achieved with diethyl ether, however.

The impure sulfone was dissolved by stirring vigorously and heating it to 34.6°C , the boiling point of the ether. Upon cooling of the solution to room temperature, the sulfone crystallized out in fine white crystals, and the impurities, which remained soluble in the ether, were removed by careful decantation of the mother liquor. It was found that the use of an ice bath to accelerate cooling decreased crystal size and yield. Although this new method of purification gave a much cleaner product than before, the melting point for this and succeeding yields of sulfone remained in a range of approximately 47°C to 55°C . Desiccation over phosphorus pentoxide failed to aid in achieving the correct melting point, so it was concluded that minor amounts of impurities and not water were responsible for the incorrect melting points.

When further yields of sulfone were prepared, the recrystallization using Nuchar and hot water was completely omitted; therefore, several recrystallizations from boiling ether were required to produce a reasonably pure yield. The yield was improved by combining all the

mother liquor that had been decanted, evaporating it to dryness, and repeating the recrystallization on the residue. It must be conceded that there was some loss due to solubility of the sulfone in cold ether, but this was slight and probably less than in cold water. In total, less loss was sustained using the new technique in place of the recommended procedure in the literature, and it was considerably more efficacious.

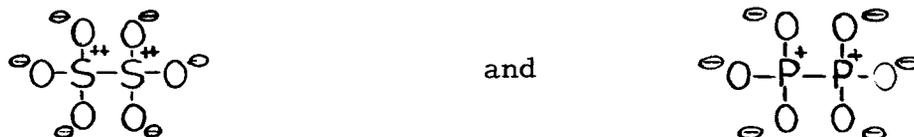
SULFUR-OXYGEN BOND CHARACTER AND ACIDIFYING INFLUENCE OF SULFONYL GROUP

Introduction: The investigation of the bonding characteristics and extent of the acidifying ability of groups containing sulfur and oxygen, for example, sulfoxide and sulfonyl groupings, has occupied the attention of no few chemists. In particular, the issue of whether or not sulfur expands its valence shell has not been clearly resolved, and the explanation of the acidifying ability of the sulfoxide and sulfonyl groupings is still under consideration, although more definite conclusions have been drawn in regard to it than to the expansion of sulfur's valence shell.

Prior to the advent of the Lewis theory, it was believed that sulfur could achieve a maximum covalency of only six, but later, acceptance of the possibility of achieving the octet structure prevailed. Then, in 1930, Ingold and Jessop postulated a ten-electron structure for the sulfur atom to account for the alkaline paraffinic decomposition of sulfones (11). The possibility of valence shell expansion became more tenable when, later, the idea was invoked to explain the activating influence of the sulfonyl group on an adjacent methylene group in the Michael condensation between benzyl p-tolyl sulfone and benzalacetophenone (5).

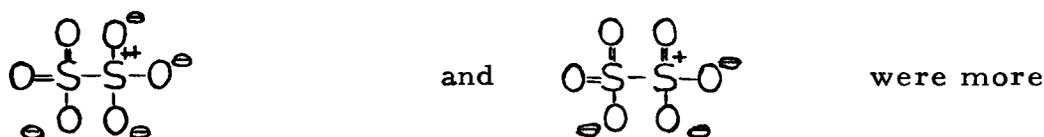
Valence Shell Expansion: Valence shell expansion theory fostered doubt with regard to the validity of the octet theory for elements

situated in the second and succeeding rows of the Periodic Table. For example, Pauling and Brockway raised the objection that similar charges on adjacent atoms negate the validity of Lewis octet structures like



which had been invoked to account for the surprising stability of dithionic acid ($\text{H}_2\text{S}_2\text{O}_6$) and of hypophosphoric acid ($\text{H}_4\text{P}_2\text{O}_6$) (18).

They suggested that such structures as

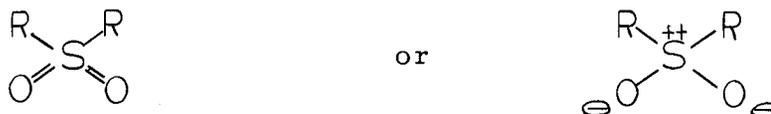


important, and in these it is recognized that an expansion of sulfur's valence shell is necessary.

Since 3d orbitals would be involved in valence-shell expansion it would be well to mention a few points in this respect. Arndt and Eistert have considered that the energy required to promote an electron to a 3d orbital should be so excessive as to not permit such a transition and therefore prohibit expansion of the valence shell (2, p. 451). Gould points out that the 3p and 4p orbitals of heavier elements are substantially greater in size than those of the first-row elements and that bonding strength would therefore be of considerably less magnitude on account of less effective orbital overlap (9, p. 219). The 3d electrons are only weakly bound, and the energy of promotion would not be

compensated by the energy gain due to an increase in covalency.

Structure of Monosulfone. It has been postulated that either the structure



may account for the bonding characteristics of sulfur in a monosulfone (13). In the latter structure, it is most likely that the four primary σ bonds occur on account of tetrahedral sp^3 hybridization in the sulfur atom's positively charged shell. Valency-shell expansion is the explanation advanced for the existence of the first structure. Because of the presence of two 3d orbitals, two strong π bonds can be formed, and also the possibility of forming two additional π bonds of much weaker strength exists through the utilization of two more d orbitals. Thus, a tetrahedral hexavalent state for sulfur in sulfones is explained.

The assumption that sulfones can possess hexavalent sulfur atoms is plausible since the existence of sulfur hexafluoride is known. The promotion of two electrons to 3d orbitals to form an sp^3d^2 hybrid is responsible for the existence of this compound. It is important to recognize that here the resultant energy from the formation of the bond is greater than that required for promotion.

Evidence for Double Bond: For sulfoxides, sulfones, and sulfur oxides, Moffitt has arrived at the conclusion, by application of the

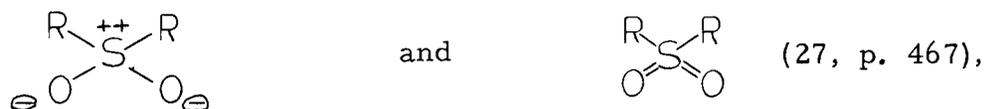
molecular orbital method, that the sulfur-oxygen bond is mainly a double bond (15, p. 409). Pauling is of this opinion also because the S-O bond length has been found to be $1.432 \pm 0.001 \text{ \AA}$ in sulfur dioxide and $1.43 \pm 0.02 \text{ \AA}$ in sulfur trioxide (17, p. 329); these distances are actually less than the calculated length of a sulfur-oxygen double bond (1.49 \AA).

Lister and Sutton have employed the techniques of electron diffraction to measure the sulfur-oxygen bond length in dimethyl sulfone. A value of $1.44 \pm 0.03 \text{ \AA}$ resulted from their work (14), a value in accordance with those given by Pauling. The very short S-O bond length, compared to that calculated for a normal sulfur-oxygen double bond has, nevertheless, been ascribed to the formulation of double bonds by contribution of pairs of electrons from negative oxygen atoms to vacant 3d orbitals in the positive sulfur atom. At least, it is certainly implied that sulfur is not tetravalent in dimethyl sulfone and that the bonds are not semipolar.

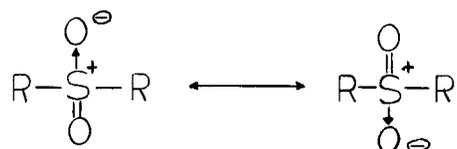
Sutton also used dipole moment data to support his view that the S-O bond has double bond character. Using the observed moments of several sulfones, he calculated that the bond-moment values ranged from 2.2 to 2.9 debyes or 31-43 percent of theoretical values for a semipolar bond (25, p. 373-419). The calculations of Cumper and Walker give higher values than Sutton; 40-62 percent ionic character is indicated by their estimates (6). Price concludes that either the double-bond or

semi-polar structure will suffice to account for the bond-moment values. Electrons will be situated more closely to sulfur in a semi-polar bond but nearer to oxygen in a covalent double bond. The greater electron affinity of neutral oxygen than of neutral sulfur or the larger electron affinity of positively charged sulfur than negatively charged oxygen could account for the difference in the direction of shift (20, 67-68).

Wheland is of the opinion that the actual structure for a monosulfone is intermediate between



and Amstutz, Hunsberger, and Chessick feel that sulfones should be represented as resonance structures, principally to account for a lack of basic character and for their stability (1).



Infrared spectra have been observed for various sulfur-oxygen compounds in an attempt to clarify the nature of the sulfur-oxygen linkage. Bernard, Fabian, and Koch measured the S-O stretching frequency in sulfur dioxide, some sulfones, and sulfonyl and thionyl halides, and they found that it was greater than that of sulfur monoxide. They concluded that a covalent double bond was substantiated and that

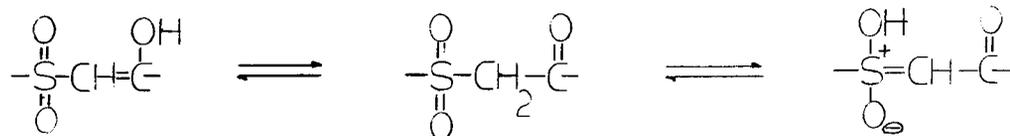
only a minor amount of semi-polar character was present. Further, they demonstrated that the S-O bond was weaker in sulfoxides than in sulfones. It is interesting to note that they were also able to show that sulfoxides and sulfones form hydrogen bonds and that such bonds are stronger in sulfoxides than in sulfones (4, p. 2449-2450). The results of Gillespie and Passerini (8), who made cyroscopic measurements on some aromatic sulfides, sulfoxides, and sulfones, are in agreement with the conclusions of Barnard, Fabian, and Koch.

Semi-polar Bond: Although convincing evidence has been presented for the case of the covalent double bond, there is information to support the case of the semi-polar bond as well. Price states, on the basis of deductions from molecular refraction data of Vogel, Cresswell, Jeffrey, and Leicester, and of Price and Gillis, that the S-O bond is definitely semi-polar. And he cites the parachor values of a number of investigators to substantiate the argument for the semi-polar bond (20, p. 91-94).

It is clear, then, that the controversy concerning the nature of the sulfur-oxygen linkage in sulfones and sulfoxides has not yet been satisfactorily resolved.

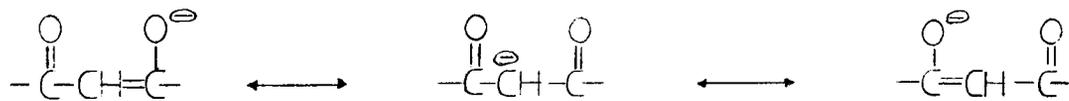
Keto-enol Tautomerism: If a β -ketosulfone were studied in which keto-enol tautomerism theoretically existed, then it might be possible to further clarify the nature of sulfur-oxygen bonds in

sulfones. The following tautomeric forms can be postulated for a β -ketosulfone, and among them it can be seen that either a carbon-

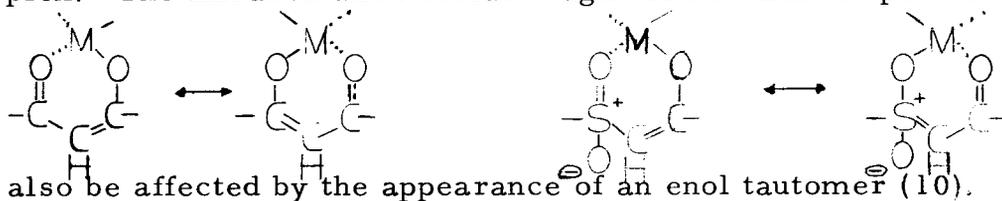


carbon or a carbon-sulfur double bond may exist. The existence of the carbon-sulfur double bond, however, is not likely, and therefore the form containing that bond will not be expected to contribute significantly to the tautomeric equilibrium. The possibility, then, of an enol form involving the sulfonyl group is remote.

Stabilization of Carbanion: Pryor mentions that a sulfonyl group in a sulfone will stabilize the carbanion, and he not only ascribes the stabilization to resonance forms but to inductive effects as well (21, p. 33), as does Gould (9, p. 369). The β -ketosulfone anion would be expected to be stabilized by resonance in a manner analogous to that in which β -diketones are thought to be so stabilized. If such resonance



stabilization for the anion does indeed occur, it should affect the acidifying ability of the sulfonyl group and the ability of the β -ketosulfone to coordinate with a metal ion by formation of the metal complex. The infrared and nuclear magnetic resonance spectra would



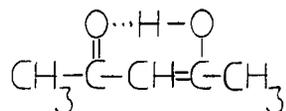
also be affected by the appearance of an enol tautomer (10).

Acidity of β -ketosulfones: It is also contended that the sulfonyl group is strongly electron-withdrawing and therefore has a high acidifying ability. It would seem that the stabilization of an enol form would be favored by the presence of such a supposed strong electron-withdrawing group.

Truce, Bannister, and Knospe have investigated the acidities of various cyclic and acyclic β -ketosulfones by evaluating their dissociation constants by potentiometric titration. For phenylsulfonylacetone, a compound under investigation in this thesis, an apparent value of 10.09 ± 0.02 was reported for the pK_a when measured in 50 percent ethanol-50 percent water mixture at 25°C (26, p. 2824). This compares with a value of 10.9 obtained by Holst and Fernelius in a 50 percent dioxane mixture at 30°C (10).

Stabilization of Enol Tautomer by Internal Hydrogen Bonding:

If internal hydrogen bonding were operative for an enol form in a β -ketosulfone, that tautomer would be more greatly stabilized. It has been well established that internal hydrogen bonding is mainly responsible for the stability of the enol tautomer of the β -diketone, acetylacetone (22, p. 1351-1365). Gould also presents evidence of this for acetyl-



acetone, stating that there is 80 percent enol content in an equilibrium mixture at 25°C in the absence of solvent (9, p. 376-377). A similar

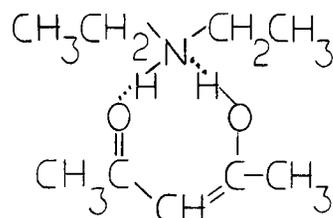
stability for a β -ketosulfone would be expected since sulfur is more electronegative than carbon and should promote acidity in the sulfonyl group sufficient to create enolization and consequent internal hydrogen bonding.

Acetylacetone-Diethylamine Complex: The work of Reeves and Schneider on the 1:1 molecular complex formed between acetylacetone and diethylamine is of interest because it has been shown that the complex arises from hydrogen bonding between the amine and the enol tautomer of the diketone. An extensive shift of the keto-enol equilibrium occurred (from 80 percent to approximately 100 percent enol), and the rate of conversion, which is normally slow, of one tautomer to the other was substantially increased. In fact, it was observed in a nuclear magnetic resonance study of the amine-diketone complex at various temperatures that no resonance signals appeared in the spectrum which could be attributed to the keto tautomer (23).

Reeves and Schneider obtained some unusual results that led to their conclusion that the complex was formed on account of hydrogen bond interaction. A rather broad, structureless peak was noted in a spectrum of a pure 1:1 acetylacetone-diethylamine mixture (m. pt., 41.5°C) at approximately 43°C , which was ascribed to rapid simultaneous exchange of protons between those of the $-\text{OH}$ and $=\text{CH}-$ groups of the enol form with those of the amine $-\text{NH}$ group. A CCl_4 solution containing 15 mole percent of the complex yielded a signal for

these protons that was sharp at 74°C but which eventually split into two separate signals at 27°C. The intensities were in a 2:1 ratio, implying that the more intense absorption was indicative of rapid exchange between the -NH and -OH protons while the less intense signal was representative of the =CH- proton and showed slow exchange between it and the protons of the other groups. The coalescence of the two signals at an elevated temperature showed that rapid exchange occurred once again among all three protons (23).

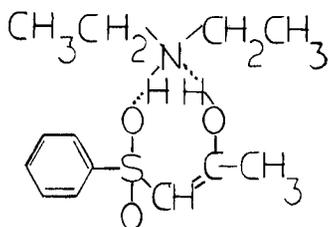
The -NH - -OH exchange was easily interpreted in terms of the disruption of the internal hydrogen bond of acetylacetone and of a formation of the hydrogen bonded complex shown below. An explana-



tion for the participation of the =CH- proton in the exchange was more difficult to find. Reeves and Schneider concluded that, upon disruption of the internal hydrogen bond of the diketone, the OH group could rotate out of the plane of the molecule so that the OH proton could be situated in juxtaposition to two electron-donating areas. Therefore, it became possible for formation of a hydrogen bond between the hydroxyl group proton and the nitrogen lone electron pair and for hydrogen bond formation between the amine proton and the carbonyl

oxygen or the π - bond of the olefinic enol tautomer. The formation of the keto tautomer as an intermediate for this particular process allowed the process to become equivalent so that the proton of $=\text{CH}-$ can participate in exchange. Therefore, the presence of the $=\text{CH}-$ group is explained (23).

In an analogous manner, it would be reasonable to postulate complex formation between diethylamine and a β -ketosulfone, for example, phenylsulfonylacetone.



EXPERIMENTAL NMR DATA FOR SULFONE, ITS ANION,
AND A SULFONE-DIETHYLAMINE MIXTURE

Investigation of Tautomerism: In an attempt to obtain information about the properties of the sulfonyl group, it was decided to prepare and investigate the compound phenylsulfonylacetone for some of the effects that have been discussed in the previous section of this thesis, namely, tautomerism, internal hydrogen bonding, and molecular complex formation via an enolic form. Phenylsulfonylacetone was prepared as has previously been described in an earlier portion of this work.

Initially, the subject of tautomerism was of main concern, for it was felt that results in this area would be more likely to lead to a definite conclusion concerning the behavior of the sulfonyl group. It was decided to seek evidence of possible tautomeric effects by using the techniques of nuclear magnetic resonance; such techniques are convenient to employ and normally permit the structure of a compound to be easily identified.

Because phenylsulfonylacetone exists in the solid state at room temperature and because the Model A-60 spectrometer used in the research herein described had no temperature control device to permit measurements to be made at other than room temperature, spectra could not be obtained for a pure liquid sample of the sulfone. It was

therefore necessary to select a suitable solvent for performing the analysis.

Solvent Considerations: An obvious requisite was that the sulfone be sufficiently soluble in the solvent in order to achieve a solution of adequate concentration to yield a desirable spectrum. It is usually satisfactory if a concentration of approximately ten mole percent can be achieved. It has been found that the chemical shift of proton signals for aromatic compounds in nonaromatic solvents is dependent upon the concentration of the solvent, and likewise, it has been discovered that the chemical shift for proton signals for nonaromatic compounds in aromatic solvents is concentration dependent (19, p. 424).

Although it was not purposely intended that a study of the sulfone at varying concentrations was to be made, during the course of investigation, several spectra were obtained for different concentrations of the compound in the same solvent; for those spectra presented in this thesis, corrections in the chemical shifts for this solvent effect have not been made and are not important.

A further consideration in choosing the solvent was that it should be one that possessed as few proton-containing groups as possible that might possibly produce interfering absorptions in regions of interest for the sulfone. In particular, the absence of methylene groups in the solvent was highly desirable, since it was expected that signals for an enolic =CH- or -OH proton might appear in the general area where

methylene proton absorptions normally occur.

Since phenylsulfonylacetone contains benzene, methyl, and methylene groups, an aprotic or nearly aprotic solvent would be a logical choice, but the insolubility of the sulfone in aprotic reagents is generally sufficiently great that they are not suitable. Non-polar solvents, with the exception of benzene, were found to be poor solvents for the sulfone, so the choice of a good solvent became quite limited.

It was finally decided to use methanol for the first spectral determination. All of the above criteria were not completely satisfied, but the sulfone was quite soluble in methanol, and it was felt that the presence of the methyl group would not interfere adversely with the spectrum. This assumption was later verified.

Spectrum of Sulfone in Methanol: The first spectrum was obtained by analyzing a portion of a solution of 1.276 grams in 3.0 milliliters of anhydrous, reagent grade methanol at the conditions of resolution given in Table I. The resulting spectrum (illustration A) yielded signals for the methyl and methylene protons of the sulfone and for the methyl and hydroxyl protons of methanol. The absence of any absorption for an enolic =CH- proton was evidence for the existence of the keto form of the sulfone in an amount greater than 95 percent.

In this and succeeding spectra that are discussed, relative chemical shifts for various signals have been calculated in parts per million of the applied magnetic field, and these are listed in Tables II and IV. It

Table I. INSTRUMENT CONDITIONS FOR SPECTRA OF SULFONE AND "COMPLEX"

Spectrum	Filter Band Width in cps	R. F. Field in mG*	Sweep Time in sec	Sweep Width in cps	Sweep Off-set in cps	Spectrum Amplitude
A. 1.276 grams Phenylsulfonylacetone in 3.0 ml CH ₃ OH	2	0.05	250	250	50	2.5
B. 1.035 grams Phenylsulfonylacetone in 3.0 ml C ₆ H ₅ NO ₂	2	0.05	500	500	50	1.6
C. 0.030 gram Phenylsulfonylacetone in 3.0 ml CCl ₄	0.4	0.2	500	500	50	40
D. 1 part Phenylsulfonylacetone to 3 parts diethylamine in 1.0 ml C ₆ H ₆ (distilled)	1	0.16	500	500	0	16
E. ~0.1 gram of 1:3 "complex" in 1.0 ml HCCl ₃ (distilled)	0.4	0.16	500	500	0	25

* mG = milligauss

Table II. CHEMICAL SHIFTS IN ppm RELATIVE TO METHYL SIGNAL OF SULFONE.

Spectrum	CH ₃ of CH ₃ OH	CH ₂ of C ₆ H ₅ SO ₂ CH ₂ COCH ₃	OH of CH ₃ OH	C ₆ H ₅ of C ₆ H ₅ SO ₂ CH ₂ COCH ₃
A.	-1.2	-2.4	-2.6	
B.		-2.2		-6.1
C.		-1.7		-5.6
D.				
E.				

Table II, Cont.

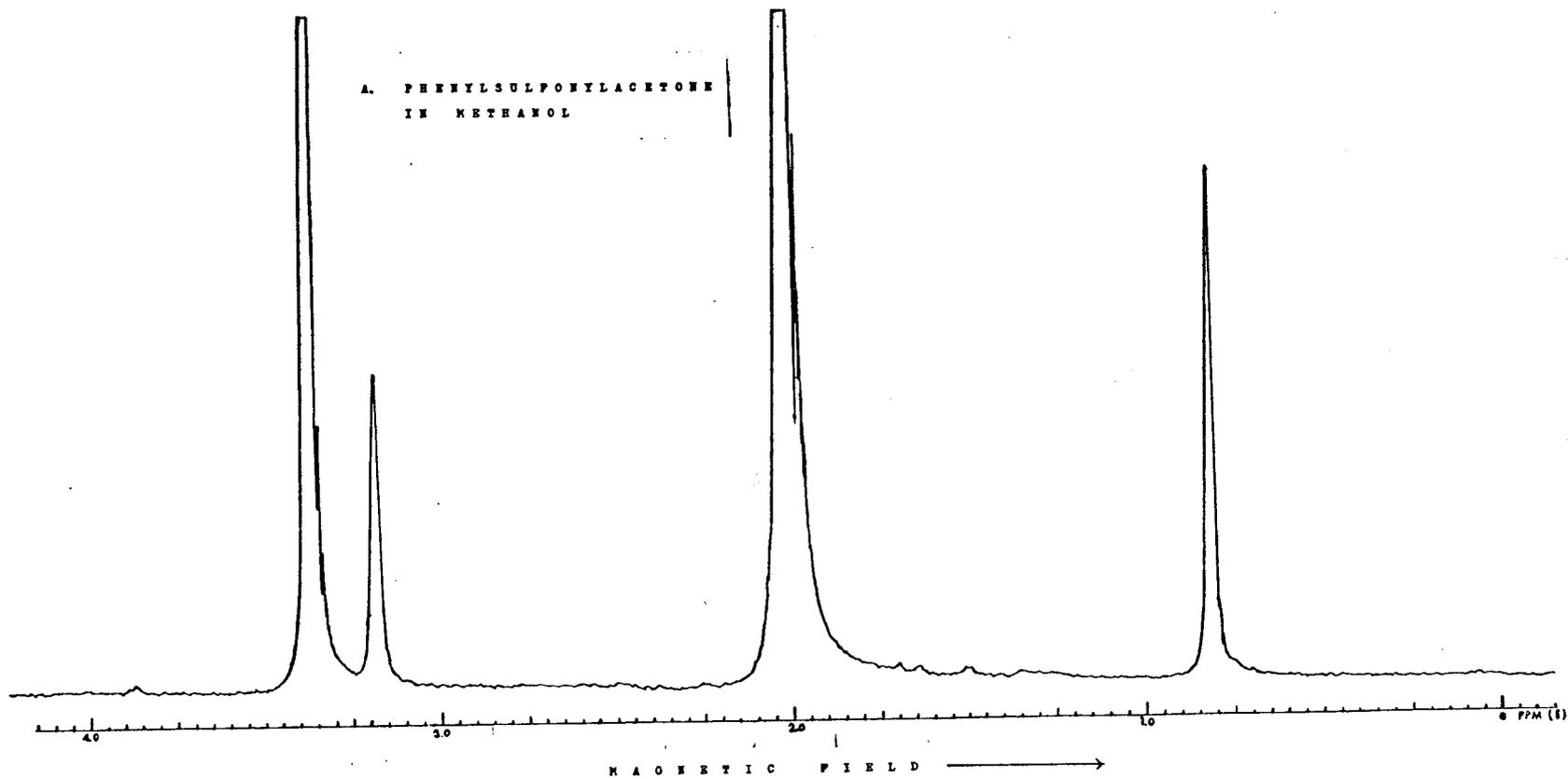
Spectrum	C ₆ H ₅ of C ₆ H ₅ NO ₂	CH ₃ of (CH ₃ CH ₂) ₂ NH	CH ₂ of (CH ₃ CH ₂) ₂ NH	NH, CH ₂ of "complex"
A.				
B.	-5.6			
C.				
D.		+1.0	-0.6	-1.3
E.		+1.3	-0.3	

should also be noted that in this and a few other spectra, certain absorptions are so intense at the spectrum amplitude used during the analysis that rectangular-shaped signals are obtained, indicating that the recorder pen was deflected off scale. It is not necessary to be greatly concerned about this, for the relative positions of the signals is of more important consideration in the work that has been undertaken.

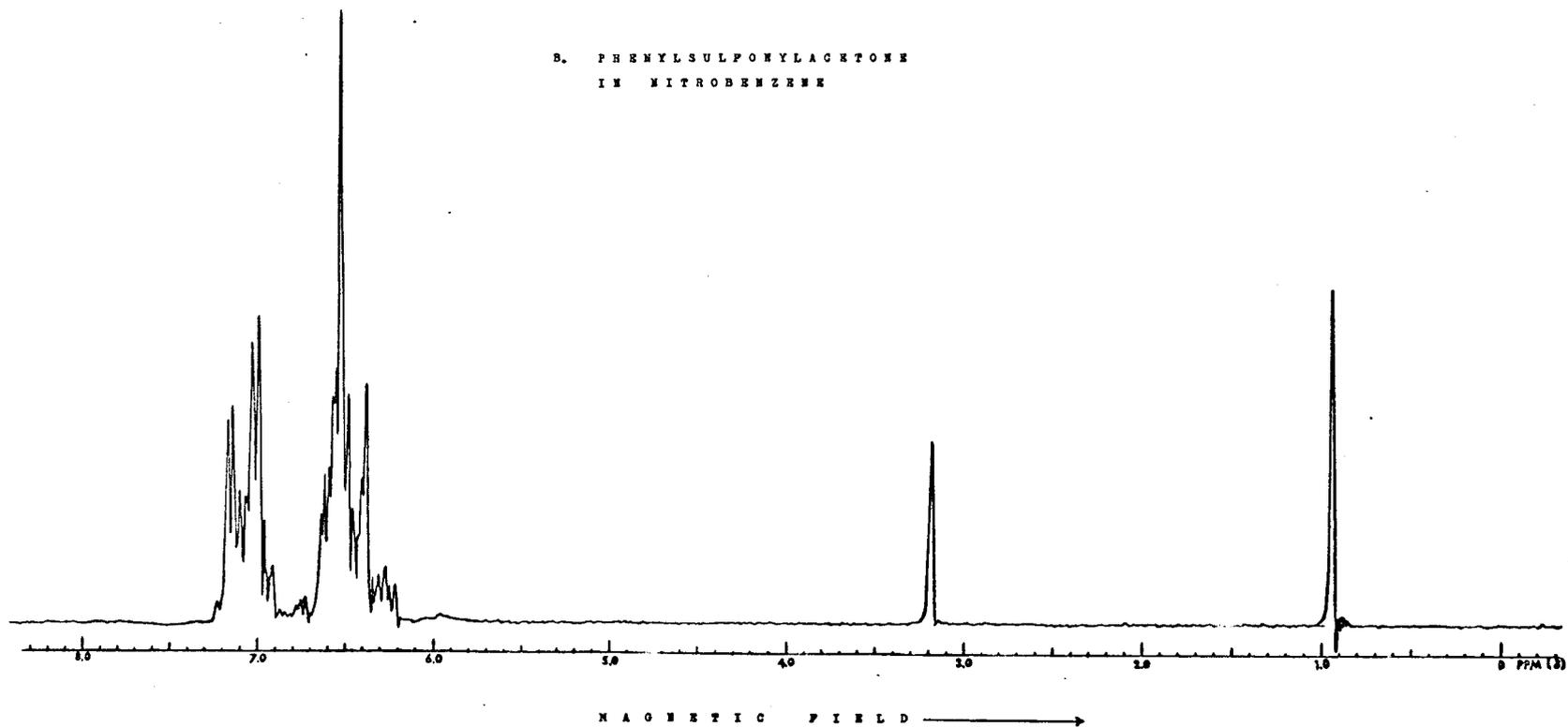
A spectrum of methanol alone was obtained, and it was observed that the signal for the hydroxyl proton in spectrum A shifted up field by approximately 0.26 ppm relative to the -OH signal of the methanol spectrum. This evidence is indicative of hydrogen bonding, occurring through interaction between the carbonyl oxygen of the ketosulfone and the hydroxyl proton of the solvent or between the oxygen of the sulfonyl group and the methanolic -OH proton. Indeed, it has been found, as was mentioned previously, by Bernard, Fabian, and Koch, that sulfones do form hydrogen bonds.

Spectrum of Sulfone in Nitrobenzene: The second spectrum obtained was for a portion of a solution of 1.035 grams of the sulfone in 30 milliliters of reagent grade nitrobenzene (illustration B). An analysis of the spectrum clearly demonstrates the presence of absorptions only for the phenyl, methyl, and methylene protons of the sulfone and for the benzene protons of the solvent. Again, the lack of an absorption for an enolic =CH- proton is to be noted, in support of findings

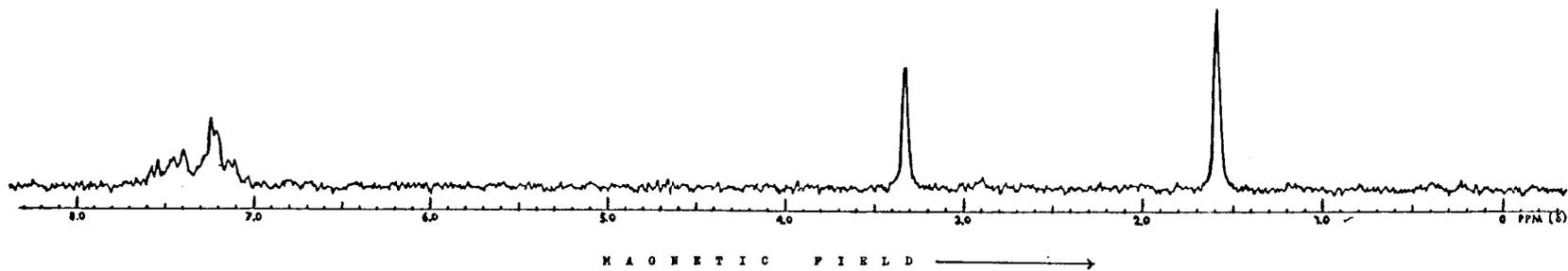
A. PHENYLSULFONYLACETONE
IN METHANOL



D. PHENYLSULFONYLACETONE
IN NITROBENZENE



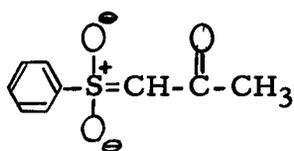
C. PHENYLSULFONYLACETONE
IN CCl_4



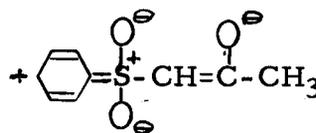
from the first spectrum that indicated essentially no tautomerism.

Spectrum of Sulfone in CCl₄: Carbon tetrachloride is a widely used solvent in nuclear magnetic resonance investigations because it is aprotic and presents no spectrum of its own to interfere with absorptions of solute molecules. It was found that phenylsulfonylacetone was not appreciably soluble in CCl₄; nevertheless, it dissolved to such a degree that a reasonably suitable spectrum could be obtained. Three milliliters of analytical reagent grade CCl₄ was used to make a solution containing 0.030 gram of the sulfone; the resultant spectrum (illustration C) again confirmed the absence of any appreciable amount of enol tautomer.

Spectrum of Sulfone Anion: At this stage of the investigation, it was felt that it would be pertinent to inquire into the nature of the sulfone anion. Fehnel and Carmack have recorded the ultraviolet spectrum for the phenylsulfonylacetone anion, formed by dissolving the sulfone in 0.01N sodium ethoxide, and they concluded that the following forms contributed to the spectrum (7).



(i)

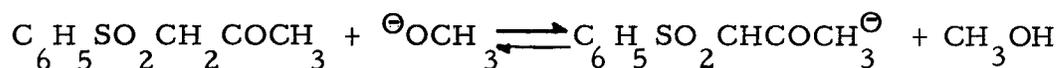


(ii)

Several proton magnetic resonance spectra were recorded for a portion of a solution containing 0.308 gram of sulfone in 1.0 milliliter

of anhydrous reagent grade methanol, each successive spectrum being observed upon the addition of small amounts of freshly prepared sodium methoxide. The shape and intensity of the signal for methylene protons was particularly noted in each spectrum, and a careful watch was kept for the appearance of an additional signal that might be attributed to an enolic =CH- proton.

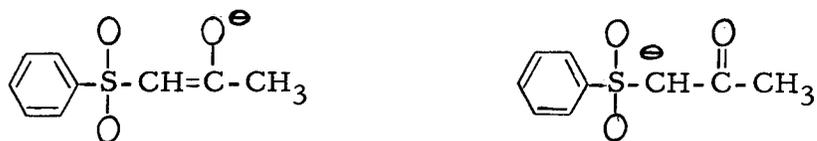
The methylene signal was seen to decrease in intensity and broaden quite a bit upon the successive addition of small, arbitrary amounts of sodium methoxide. Finally, after adding an excess of base, the signal disappeared completely, an indication that the sulfone had been completely neutralized and had been converted to the anion of the sodium salt. Broadening of the methylene signal and the corresponding reduction in intensity suggested that exchange of the nature



was occurring before neutralization became complete. An initial lack of broadening and reduction in signal intensity was attributed to an exchange rate that was at first slow enough to prevent its detection; however, with the addition of more base, the rate increased enough for it to be observed.

Since the methylene signal appeared extremely close to the methanolic hydroxyl proton absorption, any =CH- proton signal might very possibly be hidden under that intense absorption and therefore not be

identified. It could not then be concluded whether or not the anion existed in any of the forms given by Fehnel and Carmack, although it can reasonably be assumed that both of the following may exist.



Preparation of Sulfone-Amine Mixture: It was postulated previously in this thesis that complex formation between phenylsulfonyl-acetone and diethylamine, analogous to that discovered by Reeves and Schneider between acetylacetone and diethylamine, could reasonably be expected to occur. This third phase of investigation, therefore, was concerned with attempts to prepare and characterize such a complex.

Initially, varying amounts of diethylamine (reagent grade) were added to several samples of the solid sulfone, and it was found that no complex of a solid nature formed from the mixtures. With the conclusion of these and other preliminary experiments, a more concerted effort was made to effect complex formation. In succeeding work, a small amount of diethylamine was added by pipet to a stoichiometric amount of solid sulfone in a small, glass-stoppered Erlenmeyer flask. An initial increase in the temperature of the flask was noted, and this was attributed to an interaction of some sort between the two reagents.

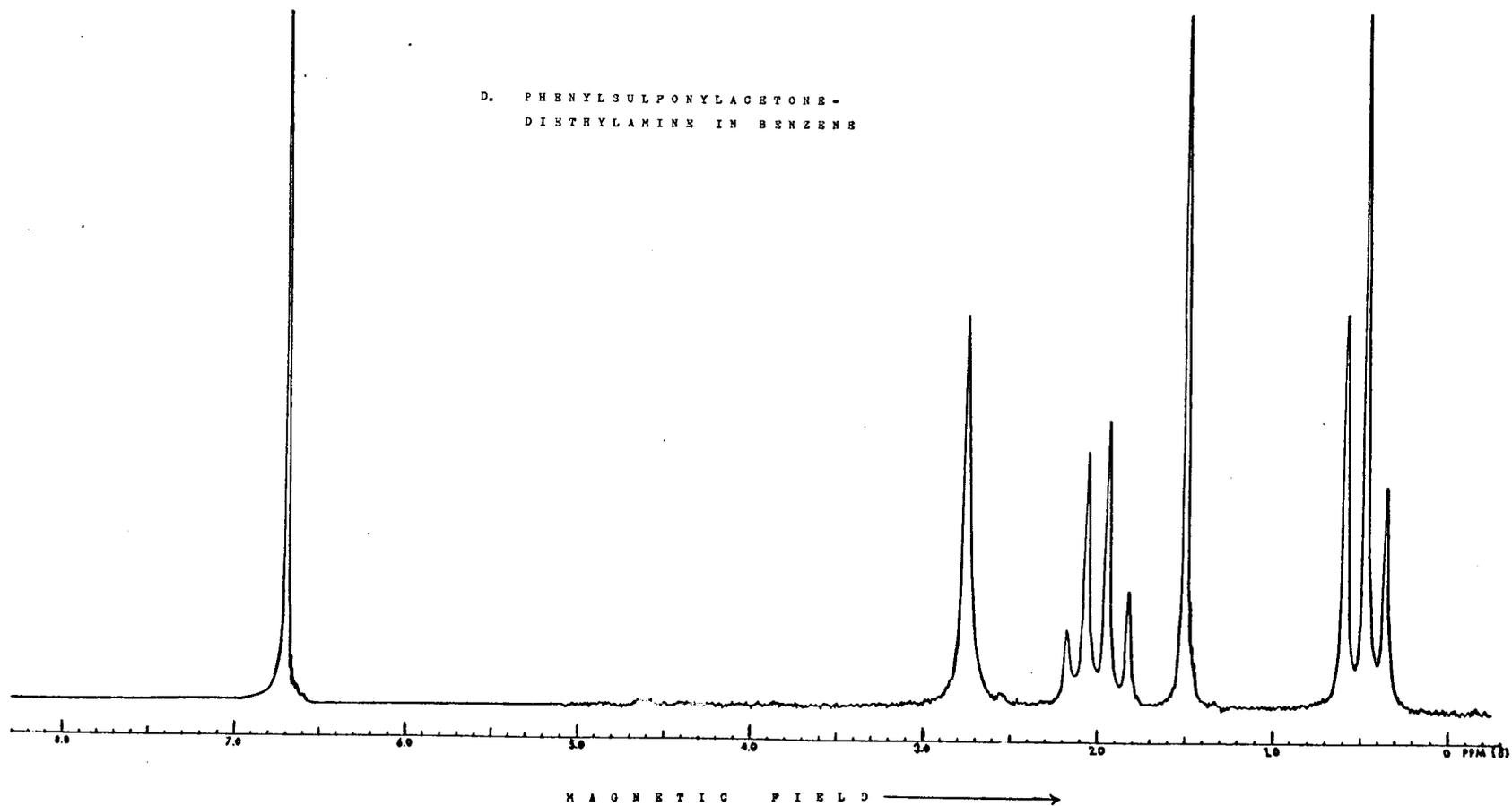
Because the volume of the amine was very small compared to the quantity of solid sulfone, complete dissolution of the sulfone could not be effected without stirring and causing a loss of amine by vaporization.

Because the two reagents used were not in the same phase prior to mixing, it was difficult to determine whether or not any complex formation occurred; it was at least observed that dissolution of the sulfone resulted upon thorough mixing and that no solid precipitated from the mixture upon standing. Further inquiry into the nature of the mixture was made by analysis on the n. m. r. spectrometer.

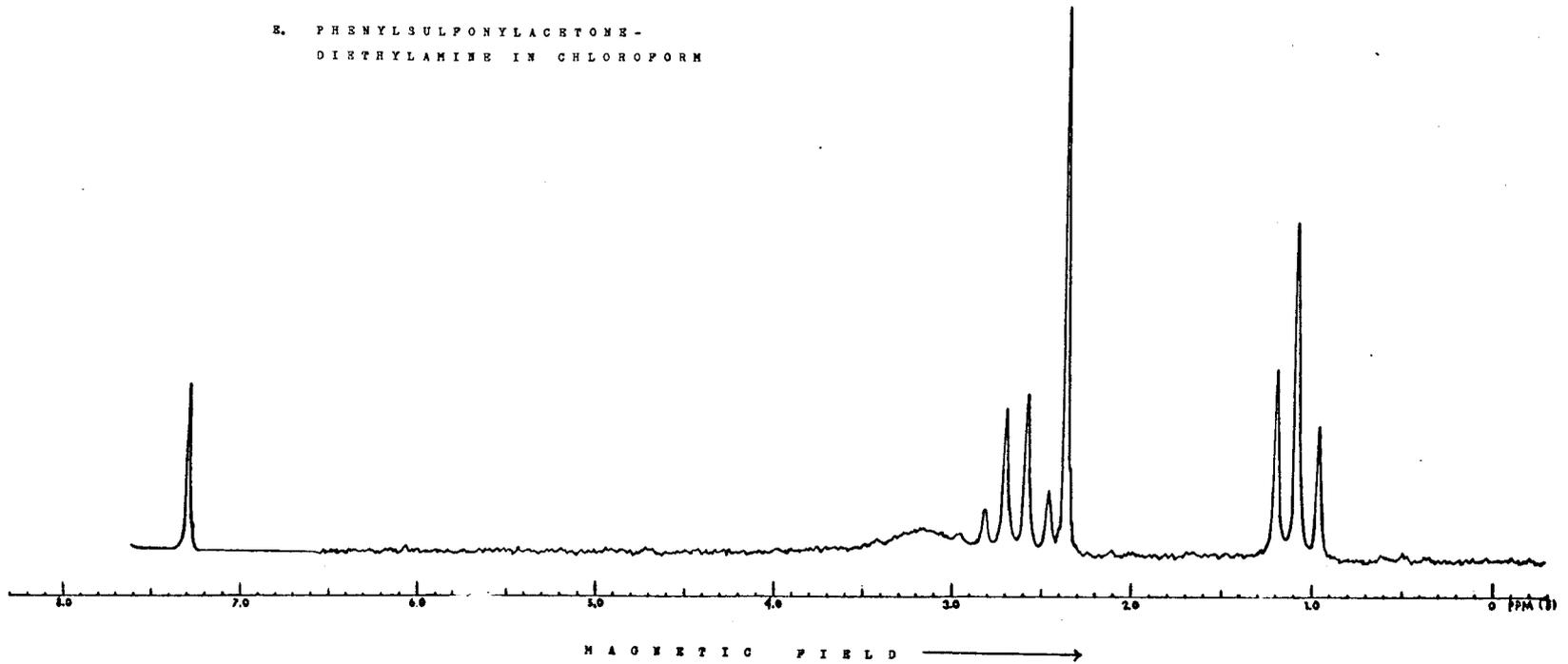
At first, an analysis of the pure amine-sulfone mixture was attempted, but it was found that the highly viscous mixture crystallized in the n. m. r. tube. The mixture's high viscosity resulted from the dissolution of a relatively large amount of solid in a very small portion of the liquid. The next analyses were performed by adding the liquid amine to the sulfone, pouring off excess liquid after thorough soaking of the solid had transpired, and dissolving it in a desirable solvent. It was found that the saturated solid lost diethylamine upon exposure to air and reverted to the sulfone. Care was exercised in allowing the saturated solid to come in contact with air for as short a time as possible.

Spectrum of "Complex" in CCl_4 : The first spectrum of the assumed complex was obtained for a portion of 1.0 milliliter saturated solution of a stoichiometric mixture of diethylamine and phenylsulfonyl-acetone in analytical reagent carbon tetrachloride. An absorption for

D. PHENYLSULPONYLACETONE-
DISTHYLAMINE IN BENZENE



E. PHENYLSULPONYLACETONE-
DIETHYLAMINE IN CHLOROPORM



the phenyl group appeared in the usual position, and the methyl triplet for the amine appeared at high field as expected. The signal for the methyl group of the sulfone was almost completely superimposed on the peak that appeared at highest field of the methylene quartet of the amine. No signals whatsoever were observed for sulfone methylene protons, the -NH proton, or any =CH- proton.

The absence of a signal for sulfone methylene protons was, in particular, surprising, considering that other signals appeared which indicated the presence of the sulfone in the analysis mixture and that in previous spectra of the sulfone alone in a solvent, such a signal had been observed. Its absence would not have been so surprising had a signal arisen for an enolic =CH- proton. An explanation for this behavior has not been satisfactorily found.

Spectra of "Complex" in Benzene: On account of the inexplicable nature of the carbon tetrachloride spectrum, it was decided to continue studies on complex formation using a different solvent. Benzene, a non-polar solvent, was chosen for further investigations because it was felt that possible complex formation would be least disturbed by solvent effects in this case. Accordingly, several spectra were obtained for reagent grade benzene solutions of stoichiometric mixtures of diethylamine and phenylsulfonylacetone.

Signals for the methyl triplet and methylene quartet of amine

protons appeared, and absorptions indicative of the phenyl and methyl groups of the sulfone were obvious. A new type of absorption was observed, however, that was broad and structurally ill-defined; its width and intensity were dependent upon the amount of amine-sulfone mixture that was dissolved in the benzene. It was noted that the addition of only sulfone to the solution caused this broad peak to sharpen greatly and shift to lower field to a position where the sulfone methylene signal normally occurred. Because of this, the broad absorption was attributed to methylene protons of the sulfone and also was assumed to account for the -NH proton of the amine, since the area under the peak was approximately equal to that which would appear for a signal representative of three protons.

The reason for the broadness of the peak was still unclear, however; it was felt that exchange of some type might be occurring between amine and sulfone protons, possibly affected by the presence of a minute amount of water. Because the sulfone used was from a sample on which a correct melting point could not be obtained, it seemed logical that the sulfone might have contained water in sufficient quantity to be responsible for the incorrect melting point and the subsequent broadening of the absorption that has been under consideration. The sulfone sample was observed to be non-hygroscopic, and desiccation over phosphorus pentoxide did not alter the observed melting point.

The anomalous melting point could therefore only be attributed to the presence of small amounts of impurities and not water as had been supposed.

Next, it was thought that the source of water might have been either the diethylamine or the benzene. Diethylamine was dried by refluxing for two hours over phosphorus pentoxide and then distilled slowly; the middle 60 percent fraction was retained for use. Benzene was purified by slow distillation for a two-hour period, and again the middle 60 percent fraction was kept.

A spectrum (illustration D) was then recorded for a portion of a one-milliliter, dry benzene solution of the dry amine-sulfone mixture. This time the mixture was prepared using three parts of diethylamine to one part of sulfone, but, as before, excess amine was removed before the saturated sulfone was dissolved in the solvent. It was felt that better mixing of the sulfone with the amine could be achieved by the addition of more than a stoichiometric quantity of amine.

Spectrum D produced signals of the same nature as those found in previous spectra for benzene solutions, except the broad, ill-defined peak was no longer present. Instead, a fairly intense, sharp field arose slightly down field from the methylene quartet of the amine. The appearance of the sharper signal, which was still estimated to account for both the methylene protons of the sulfone and the -NH proton of the amine, showed that water had indeed been responsible for

the broad absorption in previous spectra and that it was affecting the exchange rate of the $-\text{CH}_2-$ and $-\text{NH}$ protons.

The problem of being able to detect any signal for an enolic $=\text{CH}-$ proton had still not been solved, and it seemed that there was no possibility of further resolving the nature of the signal just discussed, using benzene as a solvent. Finally, chloroform was turned to, although it was a less desirable medium because of its somewhat polar character.

Spectrum of "Complex" in Chloroform: A portion of a one-milliliter, dried chloroform (reagent grade) solution containing approximately 0.1 gram of a stoichiometric mixture of three parts diethylamine to one part of sulfone was analyzed by n. m. r. methods. Again, the previously observed signals appeared (illustration E), but the absorption accounting for the sulfone $-\text{CH}_2-$ protons and amine $-\text{NH}$ proton was once more broad and structureless, and its intensity was considerably reduced.

Since all reagents used had been thoroughly dried, the broadness of the signal could not this time be attributed to the presence of water. Exchange of some nature was once again indicated, and in an attempt to clarify more definitely whether or not the absorption accounted for three protons ($-\text{CH}_2-$, $-\text{NH}$), the spectrum was integrated. It was ascertained that the absorption could very reasonably represent three protons.

Again, the presence of a signal for a =CH- proton could not be detected, and it could not be verified that the broad signal contained a contribution from a =CH- group involved in an exchange. It might have been possible to resolve the nature of the broad absorption by analyzing the sample at reduced temperatures to see if the signal would split into two separate signals, one representing an -NH proton and an enolic -OH proton, which would be twice the intensity of the other representing an enolic =CH- proton. However, instrument limitations did not allow such an analysis to be performed, for the spectrometer did not contain a device to permit measurements to be taken at other than room temperature.

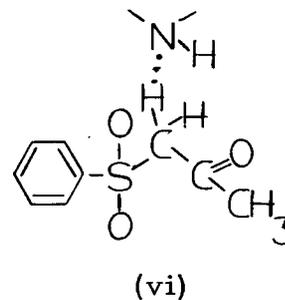
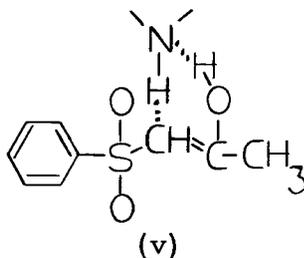
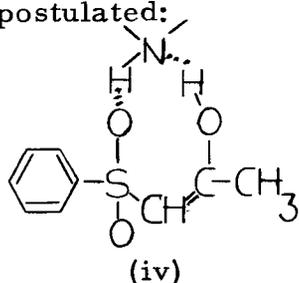
SIGNIFICANCE OF RESULTS FOR SULFONE

Absence of Enol Tautomer: It now becomes necessary to clarify the nature of the observations that have been recorded. It was clearly shown in spectra A, B, and C, that no signal arose which could be attributed to an enolic =CH- proton, and this is evidence that the keto form of the sulfone was present to an extent greater than 95 percent. (The instrument used was limited to detecting amounts only greater than five percent.) Intramolecular hydrogen bonding is therefore absent also.

The presence of the keto form in an amount greater than 95 percent and the corresponding absence of any substantial amount of enol tautomer does not support the view that the sulfonyl group is not acidic and does not therefore promote tautomerization. Indeed, it has been clearly confirmed by the experiments with sodium ethoxide that the sulfonyl group was sufficiently acidic to allow formation of the anion. Reasons other than non-acidity of the sulfonyl group must be sought to explain the absence of any substantial amount of an enolic form.

Exchange in "Complex:" Experiments involving the purported amine-sulfone complex indicated that an exchange of some type was occurring between methylene protons of the sulfone and the -NH proton of the amine. Several structures to explain this exchange can

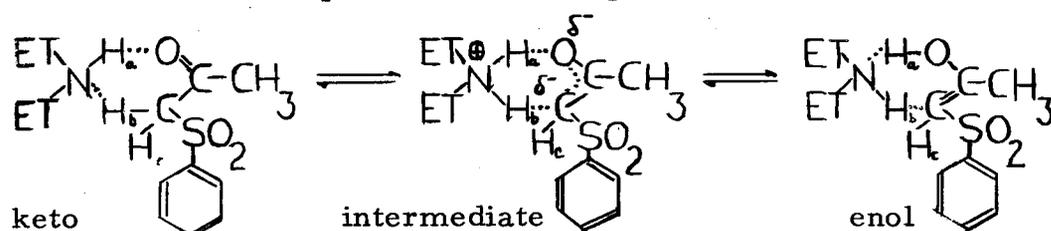
be postulated:



In spectra of the "complex," the broadness of the signal not only was indicative of exchange but further showed that rapid exchange was occurring among equivalent protons. Structure (iv) is not likely to be of importance because the broad signal is so far up field, in contrast to the position of the broad signal in Reeves' and Schneider's spectrum of the acetylacetone-diethylamine complex. In their spectrum, the broad signal was located 4.60 ppm down field relative to the methyl signal of acetylacetone (23). That the protons cannot become equivalent in structure (iv) and the fact that the sulfonyl group is known to not form strong hydrogen bonds also support the view that structure (iv) is the least plausible of the three.

It is more difficult to decide which is more likely between (v) and (vi). Because temperature-dependent studies to resolve the nature of the broad peak could not be performed on the Varian A-60 spectrometer, it cannot be demonstrated conclusively that structure (v) is or is not valid. Form (vi) is possible, but in it the amine proton ignores the presence of the nearby carbonyl group, and it is the interaction between this group and the amine proton that most

certainly accounts for the observed hydrogen-bond interaction and the existence of any possible "complex." An interaction of the type below would be more plausible, if it is presumed that the



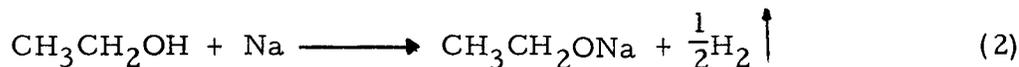
hydrogen bonds are labile enough to permit the protons to become equivalent, in other words, allow proton a to rearrange with protons b or c in either form above. The six-member hydrogen-bonded structures above indicate possible hydrogen bond interactions, but these structures are definitely non-planar.

Conclusion: The largely ketonic character of the sulfone but the proven acidity of the sulfonyl group have suggested then that the absence of any reasonable amount of enol tautomer in the sulfone might be ascribed to the lack of internal hydrogen bonding. The interaction that has been postulated for the "complex" between diethylamine and the sulfone allows for the existence of a short-lived intermediate that can account for the equivalence of all three protons. The intermediate would be highly associated by charge and hydrogen bonding interactions in benzene and chloroform. However, it cannot be established whether the keto or the enol form is relatively more important because temperature-dependent studies were not possible.

PREPARATION OF ACETOHYDROXAMIC ACID

Preparation of Sodium Salt: The preparation of acetohydroxamic acid presented more challenging problems in laboratory technique than did the synthesis of phenylsulfonylacetone. Repeated experimentation was necessitated because the literature's methods presented numerous unexpected difficulties in obtaining a yield of the acid. Revisions in procedure resulted in a method somewhat different from that given in the literature (12, p. 176).

The initial preparative step was to dissolve metallic sodium in absolute ethanol to make sodium ethoxide.



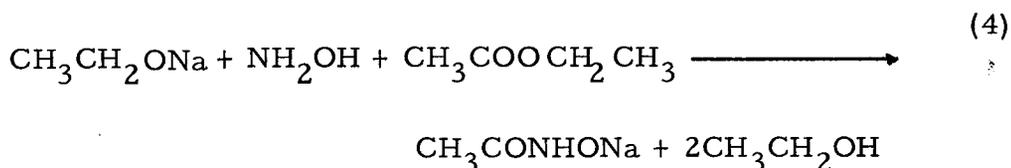
During the dissolution of the sodium, hydroxylamine hydrochloride (practical grade) was being dissolved in absolute ethanol. Vigorous stirring was required, and then not all of the hydrochloride was soluble. Once prepared, an equivalent amount of sodium ethoxide was added, with stirring, to the solution of the hydrochloride, and the resulting precipitate of sodium chloride was filtered off by suction on

(3)



a Buchner funnel.

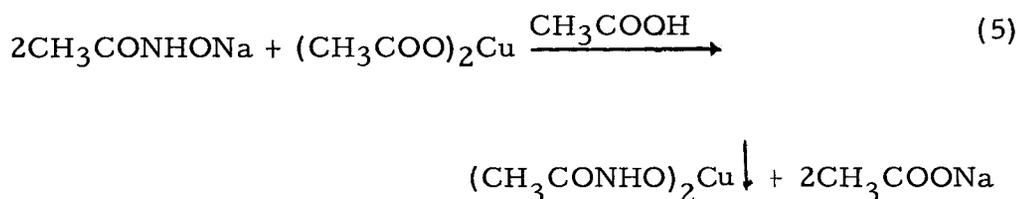
An equivalent quantity of anhydrous, reagent grade ethyl acetate, mixed with absolute ethanol, was next added, with stirring again, to the alcoholic solution of the free hydroxylamine. Another equivalent of sodium ethoxide followed the addition of the ester.



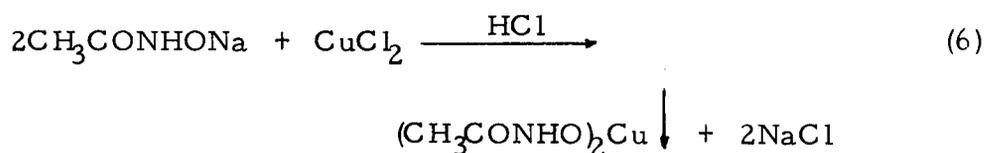
To obtain the sodium salt of the acid, evaporation of the solution was required. The literature recommended evaporation to dryness at room temperature in a current of dry air, but this proved to be slow and inefficient. It was found much more effective to carry out the evaporation under reduced pressure while rotating the solution mechanically in a round bottom flask.

Precipitation of Copper Salt: An aqueous solution of the sodium salt was made with distilled water, and it was removed from the flask and transferred to a beaker where it was acidified with acetic acid.

To precipitate the copper salt of the acid, a saturated solution of reagent grade cupric acetate was added with thorough stirring. Copious amounts of a brilliant, bright green precipitate were observed.



When difficulty was experienced in the final stages of the preparation in obtaining the solid free acid, it was noticed that the viscous acid solution smelled very strongly of acetate or acetic acid. This led to the belief that some sort of double salt might have been formed during the precipitation of the copper salt, perhaps one containing both acetate and acetohydroxamate as ligands to copper. In an attempt to circumvent this difficulty, a couple of experiments were performed using hydrochloric acid and a saturated solution of reagent grade cupric chloride in place of the acetic acid and cupric acetate. The color



of the salt was darker and its density was less; however, it too failed to produce any better results in getting the solid acid. After a few tries with cupric chloride, cupric acetate was used throughout the remainder of the work.

Tests For Impurities in Copper Salt: After precipitation, the copper salt was filtered by suction on a Buchner funnel; this required a long period of time since there were large quantities of it, and it was quite dense. The precipitate was washed thoroughly with several portions of anhydrous diethyl ether to remove impurities. When cupric chloride was used for the precipitation, a silver nitrate test for

chloride ion was performed after washing. When cupric acetate was employed as the precipitating agent, tests for acetate were attempted. The common ferric chloride test for acetate could not be employed, because acetohydroxamate itself would form a chelate with Fe^{+3} and would give a very positive test. The boiling sulfuric acid-ethanol test would yield uncertain results because it would be difficult to identify the odor on a small sample if any ester were produced. Finally, it became necessary to rely upon the sense of smell to detect the presence of acetate impurities. Usually, the acetate odor of the salt was strong, and repeated washings with ether were not successful in removing the acetate completely from the dense precipitate.

To remove acetate as much as possible, the salt was mixed with a small amount of distilled water and thoroughly stirred. The majority of the salt remained undissolved in the water and was allowed to settle after stirring so the supernatant liquid could be decanted. There was some loss due to slight solubility of the salt, but this was preferred to having a considerably impure yield.

Preparation of Free Acid: To obtain the free acid, the literature recommended precipitating the copper as the sulfide by bubbling hydrogen sulfide through an ether suspension of the salt. Considerable difficulty was encountered in precipitating the copper, for suspension of the salt could not be accomplished, and thorough stirring to agitate

the mixture and break down particle size did not noticeably aid in reaching complete precipitation. Several times, colloidal suspensions of cupric sulfide resulted, which were impossible to filter; thus, a pure solution of the free acid could not be attained.

Several ideas to remedy the situation presented themselves, but none seemed so advantageous as the use of ion exchange. Using a batch method, portions of the previously washed copper salt were added at intervals to a mixture of distilled water and Dowex 50W-X4 cation exchange resin in a large beaker. The mixture was stirred mechanically until the aqueous solution became colorless to the eye. To test for the presence of copper ion after the exchange had been effected, the dithizone test was employed. The subsequent discovery that Wise and Brandt had successfully purified hydroxamic acids by ion exchange (28) served to substantiate the use of this new technique. Wise and Brandt used methyl alcohol instead of water as an exchange medium, however.

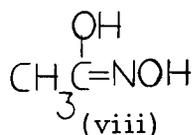
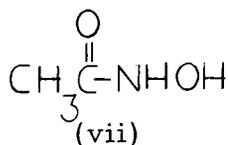
The aqueous solution of the free acid was evaporated under reduced pressure in a round bottom flask set in a water bath at 30-40°C; the flask was mechanically rotated to speed the process. In almost all cases, the aqueous solution did not evaporate to dryness to give crystals of the solid acid; instead, a small amount of brownish-yellow, viscous liquid remained, and this discoloration was taken to indicate decomposition of some sort. This liquid was, no doubt, the

hemihydrate, $\text{CH}_3\text{CONHOH} \cdot \frac{1}{2}\text{H}_2\text{O}$. Cooling directly with dry ice failed to yield any stable form of crystals, and various reagents, for example, hexane, failed to precipitate any crystals when added to portions of the liquid acid. If evaporation alone was not successful, only drying in a vacuum desiccator over concentrated sulfuric acid for a period of at least two weeks successfully removed the water to yield the solid form.

Purification of Acid: Acetone and acetonitrile were tried as solvents for recrystallization purposes, but they were found to be unsuitable. Ethyl acetate was discovered to be satisfactory, however. The solid acid was dissolved in the ester at its boiling point (77.15°C); the impurities separated as a thick syrup, and the ester layer, containing the free acid, was carefully decanted and allowed to cool. The pure crystals were dried by suction on a Buchner funnel and stored in a vacuum desiccator over calcium chloride. A melting point range of approximately $52\text{-}82^\circ\text{C}$ was obtained instead of either 59°C for the hemihydrate or $87\text{-}88^\circ\text{C}$ for the anhydrous form. Thus, portions of the acid apparently remained in the semi-hydrated form. After prolonged standing over calcium chloride, the melting point range was found to be $88\text{-}90^\circ\text{C}$, however, and this indicated that the anhydrous form had finally been obtained.

EXPERIMENTAL NMR DATA FOR ACETOHYDROXAMIC ACID

Investigation of Acid for Tautomerism: It was desired to investigate acetohydroxamic acid for possible exhibition of tautomerism, the presence of which was also sought in phenylsulfonylacetone. There is substantial reason to postulate the two tautomeric forms shown below. Although two such forms have not been chemically



isolated, reactions of the acid can be accounted for by either structure. It was therefore hoped that the sensitive techniques of nuclear magnetic resonance could be successfully employed to demonstrate the existence of the two tautomers.

Spectrum in Diglyme: Accordingly, 0.4 gram of acetohydroxamic acid, prepared as described previously, was dissolved in 1.0 milliliter of diglyme (diethylene glycol monomethyl ether), and a portion of the solution was analyzed on the Varian A-60 spectrometer. As can be seen in illustration F, two intense, closely spaced absorptions appeared for the methyl and methylene protons of the solvent, the methyl signal appearing at the higher field. An intense signal representing methyl protons of the acid was observed at high field, while at low field, a quite broad, symmetrical peak arose that accounted for

Table III. INSTRUMENT CONDITIONS FOR SPECTRA OF ACETOHYDROXAMIC ACID.

Spectrum	Filter Band Width in cps	R. F. field in mG*	Sweep Time in sec	Sweep Width in cps	Sweep Offset in cps	Spectrum Amplitude
F. 0.4 gram CH ₃ CONHOH in 1.0 ml diglyme	4	0.1	250	500	0	8.0
G. ~0.07 gram CH ₃ CONHOH in 1.0 ml acetone	4	0.1	250	500	0	8.0

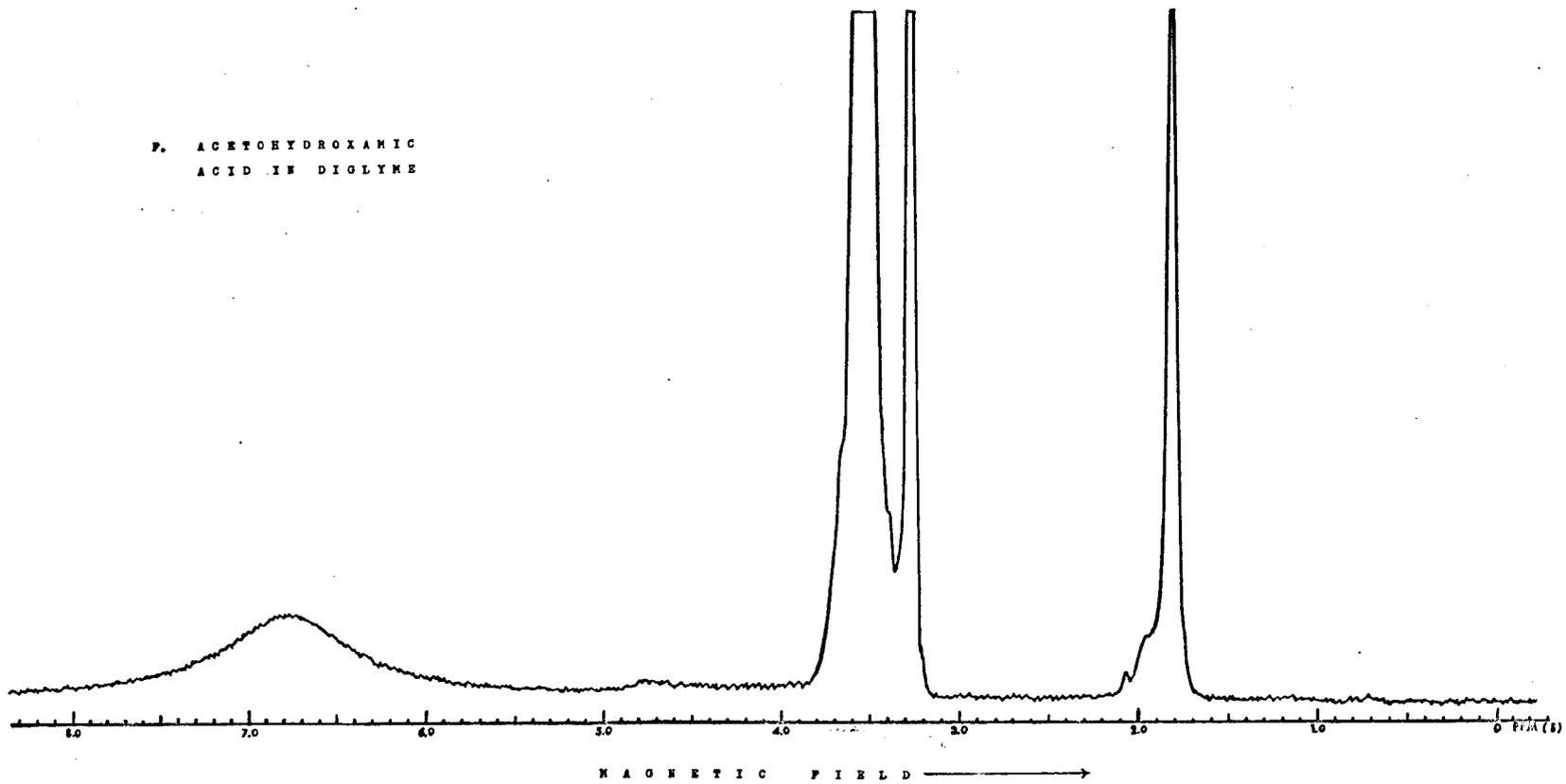
* mG = milligauss

Table IV. CHEMICAL SHIFTS IN ppm RELATIVE TO CH₃ SIGNAL OF CH₃CONHOH

Spectrum	CH ₃ of diglyme	CH ₂ of diglyme	NH, OH of CH ₃ CONHOH	CH ₃ of acetone
F.	-1.5	-1.7	-5.0	
G.			-8.5 *	-0.3

* Very weak absorption.

P. ACETOHYDROXAMIC
ACID IN DIOLYME



-NH and -OH protons of the acid.

If tautomer (viii) were present, the appearance of a signal at intermediate field would be expected for its enolic -OH proton, and the relative intensity of the signal would be equal to that of the oxime -OH proton absorption. However, no such peak was observed; only the broad signal at low field was seen. It is possible that the intense absorptions located at intermediate field for the methyl and methylene protons of diglyme obscured any signal for an enolic -OH proton of the acid, but it must be concluded that the keto form is responsible for the major contribution to the spectrum on account of the presence of the broad signal at low field due to -NH and -OH protons.

Spectrum in Acetone: A second spectrum of the acid was also recorded for a portion of a one-milliliter reagent grade acetone solution containing 0.07 gram of acid. A very intense absorption for the methyl protons of acetone arose at high field, and just slightly up field, an unsymmetrical triplet signal appeared that was ascribed to the acid's methyl protons. A broad peak very similar to that in the acid-diglyme spectrum was observed at low field, and as before, it was attributed to -NH and -OH protons of the acid. Again, no evidence for tautomer (viii) was conspicuous.

The appearance of the unsymmetrical triplet signal, however, suggests the presence of the enol tautomer. Further work to clarify the nature of this absorption would be of interest, although acetone

is not a very good solvent because the methyl and methylene absorptions somewhat obscure regions of interest for the acid. Also, a study of the copper salt in a suitable solvent might present additional evidence from which conclusions could be drawn concerning the structure of the acid.

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