SOME CHEMISTRY OF PHENYLSULFOXYACETIC ACID AND RELATED COMPOUNDS

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SOME CHEMISTRY OF PHENYLSULFOXYACETIC ACID

AND RELATED COMPOUNDS

A Thesis

by

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ABSTRACT

Syntheses of α,α-d_2-chloroacetic acid, α,α-d_2-phenylsulfoxyacetic acid, and α,α-d_2-phenylsulfonylacetic acid are described and the suitability of these acids for conductivity measurements in aqueous (H_2O) media has been investigated. The proton-deuteron exchange reaction at the methylene position of phenylsulfoxyacetic acid has been qualitatively examined and shown to be stereoselective, i.e. the two protons (or deuterons) exchange at different rates. The solvent dependence of the chemical shifts of the methylene protons in phenylsulfoxyacetic acid and some related compounds is discussed.

PREFACE

The introduction to the thesis outlines the basic philosophy which prompted the present investigation. Prior to carrying out measurements, which could prove definitive in either confirming or rejecting the inductive theory of secondary isotope effects of the second kind, studies have been made on three isotopic acid pairs considered suitable for measurement. These investigations, described in the experimental and discussion, led to a closer examination of the chemical and physical properties of phenylsulfoxy-acetic acid and some related compounds which were not strictly involved in the original aim of the work. Hence, there is an abrupt lapse in continuity between the introduction and experimental portions of the thesis.

P.D.G.

INTRODUCTION

In 1913 Soddy (1) postulated that certain elements could have the same atomic number yet differ in atomic mass. He designated these "chemical fraternal twins" as isotopes, a name derived from the Greek "ισοσ τοποσ" meaning "equal place". Soddy's postulate answered the riddle arising out of earlier research of Boltwood (2, 3, 4), Marchwald and Keetman, and Welsbach, all of whom could not effect the slightest separation between thorium and "ionium", a name given by Boltwood to the parent of radium. Soddy's postulate was substantiated by the experimental work of Moseley (5, 6), Barkla (7, 8), and J.J. Thomson (9, 10, 11, 12, 13). In 1919, with the development of his "mass spectrograph", Aston (14, 15) confirmed Soddy's postulate by demonstrating the existance of several elemental isotopes.

During the course of his investigation of isotopes, Soddy (16) commented that "independently of all other considerations, such as atomic weight,....., so far as is known, (they are) identical in chemical character". The term "chemical character" doubtless refers to such properties as valency and stoichiometry. In contrast, however, physical properties may alter with isotopic substitution. Such changes in physical properties have been termed isotope effects, and their measurement is a topic of considerable current interest.

For the sake of clarity, the presentation of the classifications of isotope effects is restricted to one isotopic

pair, namely hydrogen (H) and deuterium (D). In the case of chemical equilibria an isotope effect is defined by the ratio of K(H) to K(D), K(H) being the equilibrium constant pertaining to the proton substituted structure and K(D) the equilibrium constant appropriate to the deuterium analogue. When rate measurements are of interest the isotope effect is designated as the ratio of the corresponding rate constants k(H) to k(D). When the isotope effect is greater than unity, i.e. $K(H)/K(D)>1$ or $k(H)/k(D)>1$, it is said to be a "normal" effect, and when less than unity, i.e. $K(H)/K(D)<1$ or $k(H)/k(D)<1$, it is described as an "inverse" or "reverse" isotope effect.

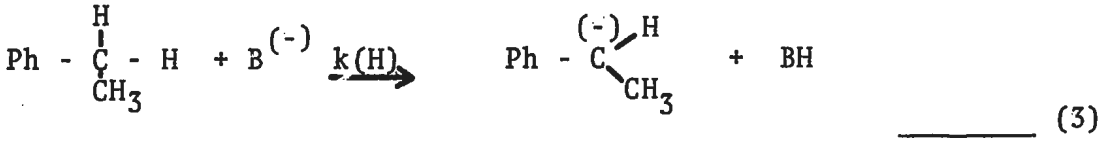
A further classification of isotope effects depends on a consideration of the effect on the bond linking the isotopic atoms to the molecular residues. If this particular bond is ruptured or partially ruptured, a "primary" isotope effect results; but if the bond remains intact in the reactants, transition states, and products, the isotope effect is "secondary", Equations (1)* and (2) serve to illustrate a primary and a secondary isotope effect respectively.

$$\begin{aligned} &Ph - CH_2 - COOH + H_2O \underset{}{\overset{K(H)}{\rightleftharpoons}} Ph - CH_2 - COO^{(-)} + H_3O^{(+)} \\ &Ph - CH_2 - COOD + D_2O \underset{}{\overset{K(D)}{\rightleftharpoons}} Ph - CH_2 - COO^{(-)} + D_3O^{(+)} \end{aligned} \qquad \text{(1)}$$

$$\begin{aligned} &Ph - CH_2 - COOH + H_2O \underset{}{\overset{K(H)}{\rightleftharpoons}} Ph - CH_2 - COO^{(-)} + H_3O^{(+)} \\ &Ph - CD_2 - COOH + H_2O \underset{}{\overset{K(D)}{\rightleftharpoons}} Ph - CD_2 - COO^{(-)} + H_3O^{(+)} \end{aligned} \qquad \text{(2)}$$

* Since hydroxyl hydrogen atoms exchange very rapidly in aqueous media, K(D) must be determined in D_2O. Consequently, K(H)/K(D) of equation (1) includes not only a primary isotope effect but also a "solvent isotope effect".

Secondary isotope effects in which the bonds from the isotopic substituents to the molecular residues undergo spatial reorientation have been described by Streitweiser (17) as secondary isotope effects of the "first kind". Secondary isotope effects of the "second kind" are those in which no spatial reorientation of the bond occurs in the equilibrium or rate process under consideration. Examples of secondary isotope effects of the first and second kind are respectively given by equations (3) and (4). These examples form part of a series of reactions investigated by Streitweiser and co-workers (18).



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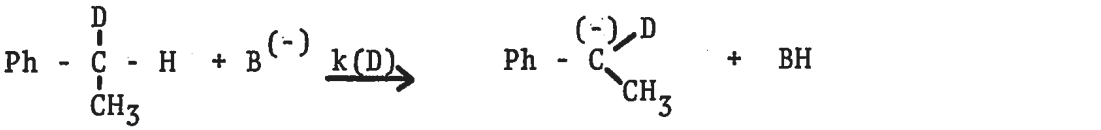

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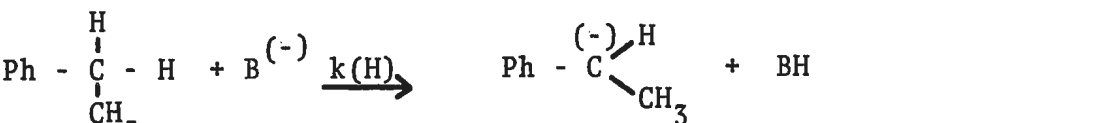


The technological, scientific, and military use of isotopes during and since World War II has attracted considerable

attention to the theoretical problems posed by the chemical and physical differences exhibited by isotopic atoms and molecules. Mayer (19), Bigeleisen (19, 20, 23), Melander (21, 22), and others (23, 24) have put forward rigorous theories based on statistical mechanics and the Redlich-Teller product rule (see (25)) which allow the accurate calculation of isotope effects in chemical reactions. Although these theories may differ slightly in emphasis, the differences are of little consequence in the present discussion. The basic parameters required for the calculation of an isotope effect are the molecular vibrational frequencies of both the ground states and the transition states of the isotopically substituted species involved in an equilibrium or rate process. Hence, the theoretical approach proposed by Bigeleisen and Melander is of limited value in its final form, for the situation seldom occurs in which either all the vibrational frequencies or the related force constants are known. (c.f. Bigeleisen and Wolfsberg (23)). A notable exception is the investigation of the formic acid system by Bell and Crooks (26). The pK_a difference between HCOOH and DCOOH observed by these workers was in good agreement with the theoretically computed value using only empirical vibrational frequencies. However, the measurement and assignment of vibrational frequencies of more complex isotopically substituted molecules in the condensed phase, in which rates and equilibria are usually examined, is

an exceedingly difficult task. Thus, an accurate calculation of isotope effects for equilibria and rates is generally impossible.

If $h\nu$ in a pair of H and D substituted analogues is large relative to kT for all frequencies, the complex theoretical expressions can be simplified to a dependence on zero-point energy terms and the isotope effect is given by

$$\frac{K(H)}{K(D)} = \exp. \frac{-h}{2kT} \left(\Sigma\Delta\nu_H - \Sigma\Delta\nu_D\right) \qquad (5)$$

where "h" is Planck's constant, "k" is Boltzmann's constant, "T" is the absolute temperature, and "$\Sigma\Delta\nu$" represents the difference in the frequency sums of the respective reactants and products. Equation (5) implies that isotope effects are quantum effects and that they depend largely on a double-difference between the vibrational frequency sums of the reactants and products of the isotopic analogues.

By applying further approximations equation (5) may be simplified to give

$$\frac{K(H)}{K(D)} = \exp. \frac{-h}{2kT} \left(1 - \frac{1}{C}\right) \left(\Sigma\nu_H - \Sigma\nu_H'\right). \qquad (6)$$

These approximations were originally proposed by Streitweiser for the calculation of isotope effects for rate processes. However, since $\frac{k(H)}{K(D)}$ is generally regarded to be equivalent to

$\frac{K(H)}{K(D)}$ (27)*, then isotope effects arising from equilibrium considerations may be calculated using equation (6). The constant "c" in equation (6) has a theoretical value of $\sqrt{2}$, but Streitweiser (28) has determined the value of "c" to be about 1.35 from a consideration of suitable spectroscopic data. By employing equation (6) to approximate an isotope effect, the sums of all the vibrational frequencies in both pairs of isotopically substituted reactants and products are no longer necessary. In this equation only the sums of those frequencies primarily associated with the motion of the hydrogen atom at the position of interest in the non-deuterated reactant and product are required, and these sums are represented by $\Sigma\nu_H$ and $\Sigma\nu_{H'}$ respectively. In extreme cases the summations may be reduced to a consideration of two or three vibrations or even a single vibration. (However, for more detailed calculations using the complete theory see Wolfberg and Stern (29) and Willi (30).)

It is generally accepted that proton-deuteron secondary isotope effects are primarily dependent upon zero-point energy differences incurred in going from reactants to products. These differences are in turn dependent upon force constant changes

* $\frac{k(H)^{\ddagger}}{k(D)}$ is actually equivalent to $\frac{K(H)^{\ddagger}}{K(D)}$ in which K(H) and K(D) are the quasi-equilibrium constants between the respective reactants and their transition states.

which can be attributed to steric interactions (28, 31, 32, 33, 34, 35, 36, 37) and such electronic effects as hyperconjugation (28, 31, 38, 39, 40, 41, 42), hybridization (28, 32, 33, 34, 43, 44), and induction (43, 45). Both Streitweiser (46) and Halevi (43) and their respective co-workers have postulated that secondary isotope effects behave like inductive effects. Halevi (43) has stated that "deuterium bonded to carbon is effectively more electropositive, but less polarizable, than protium. The principal factor responsible (for this electronic difference) seems to be the anharmonicity of the vibrations involving the motions of the hydrogen atoms, which leads to different average bond lengths and angles in deuterated and normal molecules", and hence, a different charge distribution. The hypothesis that secondary isotope effects of the second kind behave like inductive effects is supported by the effect of deuteration (at positions α and β to the carboxyl group) on the equilibria of the carboxylic acids listed in Table I. In the case of a few ammonium ion acids (47, 48, 49, 50), which show behaviour similar to that of the carboxylic acids in Table I, the effect is more marked; but this has been rationalized on the basis of opposing inductive and hyperconjugative effects in the carboxylic acids (43).

If secondary isotope effects behave like inductive effects, the magnitude of such effects should vary with structure and position of deuteration, and consequently be amenable to a

TABLE I

SOME PREDICTED AND OBSERVED ISOTOPE EFFECTS

Isotopic Pair	K(H) / K(D) Obs. (Ref.)	Calc. (Eq.)
CH_3COOH / CD_3COOH	1.035 (46)	--
$(CH_3)_3CCOOH$ / $(CD_3)_3CCOOH$	1.04 (46)	--
HCOOH / DCOOH	1.08 (43)	1.03
CH_3CH_2COOH / CD_3CH_2COOH	1.01 (48)	1.014
CH_3CH_2COOH / CH_3CD_2COOH	1.08 (48)	1.021
$PhCH_2COOH$ / $PhCD_2COOH$	1.12	1.021
$CH_3\overset{(+)}{N}H_3$ / $CD_3\overset{(+)}{N}H_3$	1.13	1.083
$(CH_3)_2\overset{(+)}{N}H_2$ / $(CD_3)_2\overset{(+)}{N}H_2$	1.32	1.18

linear free energy treatment in much the same manner as Taft (51) has treated "large scale" inductive effects. Indeed, Streitweiser (46) has successfully applied the Taft equation to estimate the magnitude of the isotope effects encountered in certain aromatic ring compounds from the isotope effects of an aliphatic series.

Using the premise that inductive effects are additive, Scott and Barnes (52) have modified the Taft equation (51) from

$$\log K = 1.721\ \sigma^* - 4.76 \qquad (7)$$

to

$$pK_a = -(0.558 \pm 0.016)\ \Sigma\sigma^* + 5.19 \pm 0.07 \qquad (8)$$

where σ^* is the Taft inductive parameter for a substituent "X" attached to the carboxyl group of a carboxylic acid. When "X" can be considered as a substituted methyl group ($-CX_1X_2X_3$), then $\Sigma\sigma^*$ is defined as

$$\Sigma\sigma^* = \sigma^*(X_1) + \sigma^*(X_2) + \sigma^*(X_3) \qquad (9)$$

This modification is similar to the Hall (53) relationships, which are given by

$$pK_a = 13.23 - 3.14\ \Sigma\sigma^* \qquad (10)$$

for primary amines and

$$pK_a = 12.13 - 3.23\ \Sigma\sigma^* \qquad (11)$$

for secondary amines. In these equations the $\Sigma\sigma^*$ parameter refers to the sum of the Taft constants for the groups attached

to the nitrogen atom. The $\Sigma\sigma^*$ values were calculated for twenty-one carboxylic acids listed in Table II, which was used in the correlation of $\Sigma\sigma^*$ and pK_a shown in Figure I. The correlation of σ^* and $\Sigma\sigma^*$ (see figure II) gives a straight line which does not pass through the origin and the slope of which is not unity. However, this plot indicates that the premise upon which the modification of the Taft equation is dependent, namely that inductive effects are additive, is by and large a good one. Although the correlation of $\Sigma\sigma^*$ and pK_a based on the modification (see Figure I) is inferior to that originally given by Taft, a more extensive range of structures is embraced by equation (8) than were used to establish equation (7). Deviations from the strict additivity of inductive effects may be a consequence of steric effects, but these should be negligible in the case of H, D, CH_3 and CD_3 substituents. (However, see Bartell's investigation of nonbonded interactions (32, 34 34).)

The value of σ^* (D) was obtained from equilibrium constant measurements made by Bates et al. (54) on the CH_3COOH / CD_3COOH system, and similarly the value of σ^* (CD_3) was obtained from a similar investigation of the $(CH_3)_3COOH$ / $(CD_3)_3COOH$ system by Streitweiser and Klein (46). These values of σ^* (D) and σ^* (CD_3) were then used in conjunction with the values of σ^*(H), $\sigma^*(CH_3)$ and σ^*(Ph) to calculate $\Sigma\sigma^*$ values of the following isotopic acid systems:

TABLE II

ACID STRENGTH DATA RELATED TO THE TAFT CORRELATION FOR SUBSTITUTED ACETIC ACIDS

ACID (X-COOH)	pK_a †	σ^*	$X \equiv CX_1X_2X_3$			$\Sigma\sigma^*$
			X_1	X_2	X_3	
CF_3COOH	0.23	--	F	F	F	9.30
CCl_3COOH	0.65	2.65	Cl	Cl	Cl	8.70
CBr_3COOH	0.66	--	Br	Br	Br	8.40
CHF_2COOH	1.24	2.05	F	F	H	6.69
$CHCl_2COOH$	1.29	1.94	Cl	Cl	H	6.29
$(CH_3)_3\overset{(+)}{N}CH_2COOH$	1.83	1.90	$(CH_3)_3\overset{(+)}{N}$	H	H	--
CH_2FCOOH	2.59	1.10	F	F	H	4.08
$CH_2(COOH)_2$	2.83	1.05	COOH	H	H	--
$CH_2Cl\ COOH$	2.87	1.00	Cl	H	H	3.88
$CH_2BrCOOH$	2.90	0.92	Br	H	H	3.78
CF_3CH_2COOH	3.07	0.85	CF_3	H	H	--
$C_6H_5OCH_2COOH$	3.12	0.85	PhO	H	H	--
CH_2ICOOH	3.18	0.52	I	H	H	3.38
$CH_3O\ CH_2COOH$	3.53	0.60	CH_3O	H	H	--
HCOOH	3.77	0.49	-	-	-	--
$NO_2CH_2CH_2COOH$	3.81	0.50	NO_2CH_2	H	H	1.48
$(C_6H_5)_2CHCOOH$	3.96	0.45	C_6H_5	C_6H_5	H	2.45
CH_2ClCH_2COOH	4.08	0.385	CH_2Cl	H	H	2.52

....Contd.

TABLE II (Contd.)

ACID (X COOH)	pK_a†	σ*	X ≡ $CX_1X_2X_3$ X_1	X_2	X_3	Σσ*
$C_6H_5CH_2COOH$	4.31	0.215	C_6H_5	H	H	1.58
$CF_3CH_2CH_2COOH$	4.18	0.320	CF_3	H	H	1.50
$C_6H_5CH_2CH_2COOH$	4.66	0.080	$C_6H_5CH_2$	H	H	1.195
CH_3COOH	4.76	0.00	H	H	H	1.47
$(CH_3)_2CHCOOH$	4.86	-0.19	CH_3	CH_3	H	0.49
CH_3CH_2COOH	4.88	-0.10	CH_3	H	H	0.98
$CH_3CH_2CH_2COOH$	4.82	-0.115	CH_3CH_2	H	H	0.88
$CH_3CH_2(CH_3)CHCOOH$	4.78	-0.21	CH_3CH_2	CH_3	H	0.39
$(CH_3)_3CCOOH$	5.05	-0.30	CH_3	CH_3	CH_3	0.00
$CNCH_2COOH$	2.43	1.30	CN	H	H	4.62

† All pK_a values were taken from (57) except those of the monohalogenoacetic acids, which were taken from (55).

FIGURE I

CORRELATIONS BETWEEN THE $\Sigma\sigma^*$ PARAMETER AND pK_a'S OF A SERIES OF SUBSTITUTED ACETIC ACIDS

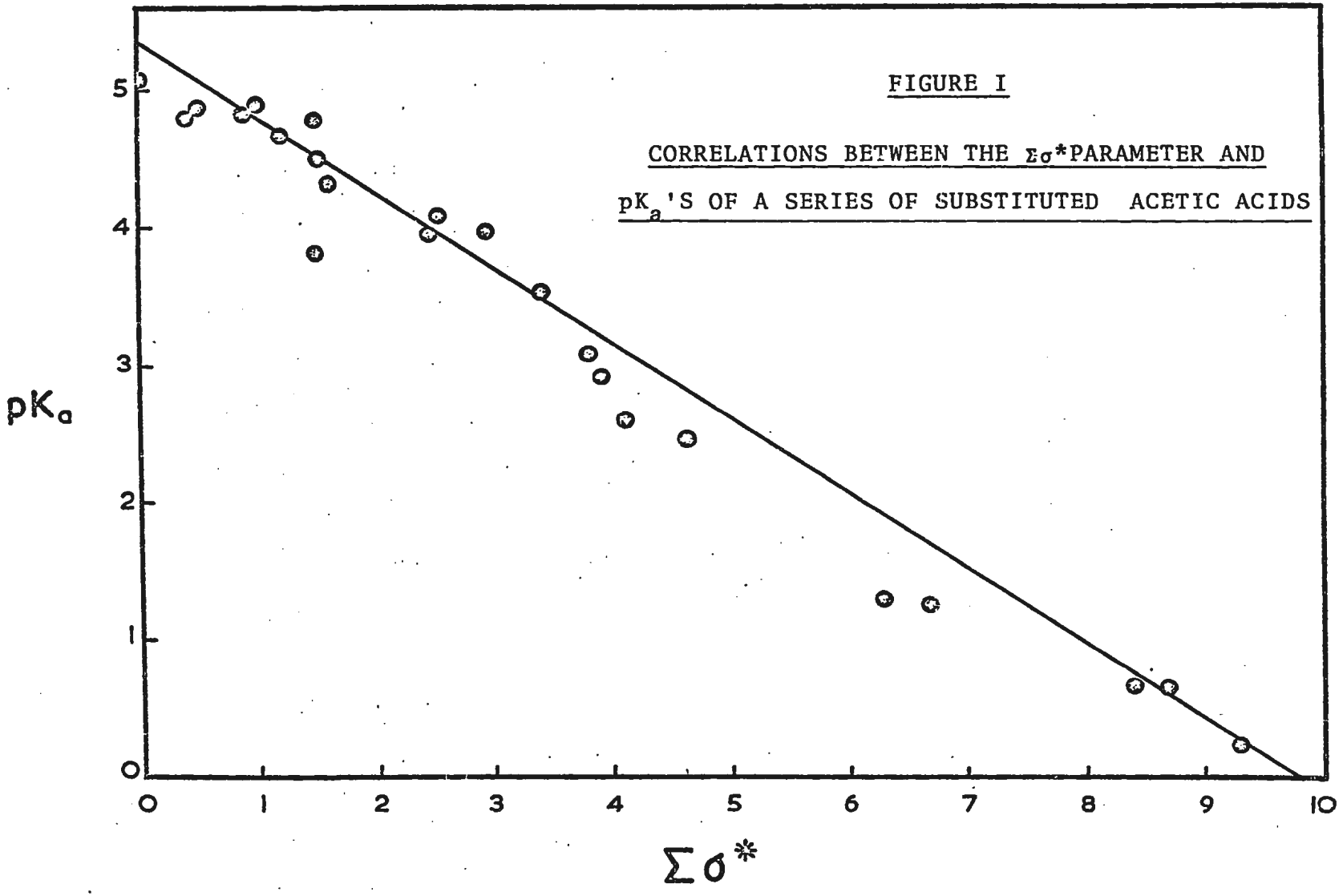
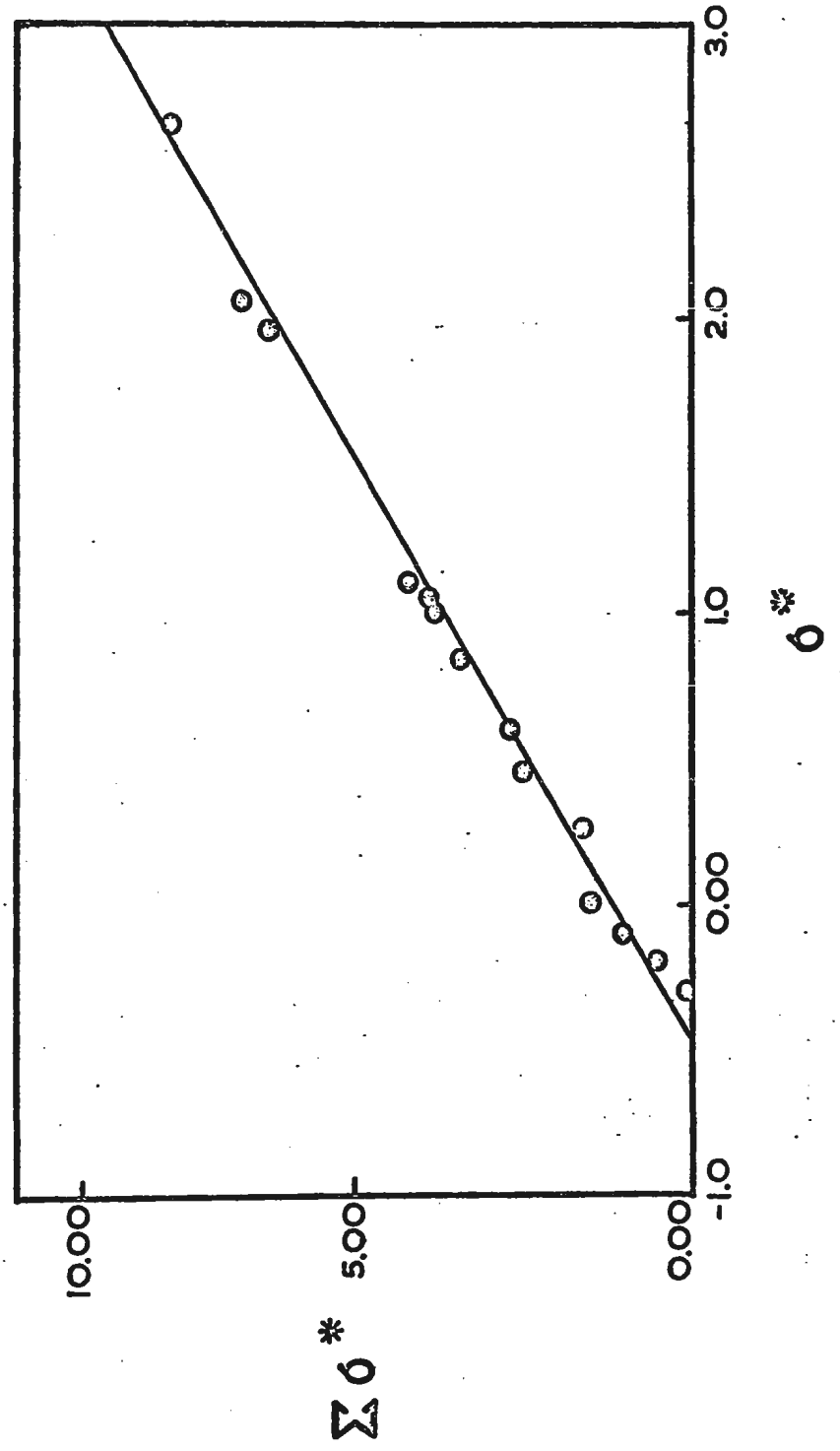


FIGURE II

CORRELATION BETWEEN $\Sigma\sigma^*$ AND σ^*



$HCOOH/DCOOH$, $CH_3CH_2COOH/CD_3CH_2COOH$, $CH_3CH_2COOH/CH_3CD_2COOH$, $PhCH_2COOH/PhCD_2COOH$, $CH_3\overset{\oplus}{N}H_3/CD_3\overset{\oplus}{N}H_3$, and $(CH_3)_2\overset{\oplus}{N}H_2/(CD_3)_2\overset{\oplus}{N}H_2$. From the calculated $\Sigma\sigma^*$ values Scott and Barnes have predicted the isotope effects of the latter systems, and these are compared (see Table I) with experimentally observed values determined by Halevi (48) and Robertson (50). Although the predictions of the isotope effects for these acid systems are qualitatively verified, the observed isotope effects generally exceeded the predicted effects by several percent.

To provide more data with which to test the Halevi-Streitweiser-Taft inductive treatment of isotope effects, Scott and Barnes carried out conductance measurements to determine the K(H)/K(D) ratios for the isotopic weak acid pairs $4\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}COOH/4\text{-}NO_2\text{-}C_6H_4\text{-}CD_2\text{-}COOH$ and $4\text{-}MeO\text{-}C_6H_4\text{-}CH_2\text{-}COOH/4\text{-}MeO\text{-}C_6H_4\text{-}CD_2\text{-}COOH$. They also redetermined the isotope effect of the $PhCH_2COOH/PhCD_2COOH$ apair. These acid systems were chosen to test the adequacy of the inductive treatment, since the inductive model requires that isotope effects be independent of the nature of any group substituted in the 4-position of the ring in the aromatic side chain.

Several methods of treating the conductance data were devised (52), and the results of these measurements are summarized

in Table III. Although the ratios indicate qualitative agreement with the Halevi - Streitweiser - Taft inductive model, a comparison of $\frac{1}{n} \log_{10} \frac{K(H)}{K(D)}$ and $pK_a(H)$ is of greater significance and interest. * The inclusion of the data for the acetic acid system (54) with the results of the latter three arylacetic acid pairs indicates a definite tendency for the magnitude of the isotope effect per deuterium atom to decline as the strength of the acid increases (see figure III).

Two observations emerge from the correlation of $pK_a(H)$ with $\frac{1}{n} \log_{10} \frac{K(H)}{K(D)}$:

(1) The predicted value of 1.02 for the isotope effect of the $PhCH_2COOH/PhCD_2COOH$ acid pair based on $\sigma^*(D)$ is now much closer to the observed value of 1.01 (see Table III), i.e. the inductive treatment is partially verified.

(2) The isotope effect appears to be variable and depends on the structure of the acid. This is not consistent with the proposed inductive model, which requires that the inductive effect per deuterium atom be independent of the molecular environment of the isotopic substituent.

* V.J. Shiner (31) originally proposed the formula $\frac{1}{n} \log_{10} \frac{K(H)}{K(D)}$ in which n = 3 for CH_3COOH/CD_3COOH and n = 2 for the arylacetic acids.

TABLE III

$p\text{-R-}C_6H_4\text{-}CH_2COOH/R\text{-}C_6H_4\text{-}CD_2COOH$

ISOTOPE EFFECTS

R	%D	Classical	Robinson & Stokes	Shedlovsky II	Shedlovsky III	Shedlovsky-Barnes-Scott	Ives
H	93.6	1.0072 ± 0.0004	1.0035 ± 0.005	1.0034 ± 0.005	1.0076 ± 0.0015	1.0082 ± 0.0015	1.018 ± 0.005
$4\text{-}NO_2$	92.5	0.9973 ± 0.002	1.0005 ± 0.005	1.004 ± 0.005	0.9962 ± 0.0013	0.9975 ± 0.0017	0.9936 ± 0.005
4-MeO	97.0	1.0045 ± 0.0007	1.0077 ± 0.002	1.0076 ± 0.0023	1.0045 ± 0.001	1.0041 ± 0.0019	0.9975 ± 0.005

The aim of the present work was to furnish further data which would extend the above correlation (Figure III) and thereby definitely establish the trend of diminishing isotope effect per deuterium atom with increasing acidity. The relatively strong isotopic acid pairs $ClCH_2COOH/ClCD_2COOH$, $PhSOCH_2COOH/PhSOCD_2COOH$, and $PhSO_2CH_2COOH/PhSO_2CD_2COOH$ were chosen for investigation because each has a $pK_a(H)$ less than 4. Previous investigations have shown the protium acids suitable for conductance measurements (55, 56). A linear least squares treatment of the Shedlovsky III results (see Figure III) was used to determine the relationship between $\frac{1}{n} \log_{10} \frac{K(H)}{K(D)}$ and $pK_a(H)$ for acetic acid and the carboxylic acids examined by Scott and Barnes. The resulting equation is

$$\frac{1}{n} \log_{10} \frac{K(H)}{K(D)} = (8.046 \times 10^{-3})\ pK_a - (3.301 \times 10^{-2}) \qquad (12)$$

This relationship was employed to predict the isotope effects of the $ClCH_2COOH/Cl\text{-}CD_2COOH$, $Ph\text{-}SO\text{-}CH_2COOH/Ph\text{-}SO\text{-}CD_2COOH$, and $PhSO_2\text{-}CH_2COOH/Ph\text{-}SO_2\text{-}CD_2COOH$ isotopic acid pairs (see Table IV and Figure IV).

FIGURE III

SHEDLOVSKY III RESULTS

Plot of 1/n log K(H) / K(D) vs $pK_a(H)$

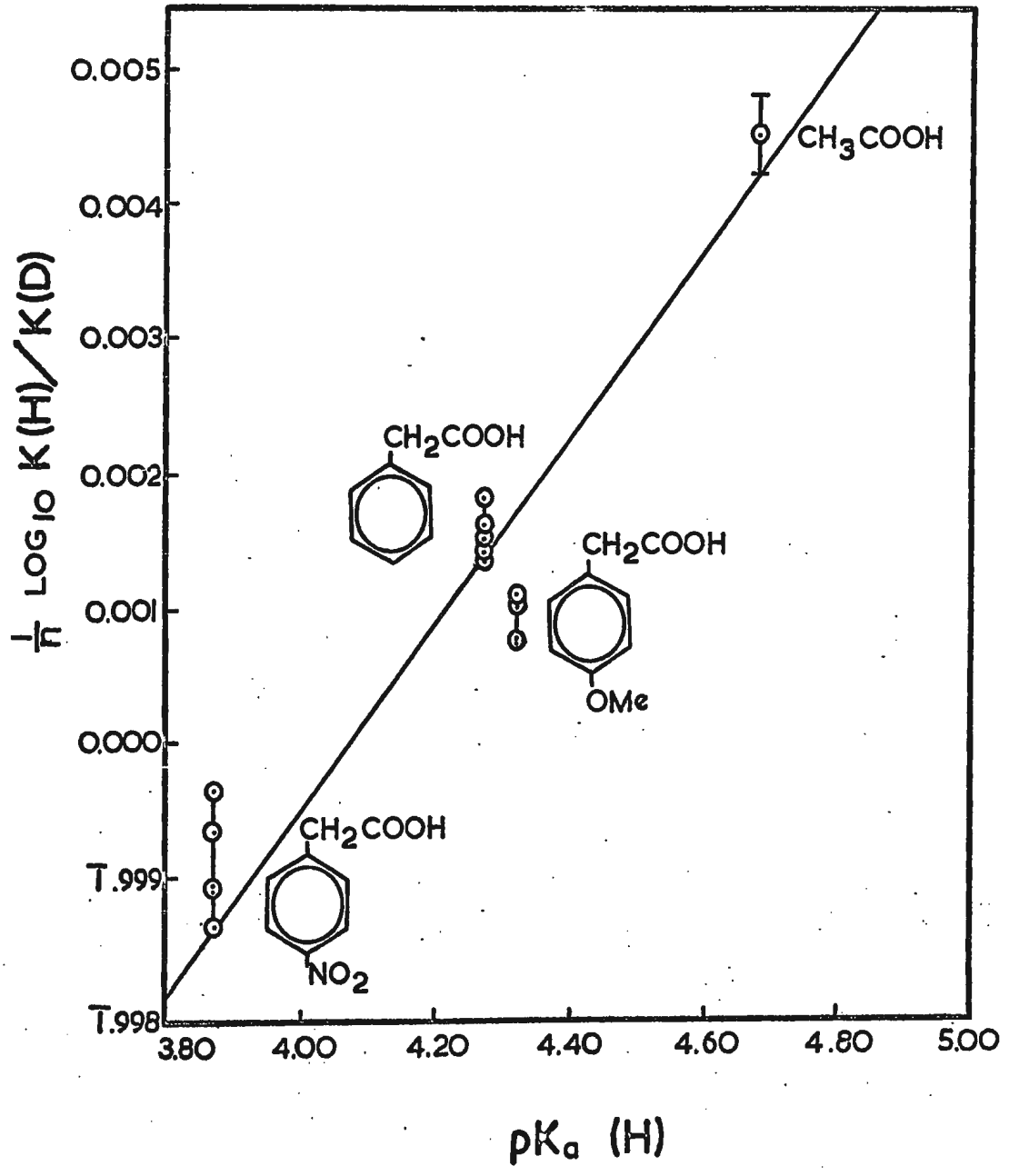


TABLE IV

THE PREDICTED ISOTOPE EFFECTS OF SOME CARBOXYLIC ACIDS CALCULATED FROM A LINEAR LEAST SQUARES TREATMENT OF OBSERVED pK_a AND ISOTOPE EFFECT VALUES

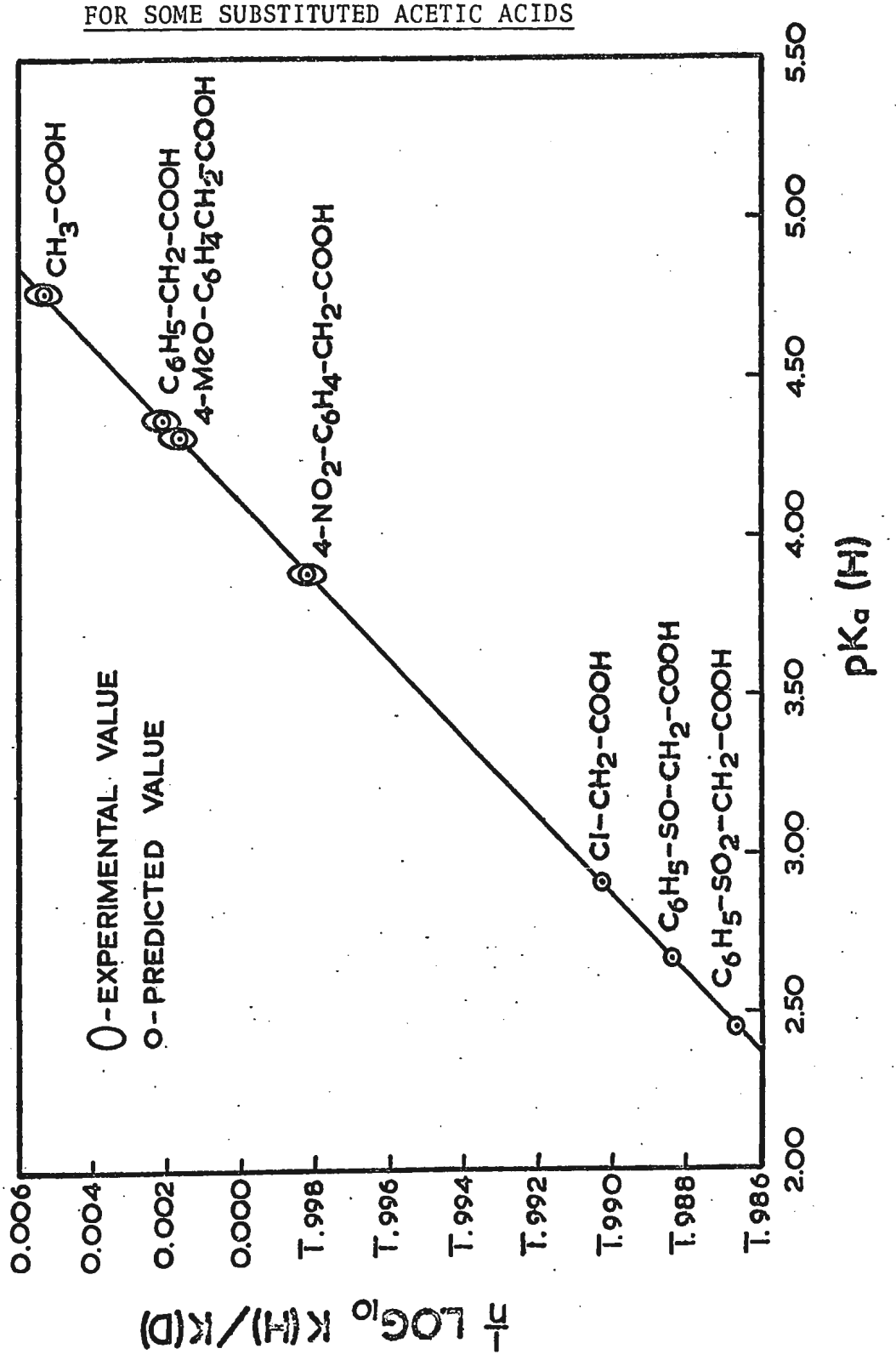
Protium Acid	pK_a(H)	Calculated K(H)/K(D)	Observed K(H)/K(D)
CH_3COOH	4.76	1.037	1.035
$C_6H_5CH_2COOH$	4.31	1.008	1.008
4-$MeOC_6H_4CH_2COOH$	4.36	1.010	1.005
4-$NO_2C_6H_4CH_2COOH$	3.88	0.992	0.996
$ClCH_2COOH$	2.90	0.956	--
$C_6H_5SOCH_2COOH$	2.66	0.948	--
$C_6H_5SO_2CH_2COOH$	2.44	0.940	--

FIGURE IV

THE PREDICTED LINEAR LEAST SQUARES CORRELATION OF

$\frac{1}{n} \text{Log}_{10}\ K(H)/K(D)$ vs. $pK_a(H)$

FOR SOME SUBSTITUTED ACETIC ACIDS



EXPERIMENTAL

INSTRUMENTATION

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian A-60 instrument at 60 Mhz with the probe temperature ca. 40° (unless otherwise specified). Infrared (i.r.) spectra were recorded on Perkin-Elmer 237B or 225 spectrometers. Gas-Liquid chromatographic (g.l.c.) analyses were carried out on a Beckman GC-2A instrument with an Apiezon-L column at 220° and 20 pounds pressure of helium carrier gas. Melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus.

MATERIALS

Chloroacetic acid.- Purified (58) red phosphorus (3 g.) and glacial acetic acid (75 g.; 1.25 mole) were mixed in a flask and weighed, after which the mixture was heated to 100°. Chlorine was bubbled into the reaction mixture and the temperature was maintained at 105 - 110°. The reaction was allowed to proceed for 3 hours, then the flask and contents were reweighed at 15 minute intervals. The reaction was terminated when the weight of the reaction mixture had increased 40 g. (59).

Purification. - N.m.r. spectra ($CDCl_3$) were recorded after each step in the purification process. The intensities of the chemical shifts at 4.0τ (CH of dichloroacetic acid) and 5.9τ (CH_2 of chloroacetic acid) were compared in each spectrum as a measure of the purity of the chloroacetic acid.

(i) The reaction mixture was distilled and the fraction which had a b.p. range of 150 - 200° was collected. This fraction was redistilled and the portion which came over at 182 - 190° was retained. A third distillation gave colourless chloroacetic acid (53.5 g., 42% yield) b.p. 188 - 190° and m.p. 56.1 - 58.5° (lit. b.p. and m.p. are 189.35° and 63.0° respectively (60)). An n.m.r. spectrum indicated this material was 93.5% pure.

(ii) The distilled product was recrystallized three times from chloroform, and an n.m.r. spectrum showed this material (needles, m.p. 59.2 - 59.6°) was 96.0% pure.

(iii) Recrystallized chloroacetic acid (5.0 g.) was melted under reduced pressure (ca. 0.10 - 0.05 mm. of Hg) in a sublimation apparatus, and the temperature was slowly raised to 62.5°. The temperature and pressure were maintained for 48 hours, after which the sublimed material was recrystallized from chloroform, m.p. 60.0 - 60.5°. This process was repeated, but n.m.r. measurements indicated that it did not increase the purity of the chloroacetic acid beyond 98.2%.

(iv) Sublimed chloroacetic acid (ca.4 g. recrystallized from chloroform was heated to 60.5°. Nitrogen was bubbled into the molten material and the temperature was raised 0.5° at hourly intervals. After 5 hours the chloroacetic acid was recrystallized from chloroform, m.p. 60.9 - 62.3° (61). N.m.r. measurements showed that this process failed to raise the purity beyond 99.6%.

(v) Process (iv) was repeated on recrystallized material until crystals began to form at 62.5°. The temperature was raised to 63.5° and the resulting liquid was allowed to cool slowly. When two-thirds of the material solidified, the remaining liquid portion was immediately decanted from the newly formed crystals. This procedure was repeated twice and the remaining needles (0.4 g.) were washed with cold chloroform and dried, m.p. 63.0 - 63.2°. N.m.r. measurements on a sample of this material indicated that no impurities were present.

Methyl chloroacetate.- Chloroacetic acid (9.45 g.; 0.10 mole), methanol (9.6 g.; 0.30 mole), and conc. H_2SO_4 (0.3 ml.) were mixed with ethylene dichloride (30 ml.) and the mixture was refluxed for 20 hours. The remaining acid was removed by successively washing the non-aqueous layer with sodium bicarbonate solution and water. The non-aqueous layer was dried over anhydrous magnesium sulfate and the ethylene dichloride was removed by distillation under reduced pressure. The residue was distilled and colourless methyl chloroacetate (7.8 g.; 72% yield) was collected, b.p. 131 - 132.2° (lit. b.p. 131.0° (62)) (63).

Methyl dichloroacetate.- Dichloroacetic acid (12.90 g., 0.10 mole), methanol (9.6 g.; 0.3 mole), and conc. H_2SO_4 (0.3 ml.) were mixed with ethylene dichloride (30 ml.). The esterification was carried out in the same manner as in the preparation of methyl chloroacetate (63). The product was distilled, and colourless

methyl dichloroacetate (9.71 g.; 68% yield) was isolated, b.p. 144.5 - 146° (lit. b.p. 143.3° at 764.5 mm. of Hg (64)).

Methyl trichloroacetate.-Trichloroacetic acid (16.34 g.; 0.10 mole) was esterified in the same manner as mono- and dichloroacetic acids (63). Pure colourless methyl trichloroacetate (13.0 g.; 73% yield) was isolated by distillation, b.p. 153-154.6° (lit. b.p. 153.8° (65)).

Separation of methyl tri-, di-, and monochloroacetate.- Five grams of each of the methyl esters were mixed and the mixture was distilled. Methyl chloroacetate (4.2 g.) was isolated over a b.p. range of 131.0 - 132.5°. N.m.r. measurements ($CDCl_3$) on this fraction after redistillation indicated that methyl dichloroacetate was absent.

Methyleneaminoacetonitrile,- Ammonium chloride (540 g.; 10 moles) and 37% formaldehyde* (1620 g.; 18.9 moles) were mixed and cooled to 0°. To the mixture sodium cyanide (490 g.; 9.8 moles) dissolved in water (850 ml.) at 5° was added dropwise over a period of 3 hours. When half of the sodium cyanide was added, glacial acetic acid (380 ml.) was added dropwise at the rate such that both additions were completed simultaneously. Ice (200 - 300 g.) was also added during the reaction to maintain the temperature at 0 - 5°. After the additions, the reaction mixture was stirred for 1.5 hours, and

* 37% solution of formaldehyde in water

then the methyleneaminoacetonitrile (436 g.; 69% yield) was collected, washed with cold water (ca. 2000 ml.) and dried over silica-gel in a vacuum desiccator, m.p. 128.5 -129.5° (lit. m.p. 128-129°). An n.m.r. spectrum (d_6-acetone) showed two chemical shifts (6.20τ and 6.31τ) of equal intensity (66).

Glycine.- Methyleneaminoacetonitrile (34 g.; 0.5 mole) was added to a solution of 95% H_2SO_4 (51.5 g.; 0.5 mole) in 95% ethanol (125 ml.) at 45 - 50°. As dissolution occurred heat was evolved and white aminoacetonitrile hydrogen sulfate began to crystallize. The mixture was allowed to stand overnight at 0 - 5°, and then the salt (51 g.; 67% yield) was collected and washed with cold ethanol (25 ml.) and dried.

Aminoacetonitrile hydrogen sulfate (30.8 g.; 0.2 mole) was added to barium hydroxide octahydrate (126.5 g.; 0.4 mole) suspended in water (500 ml.). After the evolution of ammonia the barium was quantitatively precipitated by 50% H_2SO_4. Crude glycine crystallized from the cold, concentrated filtrate and was collected. The glycine (8.2 g.; 55% yield) was recrystallized from water and decolourized with "Norite", m.p. 246° with decomposition (67).

Chloroacetic acid.- (i) Glycine (7.5 g.; 0.123 mole) was added to a solution of conc. HCl (100 ml.) and water (100 ml) at 0°. This solution was saturated with calcium chloride, and sodium nitrite (6.9 g.; 0.1 mole) in water (50 ml.)was added dropwise, after which the mixture was stirred for 2 hours at 0-5°.

The solution was filtered and the filtrate was extracted four times with ethyl ether, and the combined extracts were dried. The ethyl ether was removed by distillation under reduced pressure, and the residue was distilled, but chloroacetic acid could not be isolated (68).

(ii) Glycine (7.5 g.; 0.123 mole) was mixed with conc. HCl (75 ml.) and conc. HNO_3 (25 ml.) and was added dropwise to the solution (69). The mixture was refluxed overnight, then extracted with ethyl ether several times. The combined extracts were dried and the ethyl ether was removed by distillation under reduced pressure. The residue was dissolved in hot chloroform and chloroacetic acid (1.4 g.; 15% yield) crystallized from the cold solution, m.p. 62.9 - 63.2° (lit. m.p. 63° (60)). An n.m.r. spectrum (D_2O) had two chemical shifts, a singlet at 4.9τ (OH), and a singlet at 5.5τ (CH_2).

Phenylsulfoxyacetic acid.-* Phenylthioglycollic acid (16.9 g.; 0.1 mole) was dissolved in absolute ethanol at 0 - 5° and to this solution 30% hydrogen peroxide (12 g.; ca. 0.11 mole) was added dropwise. After standing for 2 hours, the excess hydrogen peroxide, ethanol, and water were removed by distillation under reduced pressure. The oily residue was taken up in hot benzene-ethyl acetate (3:1 by volume) and, on cooling, yielded

*The correct I.U.P.A.C. name for this compound is phenylsulfinylethanoic acid, but the trivial name of phenylsulfoxyacetic acid will be used throughout the remainder of the thesis.

white prisms of phenylsulfoxyacetic acid (14.9 g.; 81% yield), m.p. 112.5 - 113.2° (lit. m.p. 112.5 - 113.0° (56)) (Found: C,52.24; H,4.37; O,26.01; S,17.52. $C_8H_8O_3S$ requires C,52.16; H,4.39; O,26.06; S,17.40%). Phenylsulfoxyacetic acid was also prepared by the oxidation of phenylthioglycollic acid with 30% hydrogen peroxide in acetone (72% yield) and in acetic acid (89% yield). Phenylsulfoxyacetic acid (D_2O) had three chemical shifts in its n.m.r. spectrum, a multiplet at 2.4 - 2.5τ (phenyl ring), a singlet at 5.4τ (OH), and a singlet at 6.1τ (CH_2). The intensities of the shifts at 2.4 - 2.5τ and 6.1τ were in the ratio of 5 to 2. An i.r. spectrum ($CHCl_3$) of phenylsulfoxyacetic acid showed strong absorption for the SO stretching vibration at 1028 cm^{-1} (lit. 1065 - 1030 cm^{-1} (70)), and for the carbonyl stretching vibration at 1730 cm^{-1}.

Phenylsulfonylacetic acid.- Phenylthioglycollic acid (16.9 g.; 0.10 mole) was suspended in water (75 ml.), and sodium carbonate (5.3 g.; 0.055 mole) was added to the suspension with stirring. After the evolution of carbon dioxide, potassium permanganate (15.9 g.; ca. 0.101 mole) dissolved in water (200 ml.) at 0° was added dropwise, and the mixture was stirred for 18 hours. The manganese dioxide precipitate was removed by filtration through "Celite", and the clear aqueous filtrate was acidified with HCl (6N). The solution was then extracted four times with ethyl ether (200 ml. total) and the combined extracts were dried. The ethyl ether was removed by

distillation under reduced pressure, and the syrupy residue was taken up in a minimum of hot benzene. On cooling, white prisms of phenylsulfonylacetic acid (13.8 g.; 69% yield) crystallized from the mother liquor. This material was recrystallized four times from benzene, m.p. 110.8 - 111.5° (lit. m.p. 110.0 - 110.5° (56)) (Found: C, 48.16; H,4.04; O,31.86; S,15.85. $C_8H_8O_4S$ requires C,47.99; H,4.04; O,31.96; S,16.01%). An i.r. spectrum (nujol mull) of phenylsulfonylacetic acid showed strong absorption at 1170 cm^{-1} and 1305 cm^{-1} due to the respective symmetric and asymmetric stretching vibrations of the SO_2 group (lit. 1165 - 1120 cm^{-1} and 1340 - 1290 cm^{-1} (71)), and at 1715 cm^{-1}, the carbonyl stretching frequency. Phenylsulfonylacetic acid (d_6-acetone) had three chemical shifts in its n.m.r. spectrum, a multiplet at 1.9 - 2.4τ (phenyl ring), a singlet at 5.7τ (CH_2), and a broad shift at 4.6 - 5.0τ (OH). The intensities of the shifts at 1.9 - 2.4τ and 5.7τ were in the ratio of 5 to 2.

α,α-d_2-Phenylsulfoxyacetic acid.- Pure phenylsulfoxyacetic acid (8.4 g.; 0.05 mole) was dissolved in deuterium oxide (100 ml. of 99.75% pure) and stirred for 10 hours at 50°. The deuterium oxide was removed by freeze-drying and a fresh portion (100 ml.) was added. The exchange process was repeated six times and the residue was taken up in a boiling solution of anhydrous benzene-ethyl acetate (3:1 by volume). α,α-d_2-Phenylsulfoxyacetic acid (6.9 g.; ca. 0.04 mole) crystallized from the

solution as white prisms, m.p. 114.5 - 115.0°. This material was recrystallized twice from anhydrous benzene-ethyl acetate (3:1 by volume) and dried over silica-gel in a vacuum dessicator. α,α-d_2-Phenylsulfoxyacetic acid (d_6-acetone) had two chemical shifts in its n.m.r. spectrum, a multiplet at 2.5 - 3.0τ (phenyl ring), and a broad singlet at 3.4 - 3.5τ (OH). This assignment was confirmed by a marked increase in the intensity of the latter shift after a small addition of trifluoroacetic acid. Although the amplitude of the spectrum was increased, the presence of protons in the methylene position could not be detected. An i.r. spectrum ($CHCl_3$) of α,α-d_2-phenylsulfoxyacetic acid was similar to that of phenylsulfoxyacetic acid with the exception of a broad shoulder in the region of 2350 - 2200 cm^{-1}.

Sodium phenylsulfoxyacetate.-Phenylsulfoxyacetic acid (5 g.; 0.03 mole) was dissolved in a solution of ethanol-water (9:1 by weight; 50 ml.), and sodium bicarbonate (2 g.; 0.024 mole) was added slowly. After the initial evolution of carbon dioxide, the mixture was filtered and the filtrate was refluxed for an hour. The solution was concentrated to two-thirds its original volume, and ethyl ether (5 ml.) was added. The solution was allowed to stand overnight at 5°, and then the white, crystalline product was collected, washed with cold ethanol and dried. The sodium phenylsulfoxyacetate (4.6 g.; 93% yield) was recrystallized from ethanol (ca. 2% water), m.p. 221° with decomposition.

Ethyl phenylsulfonylacetate.- Phenylsulfonylacetic acid (20 g.; 0.1 mole) was dissolved in a solution of absolute ethanol (13.8 g.; 0.3 mole), conc. H_2SO_4 (0.5 ml.) and ethylene dichloride (100 ml.), and the solution was refluxed for 20 hours. The non-aqueous layer was washed successfively with water, sodium bicarbonate solution and water to remove the remaining acid, then it was dried over anhydrous magnesium sulfate. The ethylene dichloride was removed by distillation under reduced pressure (63). The residue was taken up in hot absolute ethanol and filtered. On cooling, ethyl phenylsulfonylacetate (16.4 g.; 72% yield) crystallized from the solution. It was recrystallized twice from absolute ethanol, m.p. 41.5 - 42.2° (lit. m.p. 41- 42° (72)) (Found: c,52.75; H,5.34; O,28.18; S,14.03. $C_{10}H_{12}O_4S$ requires C,52.61; H,5.31; O,28.04; S,14.04%). An i.r. spectrum (nujol mull) of ethyl phenylsulfonylacetate showed strong absorption for the SO_2 stretching frequency at 1330 -1260 cm^{-1} and 1148 cm^{-1} (71), the carbonyl stretching frequency at 1730 cm^{-1}, and the C-O stretching frequency of the ester at 1265 cm^{-1}.

Methyl phenylthioglycollate.- Phenylthioglycollic acid (25 g.; 0.148 mole) was dissolved in anhydrous ethyl ether (50 ml.) at 10°, and then thionyl chloride (18 g.; 0.151 mole) was added dropwise to the solution. The reaction mixture was allowed to come to room temperature after the addition, and the

pressure was reduced to remove sulfur dioxide. Absolute methanol (5 g.; 0.156 mole) and anhydrous ethyl ether (20 ml.) were mixed and added dropwise to the syrupy yellow residue, and the reaction mixture was refluxed for 2 hours. The mixture was distilled under reduced pressure and methyl phenylthioglycollate was collected, b.p. 95 - 96° at ca. 0.4 mm. of Hg. The ester had three chemical shifts in its n.m.r. spectrum (CCl_4), a multiplet at 2.6 - 2.9τ (phenyl ring), a singlet at 6.4τ (CH_3), and a singlet at 6.5τ (CH_2).

Phenylthioacetamide.- Methyl phenylthioglycollate (2 g.; 0.011 mole) was dissolved in methanol (25 ml.) at -40°, and liquid ammonia (ca. 25 ml.) was added to the solution. The reaction mixture was allowed to come to room temperature and was stirred for 3 - 4 hours. The solvent was removed by distillation under reduced pressure, and the residue was recrystallized from benzene giving white plates of phenylthioacetamide (1.2 g.; 67% yield), m.p. 113.0 - 113.5° (lit. m.p. 104° (73)) (Found: C,57.45; H,5.32; O,9.74; N,8.34; S,19.03. C_8H_9OS requires C, 57.47; H,5.44; O,9.57; N,8.38; S,19.14%). Phenylthioacetamide (d_6-dimethyl sulfoxide) had two chemical shifts in its n.m.r. spectrum, a broad multiplet at 2.3 - 3.0τ (phenyl ring and NH_2), and a singlet at 6.35τ (CH_2). The intensities of the two shifts were in the ratio of 7 to 2.

Methyl phenylsulfoxyacetate.- (i) Thionyl chloride (20.5 g.; 0.172 mole) was added dropwise to a solution of phenylsulfoxyacetic acid (32 g.; 0.174 mole) and anhydrous ethyl ether (100 ml.) at 0^{o}. After the addition, the mixture was allowed to come to room temperature and sulfur dioxide was removed by gentle pumping. The mixture was stirred for 2 hours, and then a solution of absolute methanol (30 ml.), anhydrous pyridine (2 ml.) and anhydrous ethyl ether (20 ml.) was slowly added. The resulting solution was refluxed for 3 hours and then washed with sodium bicarbonate solution and water. The non-aqueous layer was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. Attempts to crystallize or distill the thick oily residue (ca. 5 g.) were unsuccessful.

(ii) Phenylsulfoxyacetic acid (20 g.; 0.11 mole) was dissolved in absolute methanol (50 ml.) saturated with dry HCl. The solution was refluxed overnight and then washed with sodium bicarbonate solution and water. The residue was taken up in ethyl ether and dried over anhydrous magnesium sulfate. After the removal of ethyl ether the residue was distilled under reduced pressure. The first three fractions distilled below 104^{o} at ca. 0.2 mm. of Hg, and the fourth fraction was collected, b.p. 104 - 107.5^{o} at ca. 0.2 mm. of Hg. The latter fraction had four chemical shifts in its n.m.r. spectrum (CCl_4), a multiplet at 2.5 - 2.9τ , and three singlets at 4.95τ , 6.4τ and 6.6τ . A qualitative assignment of the groups present on the basis of

intensity and chemical shift was a phenyl ring, a CH group, and two different methoxy groups. An i.r. spectrum (nujol mull) of this material showed strong absorption at 1660 cm^{-1} for the carbonyl stretching frequency, but absorption in the SO stretching region was absent. A g.l.c. analysis of this material showed two peaks, one of which was 5-7% of the other. The retention time of the main peak was 6 minutes.

The fourth fraction (0.5 g.) of the distillate was refluxed overnight with aqueous NaOH (0.01 mole) and methanol (3 ml.). The solution was freeze- dried, and the residue was washed successively with ethyl ether and hot acetone to remove the remaining ester. The dried residue had chemical shifts at 2.7 - 3.1 τ, 5.1τ, and 6.6τ in its n.m.r. spectrum (trifluoroacetic acid), indicating the saponification of the methoxy group previously at 6.4τ. The residue was acidified and the resulting acid was collected, m.p. 137 - 138°.

(iii) Methyl thioglycollate (18.2 g.; 0.1 mole) was dissolved in absolute ethanol (50 ml.) and 30% hydrogen peroxide (14 g.; ca. 0.12 mole) was added dropwise to the solution. After the addition, the mixture was stirred for 6 hours at room temperature, then the ethanol, water, and excess hydrogen peroxide were removed by distillation under reduced pressure. The residue was distilled and three fractions were collected at 52° and 0.4 mm. of Hg, 52 - 65° and 0.4 mm. of Hg, and 104.5 - 107.5° and 0.2 mm. of Hg. A g.l.c. analysis of the second fraction (b.p. 52 - 65° and 0.4 mm. of Hg) showed three peaks

at retention times of 0.7 minutes, 3.6 minutes and 4.9 minutes. A g.l.c. analysis of the third fraction (b.p. 104.5 - 107.5° and 0.2 mm.of Hg) showed peaks at retention times of 3.6 minutes and 4.9 minutes. A g.l.c. analysis of pure methyl phenylthioglycollate had only one peak at a retention time of 3.6 minutes.

The oxidation of methyl phenylthioglycollate was repeated and the solution was allowed to stand for 20 hours at room temperature. A white crystalline material precipitated from the mother liquor and was collected. It was recrystallized from methanol-water (9 : 1 by volume), m.p. 58.5 - 59.5° (lit. m.p. 60° (74)). Conc. H_2SO_4 was added to a small portion of the material and the solution turned red and then purple in colour, indicating a positive qualitative test for diphenyl disulfide (Found: C,65.92; H,4.49; S,29.51. $C_{12}H_{10}S_2$ requires C,66.00; H,4.63; S,29.37%). N.m.r. spectra (CCl_4; d_6-dimethyl sulfoxide) showed the only protons present were attached to the aromatic rings.

After the removal of the precipitated diphenyl disulfide, the filtrate settled into two layers which were separated. A g.l.c. analysis of the top layer revealed two peaks at retention times of 3.6 minutes and 10.0 minutes. The bottom layer (2 g.),dissolved in a minimum of ethyl ether (3 ml.), was placed on a column of neutral alumina (100 g.). The column was eluted with petroleum ether (b.p. 40 - 60°), carbon tetrachloride, benzene, and chloroform in graduated steps of increasing polarity.

The first eight fractions from the alumina column were examined by g.l.c. The first three fractions contained about 5% methyl phenylthioglycollate, and the remainder was a product with the retention time of 10.0 minutes. Fractions four, five, and six showed a substantial increase in the percentage of starting material. Fractions seven and eight contained the latter two compounds as well as some low boiling material with retention times of less than two minutes.

(iv) Phenylsulfoxyacetic acid (18.4 g.; 0.1 mole) was refluxed overnight with methanol (9.6 g.; 0.3 mole), conc. H_2SO_4 (1 ml.) and ethylene dichloride (30 ml.). The reaction mixture was thoroughly washed with sodium bicarbonate solution and water, and the non-aqueous layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and the residue was analyzed by g.l.c. The retention times of the peaks corresponded to those of the products in the reaction of phenylsulfoxyacetic acid with methanol saturated with dry HCl (see part (ii)). A white solid crystallized from the residue and was collected and recrystallized from methanol-water (9:1 by volume), m.p. 58.7 - 59.3°. The i.r. spectrum (nujol mull) of this material was similar to the i.r. spectrum of pure diphenyl disulfide in all respects.

(v) Phenylsulfoxyacetic acid (5.0 g.; 0.027 mole) was dissolved in ethyl ether and diazomethane (ca. 3 g.; 0.07 mole), prepared from "Diazald", was added slowly. After the

evolution of nitrogen, the solvent was evaporated slowly. A g.l.c. analysis of the residue showed that the product represented by the peak at retention time 10.0 minutes was ca. 60% of the residue. The residue was distilled under reduced pressure and a g.l.c. analysis showed that the product (retention time 10.0 minutes) was about 5 - 10% of the first fraction (b.p. 125 - 135°), 20% of the second fraction (b.p. 135 - 145°), 40 - 50% of the third fraction (b.p. 145 - 155°) and 60% of the fourth fraction (b.p. 155 - 160°).

This preparation of methyl phenylsulfoxyacetate was repeated, and the residue was taken up in hot petroleum ether (b.p. 40 - 60°). On cooling, white prisms crystallized from the solution, m.p. 51.5 - 52.2°. The prisms were successively recrystallized from n-butyl ether and mixtures of benzene-petroleum ether (b.p. 40 - 60°) and chloroform-petroleum ether (Found: C,54.52; H,5.06; O,24.13; S,16.29. $C_9H_{10}O_3S$ requires C,54.54; H,5.10; O,24.22; S,16.15%). An i.r. spectrum (liquid film) showed strong absorptions for the carbonyl stretching frequency at 1735 cm^{-1}, the C-O stretching frequency of the ester at 1265 cm^{-1}, and the SO stretching frequency at 1045 cm^{-1}. An n.m.r. spectrum (CCl_4) had three chemical shifts, a multiplet at 2.2 - 2.6τ (phenyl ring), a shift at 6.3τ which appeared as a singlet (CH_2), and a singlet at 6.4τ (CH_3). The intensities of these shifts were in the ratio of 5 : 2 : 3.

Methyl phenylsulfoxyacetate (1 g.) was dissolved in a minimum of ethyl ether and placed on a column of neutral alumina (75 g.). The column was eluted with petroleum ether (500 ml.; b.p. 40 - 60°), mixtures of benzene-petroleum ether (500 ml. of 1 : 9 by volume; 500 ml. of 1 : 3 by volume; 500 ml. of 1 : 1 by volume, 500 ml. of 3 : 1 by volume), and benzene (1000 ml.). The only material retrieved from the column was a white, crystalline solid, m.p. 87 - 88°. An i.r. spectrum ($CHCl_3$) showed strong absorptions at 1320 cm^{-1} and 1150 cm^{-1}, which corresponded to the SO_2 stretching frequencies of a sulfone (71). The stretching frequencies of the carbonyl group and the C-O of the ester were absent. An n.m.r. spectrum ($CDCl_3$) had two chemical shifts, a multiplet at 1.9 - 2.5τ (phenyl ring), and a singlet at 7.0τ (CH_3 adjacent to SO_2). The intensities of the shifts were in the ratio of 5 to 3. The compound was identified as phenyl methyl sulfone (lit. m.p. 87 - 88° (75)) (Found: C,53.97: H,5.25; O,20.66; S,20.71. $C_7H_8O_2S$ requires C,53.82; H,5.16; O,20.48; S,20.53%).

Phenylsulfonylacetamide.- 30% hydrogen peroxide (9 g.; 0.64 mole) was added dropwise to a solution of phenylthioacetamide (5 g.; 0.03 mole) in acetone (20 ml). After 4 days, the solvent and excess hydrogen peroxide were removed by distillation under reduced pressure, and recrystallization of the residue from methanol gave pure phenylsulfonylacetamide

(4.2 g.; 70% yield), m.p. 156 - 156.5° (Found: C,48.29; H,4.67; O,24.08; N,7.02; S,16.16. $C_8H_9O_3NS$ requires C,48.24; H,4.56; O,24.10; N,7.03; S,16.07%). An n.m.r. spectrum (d_6-dimethyl sulfoxide) showed a broad multiplet at 2.3 - 3.0τ (phenyl ring and NH_2), and a singlet at 6.4τ (CH_2). An i.r. spectrum (nujol mull) showed strong absorptions at 1300 cm^{-1} and 1170 cm^{-1} for the SO_2 stretching frequencies, 1658 cm^{-1} with a shoulder at 1685 cm^{-1} for the carbonyl stretching frequency, and 3200 cm^{-1} with shoulders at 3420, 3310 and 3260 cm^{-1} for the NH_2 stretching frequencies (76).

Phenylsulfoxyacetamide.- (i) Phenylthioacetamide (5 g.; 0.03 mole) dissolved in acetone (20 ml.) was oxidized by 30% hydrogen peroxide (4 g.; ca. 0.029 mole). After 4 days, the acetone and excess hydrogen peroxide were removed by distillation under reduced pressure, and recrystallization of the residue from methanol gave pure phenylsulfoxyacetamide (3.0 g.; 58% yield), m.p. 138 - 139°. An n.m.r. spectrum (d_6-dimethyl sulfoxide) had a multiplet at 2.2 - 2.6τ(phenyl ring), a broad singlet at 2.7τ (NH_2), and a singlet at 6.3τ (CH_2). An i.r. spectrum (nujol mull) showed the SO frequency absorbed at 1033 cm^{-1} (s.), the carbonyl stretching frequency absorbed at 1665 cm^{-1} (s.), and 3385 cm^{-1} (m.) and 3180cm^{-1} (m.) were the NH_2 stretching frequency absorptions (76).

(ii) Methyl phenylsulfoxyacetate (2 g.; 0.01 mole) was dissolved in methanol (10 ml.) at -40°. Liquid ammonia

(25 ml.) was added to the solution and it was allowed to come to room temperature. After 3 hours the solvent was removed by distillation under reduced pressure, and recrystallization of the residue from methanol gave pure phenylsulfoxyacetamide (1.8 g.; 92% yield), m.p. 138 - 139° (Found: C,52.29; H,5.01; O,17.65; N,7.41; S,17.64. $C_8H_9O_2NS$ requires C,52.43; H,4.96; O,17.46; N,7.65; S,17.56%). The n.m.r. spectrum (d_6-dimethyl sulfoxide) and the i.r. spectrum (nujol mull) of this material were similar in all respects to those of the phenylsulfoxy-acetamide prepared in (i).

Diethyl-2,4-dinitrophenylthiomalonate.- (i) Super dry (77) absolute ethanol (50 ml.) was reacted with sodium (2.3 g.; 0.10 mole) under anhydrous conditions. After the evolution of hydrogen, diethyl malonate (18.8 g.; 0.12 mole) was added and the solution was refluxed for 0.5 hour. 2,4-Dinitrophenylsulfenyl chloride (19 g.; 0.081 mole) was added to the solution and the mixture was refluxed overnight. After the removal of the solid material by filtration, yellow plates crystallized from the mother liquor. Recrystallization from ethanol gave pure ethyl-2,4-dinitrophenylsulfenate (7.5 g.; 38% yield), m.p. 125.5 - 126.5° (lit. m.p. 124 - 125° (78)). An n.m.r. spectrum ($CDCl_3$) had a doublet at 0.9τ (J_{H_3/H_5} = 2 c.p.s.) for the proton at the 3-position, a quartet at 1.5τ (J_{H_5/H_3} = 2 c.p.s.; J_{H_5/H_6} = 10 c.p.s.) for the proton at the

5- position, and a doublet at 2.1τ (J_{H_6/H_5} = 10 c.p.s.) for the proton at the 6-position of the phenyl ring. The methylene protons of the ethyl group appeared as a quartet at 6.0τ (J_{CH_2/CH_3} = 7 c.p.s.) and the methyl protons of the same group were assigned to the triplet at 8.55τ (J_{CH_3/CH_2} = 7 c.p.s.).

(ii) The reaction was repeated but the sodium ethoxide was thoroughly dried of absolute ethanol which remained after the reaction with sodium by distillation under reduced pressure. Anhydrous toluene (200 ml.) was used as a solvent and the procedure was continued as in (i). After the removal of the solid material by filtration, the toluene was removed by distillation under reduced pressure. The reddish-brown residue could not be crystallized and no attempt to distill it was made. An n.m.r. spectrum ($CDCl_3$) and an i.r. spectrum ($CHCl_3$) of the residue both indicated that ethyl-2,4-dinitrophenylthiomalonate could be present. A similar examination of the solid material removed by filtration, m.p. above 300°, showed that ethyl-2,4-dinitrophenylthiomalonate was not present.

<u>α-d-Phenylsulfoxyacetic acid.</u>- (i) Diethyl oxalate (85 g.; 0.58 mole) in anhydrous ethyl ether (100 ml.) was slowly added to sodium ethoxide (prepared from sodium (11.5 g.; 0.5 mole) and excess absolute ethanol) suspended in anhydrous ethyl ether (100 ml.). The mixture was refluxed until the solution became clear, <u>ca</u>.20 minutes. Ethyl phenylthioglycollate

(85 g.; 0.434 mole) in anhydrous ethyl ether (150 ml.) was slowly added to the solution and the yellow mixture was refluxed for 2 hours (79). The ethereal solution was poured onto ice (400g.), and the red aqueous layer was separated from the yellow ethereal layer. The non-aqueous layer was washed with 3 portions of water (50 ml.), and acidified with conc. HCl (45 ml.) under fresh ethyl ether (100 ml.). The acidic aqueous layer was separated and washed with 3 portions of ethyl ether and the combined ethereal solutions were dried over anhydrous magnesium sulfate. The ethyl ether was removed from the crude diethyl-2-oxalophenylthioglycollate by distillation under reduced pressure. The crude diethyl-2-oxalophenylthioglycollate was heated to 170° at 50 mm. of Hg for 1 hour. The residue was fractionally distilled under reduced pressure and the starting materials were removed below 92° and 23 mm. of Hg. Diethyl phenylthiomalonate (103 g.; 89% yield) was collected as a yellow liquid, b.p. 203 - 205° at 23 mm. of Hg (lit. b.p. 203 - 205° at 23 mm. of Hg (79)). An n.m.r. spectrum (CCl_4) had a multiplet at 2.4 - 2.9τ (phenyl ring), a singlet at 5.6τ (CH), a quartet at 5.9 (CH_2; J_{CH_2/CH_3} = 7 c.p.s.), and a triplet at 8.8τ (CH_3; J_{CH_3/CH_2} = 7 c.p.s.). The ratio of the intensities of the respective shifts was 5 : 1 : 2 : 3.

Diethyl phenylthiomalonate (48.8g.; 0.175 mole) was added to KOH (22.4 g.; 0.400 mole) dissolved in absolute ethanol (300 ml.) at 30°. After 2 hours, the dipotassium

phenylthiomalonate, which precipitated from the mother liquor as a yellow crystalline solid (48.4 g.; 96% yield), was collected, washed thoroughly with ethyl ether, and dried in a vacuum desiccator over anhydrous calcium chloride.

Dipotassium phenylthiomalonate (26.0 g.; 0.09 mole) was suspended in anhydrous ethyl ether and DCl (0.5 mole prepared from thionyl chloride (30 g.; 0.25 mole) and deuterium oxide (100 ml.)) was added slowly. The ethereal layer was separated immediately and dried over anhydrous magnesium sulfate. The ethyl ether was removed by distillation under reduced pressure, and the residue was refluxed at 135° and ca. 2 mm. of Hg for 0.5 hour. The residue was then taken up in hot cyclohexane-benzene (9 : 1 by volume), and, on cooling, α,α-d_2-phenylthioglycollic acid and α-d-phenylthioglycollic acid (7.4 g.; 49% yield) crystallized as white prisms, m.p. 62 - 63°. The mixture (1.2 g.) was sublimed at 62° and ca. 0.05 mm. of Hg. Assuming phenylthioglycollic acid was absent, an n.m.r. spectrum ($CDCl_3$) indicated from the intensities of the chemical shifts that the mixture was 62% α-d-phenylthioglycollic acid and 38% α,α-d_2-phenylthioglycollic acid. An i.r. spectrum (CCl_4) of this material was similar in all respects to the i.r. spectrum of pure phenylthioglycollic acid with the exception of a broad band ca. 2200 cm^{-1}, the CD stretching frequency (80).

The mixture of α-d-phenylthioglycollic acid and α,α-d_2-phenylthioglycollic acid (6.4 g.; ca. 0.038 mole) was dissolved in anhydrous acetone (100 ml.) at 5°, and 30% hydrogen peroxide (5 g.; 0.044 mole) was added slowly to the solution. After 2 days the solvent and excess hydrogen peroxide were removed by distillation under reduced pressure, and the residue was recrystallized from anhydrous benzene-ethyl acetate (3 : 1 by volume), m.p. 115 - 115.5°. N.m.r. spectra (d_4-acetic acid; d_6-dimethyl sulfoxide) showed that after oxidation the mixture contained ca. 40% phenylsulfoxyacetic acid.

(ii) Diethyl malonate (22.5 g.; 0.14 mole) was slowly added to sodium ethoxide (prepared from sodium (3.2 g.; 0.14 mole) and absolute ethanol (100 ml.)) suspended in anhydrous toluene (100 ml.), and the mixture was refluxed for 1 hour. Phenylsulfenyl chloride (20.0 g.; 0.138 mole) dissolved in anhydrous toluene (100 ml.) was added dropwise to the mixture and the suspension was refluxed overnight. The mixture was filtered and a white, crystalline solid separated from the cold, concentrated filtrate, m.p. 59 - 60°. This material was identified as diphenyl disulfide from n.m.r. ($CDCl_3$) and i.r. ($CHCl_3$) spectra, and appeared to be the major product of the reaction.

(iii) Ferrous sulfate (0.001 mole) and platinum oxide (0.5 g.) were added to a solution of glyoxylic acid monohydrate

(5 g.; 0.0543 mole) and deuterium oxide (100 ml.). The mixture was stirred under 1 atm. of deuterium for 40 hours at room temperature, and ca. 0.028 mole of deuterium was consumed in the reduction. After filtration, the deuterium oxide was removed by freeze-drying.

Thionyl chloride (18.3 g.; 0.154 mole) dissolved in anhydrous pyridine (12.3 g.; 0.154 mole) at 0^{o} was added to the dry residue. After the evolution of sulfur dioxide and the formation of pyridinium chloride, the mixture was warmed slightly to remove the excess thionyl chloride. On heating, the reaction mixture polymerized and formed a brown tar.

Chloroacetic acid (5.67 g.; 0.06 mole) and phenyl-thiocyanate (6.25 g.; 0.05 mole) were dissolved in absolute methanol (50 ml.) at -50^{o}. KOH (10.46g.; 0.535 mole) dissolved in methanol-water (1 : 1 by volume) was added slowly to the solution. The reaction mixture was allowed to come to room temperature with constant stirring. After 3 hours, the solid material was removed by filtration from the cold, concentrated mother liquor, washed thoroughly with ethyl ether, and acidified with HCl (6N). The aqueous solution was extracted with 3 portions of ethyl ether (150 ml. total), and the combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and the residue was dissolved in hot cyclohexane-benzene (9 : 1 by volume).

On cooling, phenylthioglycollic acid (2.5 g.; 36% yield) crystallized as white prisms from the solution, m.p. 61 - 62°, and when mixed with pure phenylthioglycollic acid showed no depression in the melting point. N.m.r. spectra ($CDCl_3$; CCl_4) and an i.r. spectrum (CCl_4) confirmed the structure and purity of the phenylthioglycollic acid. (81)

The phenylthioglycollic acid was oxidized with 30% hydrogen peroxide (1.7 g; 0.01 mole) in acetone (10 ml.) to phenylsulfoxyacetic acid (74% yield), m.p. 114 - 115°.

Methyl α-d-phenylsulfoxyacetate.- (i) Methyl phenylsulfoxyacetate (8.0 g.; 0.0404 mole) dissolved in anhydrous ethyl ether (200 ml.) was added dropwise to sodium hydride (1.70 g. of 58.5% mixture with mineral oil; 0.0413 mole) suspended in anhydrous ethyl ether (100 ml.), and the mixture was stirred overnight at room temperature. Deuterium oxide (50 ml.) was added slowly to the solution, and after the dissolution of the solid material, the ethereal layer was separated and dried. After the removal of ethyl ether, the product could not be isolated from the residue.

(ii) Methyl phenylsulfoxyacetate (9.9 g.; 0.05 mole) dissolved in anhydrous ethyl ether (100 ml.) was added to a refluxing mixture of sodium methoxide (0.0574 mole prepared from sodium (1.32 g.; 0.0574 mole) and absolute methanol (50 ml.)) suspended in anhydrous ethyl ether (100 ml.). After 2 hours the

yellow salt which precipitated out of the mother liquor was washed with 4 portions of anhydrous ethylether (200 ml. total) to remove the unreacted ester. DCl in deuterium oxide (100 ml.) was added to the solid until the pH of the solution was ca. 7.0 and then the solution was extracted with anhydrous ethyl ether. The ethyl ether extract was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was taken up in hot petroleum ether (b.p. 40 - 60°), and white prisms of methyl α,α-d_2-phenylsulfoxyacetate crystallized from the cold solution, m.p. 51 - 52°. An n.m.r. spectrum ($CDCl_3$) had a multiplet at 2.2 - 2.5τ (phenyl ring) and a singlet at 6.3τ (CH_3), but the presence of the methylene protons could not be detected.

Phenylselenoglycollic acid.- Powdered selenium metal (20 g.; 0.253 mole) was slowly added to phenylmagnesium bromide (prepared from bromobenzene (39 g.; 0.248 mole) and magnesium (6 g.; 0.246 mole)) dissolved in ethyl ether (200 ml.). When the reaction was complete, the mixture was poured onto ice (200 g.) and acidified with HCl (2N). After the evolution of hydrogen selenide and the precipitation of red selenium, the ethereal layer was separated and extracted with an aqueous NaOH solution (7 g. / 60 ml. of water). To the hot aqueous extract, a solution of sodium chloroacetate (prepared from chloroacetic acid (11.8 g.; 0.125 mole) and sodium carbonate (6.7 g.; 0.063 mole)) in water-ethanol (1 : 2 by volume; 150 ml.) was slowly added. Sodium glycollate, which precipitated from the hot mother liquor, was removed by filtration, and the

filtrate was concentrated to half its original volume. Sodium phenylselenoglycollate crystallized as white plates from the cold solution and was recrystallized from ethanol-water (19 : 1 by volume). An aqueous solution of the salt was acidified with HCl (2N) and extracted with ethyl ether. The extract was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. Recrystallization of the residue from petroleum ether (b.p. 40 - 60°) gave white needles of phenylselenoglycollic acid (3.2 g.; 12% yield), m.p. 39-40° (lit. m.p. 40°) (82). An n.m.r. spectrum (d_4-acetic acid) had a multiplet at 2.3 - 2.8τ (phenyl ring) and a singlet at 6.5τ (CH_2) (82).

Phenylselenoxyacetic acid.- (i) Phenylselenoacetic acid (2.15 g.; 0.01 mole) was oxidized at room temperature with 30% hydrogen peroxide (1.13 g.; 0.01 mole) in glacial acetic acid (50 ml.) The reaction mixture was poured onto ice (200 g.) and the subsequent aqueous layer was extracted with ethyl ether. The non-aqueous extract was dried and the solvent was removed by distillation under reduced pressure. The residue was taken up in hot ethanol-water (9 : 1 by volume) and yellow diphenyl diselenide crystallized from the cold solution, m.p. 60 - 61° (lit. m.p. 62° (83)).

(ii) Phenylselenoacetic acid (2.15 g.; 0.01 mole) was oxidized with potassium permanganate (1.58 g.; 0.01 mole)

in acetone. The resulting precipitate of manganese dioxide and potassium phenylselenoxyacetate was filtered from the mother liquor and leached with hot water. The aqueous filtrate was acidified with dilute H_2SO_4 (2N), and the resulting yellow oil solidified on cooling. Recrystallization of the yellow solid from ethanol-water (9:1 by volume) yielded yellow needles of diphenyl diselenide, m.p. 59.5 - 60.2° (Found: C,45.98; H,3.24; $C_{12}H_{10}Se_2$ requires C,46.17; H,3.24%). A multiplet at 2.3 - 2.8τ (phenyl ring) was the only chemical shift in the n.m.r. spectrum (d_4-acetic acid).

Potassium phenylselenoxyacetate.- Phenylselenoacetic acid (4.3 g.; 0.020 mole) was neutralized with potassium bicarbonate (1.85 g.; 0.019 mole) in ethanol-water (19 : 1 by volume). Potassium phenylselenoacetate crystallized from the cold solution and was recrystallized from ethanol-water (19 : 1 by volume).

Potassium phenylselenoacetate (3 g.; 0.012 mole) was oxidized by potassium permanganate (1.9 g.; 0.012 mole) in neutral aqueous media. The manganese dioxide which precipitated from the mother liquor was removed by filtration through "Celite", and the clear aqueous filtrate was distilled to dryness under reduced pressure. The solid residue was taken up in hot ethanol - water (19 : 1 by volume) and potassium phenylselenoxyacetate crystallized from the cold solution. An n.m.r. spectrum (D_2O) had a multiplet at 2.1 - 2.5τ (phenyl ring), a

quartet at 5.9τ and 6.1τ (nonequivalent protons of the methylene group; J_{AB} = c.p.s.).

Proton - deuteron exchange at the methylene position of chloroacetic acid.- N.m.r. spectra of chloroacetic acid (20 ± 2% by weight) dissolved in deuterium oxide (99.75% pure) at 25° were recorded at various intervals during a 48 hour period. Chloroacetic acid (20 ± 2% by weight) and triethylamine (5 ml.) dissolved in deuterium oxide at 25° were examined in the same manner. The temperature of both samples was raised to 55° and n.m.r. spectra were recorded during an additional 48 hour period. The intensity of the shift at 5.9τ (CH_2 of chloroacetic acid) did not diminish throughout the experiment, indicating that proton-deuteron exchange did not occur (84).

Proton - deuteron exchange at the cyclic and exocyclic methylene positions of methyleneaminoacetonitrile (trimer).- Methyleneaminoacetonitrile (5 g.) was dissolved in deuterium oxide (10 ml.) at 25°. After 35 hours the deuterium oxide was removed by distillation under reduced pressure and the residue was recrystallized from ethanol-water (19 : 1 by weight). N.m.r. measurements (d_6-acetone) indicated proton-deuteron exchange had occurred at the exocyclic methylene positions.

Partially exchanged methyleneaminoacetonitrile (1 g.)

was dissolved in a solution of triethylamine (5 ml.) and deuterium oxide (25 ml.) at 25°. The solution was treated in the same manner as the latter one and an n.m.r. spectrum (d_6-acetone) indicated complete proton-deuteron exchange at the exocyclic methylene positions while no exchange occurred at the cyclic methylene positions.

N.m.r. spectra of phenylsulfoxyacetic acid and related compounds.- N.m.r. spectra of phenylsulfoxyacetic acid, methyl phenylsulfoxyacetate, phenylsulfoxyacetamide, sodium phenylsulfoxyacetate and potassium phenylselenoxyacetate dissolved in various solvents were recorded, and the resulting data are given in Tables V - VIII.

N.m.r. spectra of sodium phenylsulfoxyacetate (30 ± 1 % by weight) dissolved in deuterium oxide were recorded at intervals over a temperature range of -10° to 90°,and the resulting data are given in Table IX.

N.m.r. spectra of phenylsulfoxyacetic acid (25 ± 1% by weight) dissolved in mixtures of trifluoroacetic acid and d_6-dimethyl sulfoxide, which varied over a wide range of concentrations, were recorded and the pertinent data are tabulated in Table X.

N.m.r. spectra of methyl phenylsulfoxyacetate (30 ± 2% by weight) dissolved in d_4-acetic acid were recorded at 43°, 60°,

80° and 100°, and the resulting data are given in Table XI. N.m.r. spectra of solutions of methyl phenylsulfoxyacetate and pivalic acid, which varied over a wide range of concentrations, were recorded at 55°, 65°, 75°, 85°, and 95° and the resulting data are tabulated in Tables XII - XVI.

Proton-deuteron exchange at the methylene position of phenylsulfoxyacetic acid.- α,α-d_2-Phenylsulfoxyacetic acid (5 g.) was dissolved in pure water (100 ml.) at 25°, and aliquots (10 ml.) of this solution were taken at various intervals. The partially exchanged acid was isolated by freeze-drying the aliquots. N.m.r. spectra (moist trifluoroacetic acid/benzene; d_6-dimethyl sulfoxide) of the recovered material were recorded, and the resulting data are given in Table XVII.

Phenylsulfoxyacetic acid (4.32 g.) was dissolved in deuterium oxide (48.0 ml.) at 40.0°. Aliquots (3 ml.) of this solution were taken at 1 hour intervals, and the partially exchanged acid was isolated by freeze-drying the aliquots. N.m.r. spectra (d_6-dimethyl sulfoxide) of the recovered acid were recorded, and the pertinent data are tabulated in Table XVIII.

TABLE V

THE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF PHENYLSULFOXYACETIC ACID DISSOLVED IN VARIOUS SOLVENTS

Solvent	Chemical Shifts (τ)				J_{AB} (c.p.s.)
	C_6H_5	CH_2 (A)	CH_2 (B)	CH_2 *	
CF_3COOH	2.02-2.44	5.67	5.88	-	15.1
CF_3COOH/C_6H_6	-	6.36	6.51	-	15.0
CD_3COOD	2.09-2.51	5.88	6.02	-	14.9
CD_3COCD_3	2.09-2.49	-	-	6.09	-
D_2O **	2.42-2.50	-	-	6.16	-
CD_3SOCD_3	2.15-2.52	5.99	6.10	-	14.5

* The methylene protons appear as an unresolved quartet, i.e. a singlet.

** The chemical shifts of all solutes in D_2O are not directly related to the τ-scale.

The asterisk and double-asterisk retain these meanings throughout the following tables.

TABLE VI

THE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF METHYL PHENYLSULFOXYACETATE DISSOLVED IN VARIOUS SOLVENTS

Solvent	Chemical Shifts (τ)					J_{AB} (c.p.s.)
	C_6H_5	CH_2 (A)	CH_2 (B)	CH_2 *	CH_3	
CF_3COOH	2.03-2.46	5.68	5.80	5.74	6.13	15.0
$CF_3COOH/C_6H_5NO_2$	-	5.77	5.91	5.84	6.27	14.6
$(CH_3)_3CCOOH$	2.17-2.65	6.08	6.18	6.13	6.44	14.0
CD_3COOD	2.12-2.50	5.89	6.08	5.99	6.33	14.0
$CDCl_3$	2.19-2.59	6.17	6.13	6.24	6.32	13.6
CH_2Cl_2	2.25-2.58	-	-	6.29	6.34	14.2
$C_6H_5NO_2$	-	-	-	6.13	6.34	-
C_6H_6	-	-	-	6.47	6.70	14.2
CCl_4	2.54-2.82	-	-	6.47	6.38	11.0
CD_3SOCD_3	2.12-2.50	5.90	6.08	5.99	6.36	14.0
Neat (135°)	2.20-2.61	-	-	6.15	6.41	-

TABLE VII

THE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF PHENYLSULFOXYACETAMIDE DISSOLVED IN VARIOUS SOLVENTS

Solvent	Chemical Shifts (τ)			J_{AB} (c.p.s.)
	C_6H_5	CH_2 *	NH_2	
CF_3COOH	2.05-2.43	5.80	2.50-2.65	14.1
CF_3COOH/C_6H_6	-	6.88	-	14.0
CD_3COOD	2.13-2.53	6.03	2.13-2.53	-
CD_3SOCD_3	2.14-2.52	6.24	2.68-2.72	13.8

TABLE VIII

THE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF SODIUM PHENYLSULFOXYACETATE AND POTASSIUM PHENYLSELENOXYACETATE DISSOLVED IN DEUTERIUM OXIDE

Compound	Chemical shifts (τ)			J_{AB} (c.p.s.)
	C_6H_5	CH_2 (A)	CH_2 (B)	
$C_6H_5SOCH_2COONa$	2.24 - 2.53	6.05	6.26	14.0
$C_6H_5SeOCH_2COOK$	2.09 - 2.49	5.88	6.14	14.0

TABLE IX

THE VARIATION OF THE CHEMICAL SHIFTS FOR THE METHYLENE PROTONS OF SODIUM PHENYLSULFOXYACETATE (30 ± 1% BY WEIGHT IN DEUTERIUM OXIDE) WITH TEMPERATURE

Temperature °C	$\lvert\delta H_A - \delta H_B\rvert$, c.p.s.
90	8.3
80	8.2
70	8.5
60	9.1
50	9.5
40	9.7
30	9.9
20	10.3
10	10.7
0	10.8
- 10	11.2

TABLE X

THE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF THE METHYLENE PROTONS OF PHENYLSULFOXYACETIC ACID (25 ± 1% by weight) DISSOLVED IN MIXTURES OF TRIFLUOROACETIC ACID AND d_6-DIMETHYL SULFOXIDE

Solvent Composition		Type of	Chemical Shifts (τ)			
% CD_3SOCD_3	% CF_3COOH	Chemical Shift	CH_2(A)	CH_2(B)	CH_2*	J_{AB} (c.p.s.)
100	0	quartet	5.96	6.14	-	14.2
90	10	quartet	5.99	6.14	-	14.2
80	20	quartet	6.02	6.13	-	14.2
70	30	singlet	-	-	6.11	14.2
60	40	singlet	-	-	6.11	-
50	50	quartet	6.00	6.11	-	14.1
40	60	quartet	5.92	6.04	-	14.1
30	70	quartet	5.88	5.99	-	14.0
20	80	quartet	5.68	5.88	-	15.2
10	90	quartet	5.67	5.88	-	15.1
0	100	quartet	5.67	5.88	-	15.1

TABLE XI

THE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF THE METHYLENE PROTONS OF METHYL PHENYLSULFOXYACETATE (30 ± 2% by weight) DISSOLVED IN d_4-ACETIC ACID

Temperature (° C)	Chemical Shifts (τ)					J_{AB} (c.p.s.)
	C_6H_5	CH_2(A)	CH_2(B)	CH_2*	CH_3	
43	2.13 - 2.50	5.90	6.08	5.99	6.33	14.2
60	2.13 - 2.52	5.92	6.05	5.99	6.33	14.0
80	2.12 - 2.52	5.93	6.05	5.99	6.33	14.0
100	2.11 - 2.53	5.93	6.07	6.00	6.32	14.0

TABLE XII

THE CHEMICAL SHIFTS, COUPLING CONSTANTS, AND DIFFERENCES BETWEEN THE CHEMICAL SHIFTS OF THE METHYLENE PROTONS OF METHYL PHENYLSULFOXYACETATE DISSOLVED IN PIVALIC ACID AT 55°

$(CH_3)_3$ CCOOH moles x 10^{-4}, (X)	$C_6H_5SOCH_2COOCH_3$ moles x 10^{-4}, (Y)	Mole Ratio X/Y	Chemical Shifts (τ)			$\lvert CH_2(A)-CH_2(B)\rvert$ (c.p.s.)	J_{AB} (c.p.s.)
			$CH_2(A)$	$CH_2(B)$	CH_2*		
45.06	2.52	17.9	5.95	6.20	-	15.0	14.0
39.16	5.04	7.8	5.99	6.18	-	11.3	13.9
34.27	7.57	4.5	6.00	6.16	-	9.5	13.5
29.37	10.09	2.9	5.99	6.12	-	7.7	13.7
24.48	12.60	1.9	6.08	6.17	-	5.4	14.0
19.58	15.13	1.3	-	-	6.10	-	14.0
14.69	17.65	0.83	-	-	6.07	-	14.0
9.79	20.18	0.49	-	-	6.05	-	14.0
4.90	22.70	0.22	-	-	6.06	-	14.0

TABLE XIII

THE CHEMICAL SHIFTS, COUPLING CONSTANTS, AND DIFFERENCES BETWEEN THE CHEMICAL SHIFTS OF THE METHYLENE PROTONS OF METHYL PHENYLSULFOXYACETATE DISSOLVED IN PIVALIC ACID AT 65°

$(CH_3)_3$ CCOOH moles x 10^{-4}, (X)	$C_6H_5SOCH_2COOCH_3$ moles x 10^{-4}, (Y)	Mole Ratio X/Y	Chemical Shifts (τ)			$\lvert CH_2(A)-CH_2(B)\rvert$ (c.p.s.)	J_{AB} (c.p.s.)
			$CH_2(A)$	$CH_2(B)$	CH_2*		
45.06	2.52	17.9	5.96	6.21	-	15.1	13.9
39.16	5.04	7.8	5.94	6.13	-	11.4	14.2
34.27	7.57	4.5	6.00	6.16	-	9.4	14.0
29.37	10.09	2.9	6.05	6.18	-	7.8	14.0
24.48	12.60	1.9	-	-	6.09	-	14.2
19.58	15.13	1.3	-	-	6.10	-	14.1
14.69	17.65	0.83	-	-	6.09	-	14.0
9.79	20.18	0.49	-	-	6.09	-	14.0
4.90	22.70	0.22	-	-	6.09	-	14.1

TABLE XIV

THE CHEMICAL SHIFTS, COUPLING CONSTANTS, AND DIFFERENCES BETWEEN THE CHEMICAL SHIFTS OF THE METHYLENE PROTONS OF METHYL PHENYLSULFOXYACETATE DISSOLVED IN PIVALIC ACID AT 75°

$(CH_3)_3$ CCOOH moles x 10^{-4}, (X)	$C_6H_5SOCH_2COOCH_3$ moles x 10^{-4}, (Y)	Mole Ratio X/Y	Chemical Shifts (τ)			$\lvert CH_2(A)-CH_2(B)\rvert$ (c.p.s.)	J_{AB} (c.p.s.)
			$CH_2(A)$	$CH_2(B)$	CH_2*		
45.06	2.52	17.9	5.97	6.22	-	14.6	14.0
39.16	5.04	7.8	6.00	6.19	-	11.3	14.0
34.27	7.57	4.5	6.00	6.16	-	9.7	14.0
29.37	10.09	2.9	6.03	6.16	-	7.8	14.0
24.48	12.60	1.9	-	-	6.10	-	14.0
19.58	15.13	1.3	-	-	6.09	-	14.0
14.69	17.65	0.83	-	-	6.09	-	-
9.79	20.18	0.49	-	-	6.10	-	-
4.90	22.70	0.22	-	-	6.09	-	-

TABLE XV

THE CHEMICAL SHIFTS, COUPLING CONSTANTS, AND DIFFERENCES BETWEEN THE CHEMICAL SHIFTS OF THE METHYLENE PROTONS OF METHYL PHENYLSULFOXYACETATE DISSOLVED IN PIVALIC ACID AT 85°

$(CH_3)_3$ CCOOH moles x 10^{-4}, (X)	$C_6H_5SOCH_2COOCH_3$ moles x 10^{-4}, (Y)	Mole Ratio X/Y	Chemical Shifts (τ)			$\lvert CH_2(A)-CH_2(B)\rvert$ (c.p.s.)	J_{AB} (c.p.s.)
			$CH_2(A)$	$CH_2(B)$	CH_2*		
45.06	2.52	17.9	6.00	6.23	-	13.9	14.0
39.16	5.04	7.8	5.99	6.18	-	11.2	14.0
34.27	7.57	4.5	6.03	6.19	-	9.7	13.9
29.37	10.09	2.9	6.06	6.20	-	8.2	13.8
24.48	12.60	1.9	-	-	6.09	-	13.9
19.58	15.13	1.3	-	-	6.09	-	14.0
14.69	17.65	0.83	-	-	6.09	-	-
9.79	20.18	0.49	-	-	6.09	-	-
4.90	22.70	0.22	-	-	6.09	-	-

TABLE XVI

THE CHEMICAL SHIFTS, COUPLING CONSTANTS, AND DIFFERENCES BETWEEN THE CHEMICAL SHIFTS OF THE METHYLENE PROTONS OF METHYL PHENYLSULFOXYACETATE DISSOLVED IN PIVALIC ACID AT 95°

$(CH_3)_3$ CCOOH moles x 10^{-4}, (X)	$C_6H_5SOCH_2COOCH_3$ moles x 10^{-4}, (Y)	Mole Ratio X/Y	Chemical Shifts (τ)			$\lvert CH_2(A)-CH_2(B)\rvert$ (c.p.s.)	J_{AB} (c.p.s.)
			$CH_2(A)$	$CH_2(B)$	CH_2*		
45.06	2.52	17.9	6.00	6.23	-	13.9	14.0
39.16	5.04	7.8	6.02	6.21	-	11.9	14.0
34.27	7.57	4.5	6.04	6.20	-	9.8	14.0
29.37	10.09	2.9	6.05	6.18	-	7.7	13.9
24.48	12.60	1.9	6.09	6.18	-	5.6	13.5
19.58	15.13	1.3	-	-	6.11	-	13.5
14.69	17.65	0.83	-	-	6.11	-	13.9
9.79	20.18	0.49	-	-	6.10	-	-
4.90	22.70	0.22	-	-	6.09	-	-

TABLE XVII

THE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF THE METHYLENE PROTONS APPROPRIATE TO ISOTOPICALLY SUBSTITUTED PHENYLSULFOXYACETIC ACID

Acid	Solvent	Chemical Shifts (τ)			J_{AB} (c.p.s.)
		CH_2(A)		CH_2(B)	
$C_6H_5SOCH_2COOH$	moist CF_3COOH/C_6H_6	6.36	-	6.56	15.0
	CD_3SOCD_3	5.99	-	6.10	14.5
		CH(a)††			
†$C_6H_5SOCHDCOOH$(a)	moist CF_3COOH/C_6H_6	-	6.32	-	-
	CD_3SOCD_3	-	6.13	-	-
		CH(b)††			
†$C_6H_5SOCHDCOOH$(b)	moist CF_3COOH/C_6H_6	-	6.62	-	-
	CD_3SOCD_3	-	5.98	-	-

† The diastereoisomers of $C_6H_5SOCHDCOOH$ are arbitrarily designated as (a) and (b).

†† The relative positions of the n.m.r. chemical shifts of CH(a) and CH(b) invert in the two non-aqueous solvents used.

The cross and double cross retain these meanings throughout the remainder of the tables.

TABLE XVIII

THE RELATIVE INTENSITIES OF THE CHEMICAL SHIFTS OF PHENYLSULFOXYACETIC ACID ISOLATED FROM DEUTERIUM OXIDE

Time (Hours)	C_6H_5	CH_2	CH(a) ††	CH(b) ††
1.5	1000	285	13	55
2.0	1000	227	15	60
3.0	1000	226	21	69
4.0	1000	197	23	74
4.5	1000	173	24	68
5.5	1000	161	19	77
6.0	1000	159	21	77
6.5	1000	143	24	78
7.0	1000	138	23	80
7.5	1000	126	24	86
8.0	1000	132	25	82
8.5	1000	133	23	81
9.0	1000	126	24	80
9.5	1000	115	25	79
10.0	1000	116	26	83

DISCUSSION

Preparation of α,α-dideutero substituted acetic acids

Carboxylic acids of the type $X\text{-}CD_2COOH$ may be conveniently synthesized either from compounds already isotopically substituted at the appropriate position (c.f. Halevi, Nussim, Ron (48)), or by direct proton-deuteron exchange at the α-positions of the corresponding protium acids. The limitations of the latter technique deserve some general comment. Although a large inductive effect of the "X" substituent appears to be a prerequisite for proton-deuteron exchange at the methylene position, the ability of the "X" substituent to stabilize the incipient carbanion also seems important. The exchange process is probably pH dependent, and, although the methylene protons of some acids exchange readily at room temperature under acidic conditions, the rate of exchange presumably increases with pH*. Proton-deuteron exchanges at the α- positions of some substituted acetic acids are detailed in Table XIX.

Chloroacetic acid and α,α-d_2-chloroacetic acid

Since proton-deuteron exchange does not occur at the methylene position of chloroacetic acid in acidic or basic media, two syntheses of α,α-d_2-chloroacetic acid were considered. The first preparation involved the chlorination of deuterated

* Discussed in more detail below.

TABLE XIX

PROTON-DEUTERON EXCHANGE REACTIONS OF SOME SUBSTITUTED ACETIC ACIDS

Direct H→D Exchange Possible		Direct H→D Exchange Not Possible**	
Acid ($X-CH_2COOH$)	"X" Substituent	Acid ($X-CH_2COOH$)	"X" Substituent
* $CN-CH_2COOH$	$CN-$	$Cl-CH_2COOH$	$Cl-$
* $C_6H_5SO-CH_2COOH$	C_6H_5SO-	$C_6H_5S-CH_2COOH$	C_6H_5S-
* $C_6H_5SO_2-CH_2COOH$	$C_6H_5SO_2-$	$H-CH_2COOH$	$H-$
$C_6H_5-CH_2COOH$	C_6H_5-	$C_6H_5O-CH_2COOH$	C_6H_5O-
$4-MeO-C_6H_4-CH_2COOH$	$4-MeO-C_6H_4-$		
* $4-NO_2-C_6H_4-CH_2COOH$	$4-NO_2-C_6H_4-$		

* Basic media are unnecessary for H→D exchange in these acids.

** With or without base, e.g. triethylamine, these systems do not undergo exchange at the methylene position.

acetic acid, which may be prepared from malonic acid (85).

$$CH_2(COOH)_2 \xrightarrow[\text{dioxan}]{D_2O} CD_2(COOD)_2 \xrightarrow[\text{reflux}]{-CO_2} CD_3COOD$$

$$CD_3COOD \xrightarrow{H_2O} CD_3COOH \qquad \text{(13)}$$

$$CD_3COOH \xleftarrow[\text{red P/105-110}^o]{Cl_2} Cl\text{-}CD_2COOH + DCl$$

Before the preparation of α,α-d_2-chloroacetic acid was attempted acetic acid was chlorinated to investigate the reaction conditions and the isolation procedure necessary to obtain the optimum yield of pure chloroacetic acid. A 42% yield of chloroacetic acid was obtained after distillation of the reaction product, but this material was contaminated with dichloroacetic acid (ca. 7.5%). The physical separation of these acids was achieved through a series of purification procedures, namely distillation, recrystallization, sublimation, treatment with nitrogen, and fractional freezing. An alternative separation was also attempted by esterification of the acids and fractional distillation of the esters. Although both separation procedures were successful, the yield of pure chloroacetic acid in each case was appreciably reduced, thereby limiting the usefulness of this synthesis for the preparation of α,α-d_2-chloroacetic acid.

The second synthesis proposed for the preparation of $Cl\text{-}CD_2\text{-}COOH$ involved deuterating the exocyclic methylene groups

of methyleneaminoacetonitrile, which could be converted into α,α-d_2-chloroacetic acid, as shown in Figure V, The outlined reaction sequence was followed using nondeuterated materials.

The overall yield of pure chloroacetic acid in both reactions was not significantly different; however, the latter method avoids a troublesome purification procedure.

Phenylsulfoxyacetic acid

Phenylsulfoxyacetic acid was prepared by the oxidation of phenylthioglycollic acid with hydrogen peroxide in absolute ethanol. Although higher yields of product may be obtained by oxidation with hydrogen peroxide in glacial acetic acid or sodium metaperiodate in aqueous methanol (86, 87), the one-step isolation of phenylsulfoxyacetic acid from ethanol was more convenient. As phenylthioglycollic acid contains no asymmetric centers, oxidation forms a racemic mixture of the two enantiomers of phenylsulfoxyacetic acid.* Piechulek and Suszko (89) have resolved the enantiomers (m.p. 119-120°) using the cinchonidine and cinchonine salts of the acid.

The n.m.r. spectra of phenylsulfoxyacetic acid and some related compounds

A description of the stereochemistry of phenylsulfoxyacetic acid is necessary prior to the discussion of both the

* A seminar by G.P. Daumit (88) presents a concise discussion of the preparation of optically active sulfoxides, their absolute configuration and racemization.

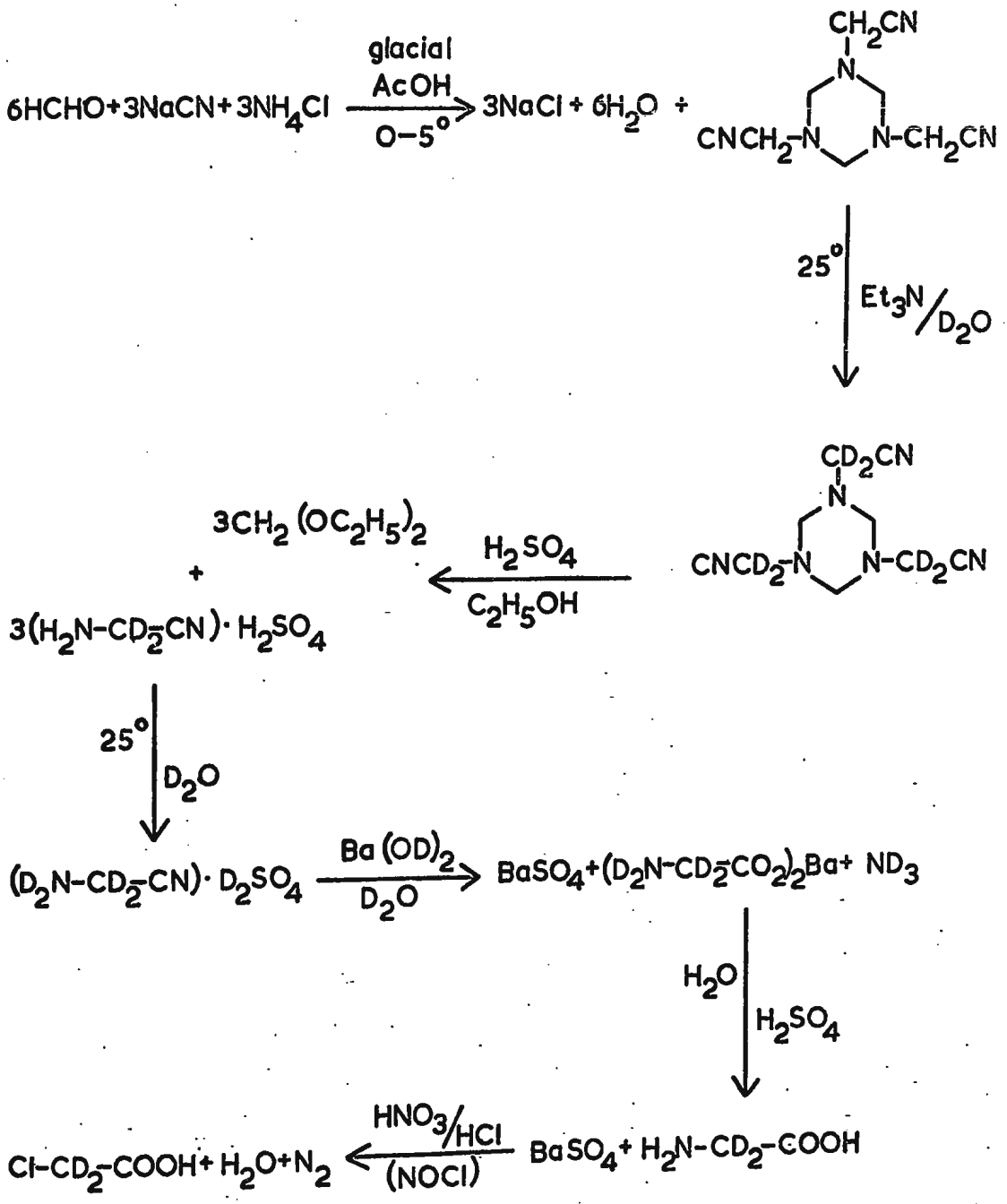


FIGURE V

THE SYNTHESIS OF α,α-d_2-CHLOROACETIC ACID FROM METHYLENEAMINOACETONITRILE

n.m.r. spectra and the H→D exchange of the acid described in this thesis. Several observations have also been made on some derivatives of the acid, and the following stereochemical discussion, which is confined only to the acid, will have some relevance to the derivatives also.

On the assumption that "staggered" conformations are more stable than "eclipsed" ones (90), the two enantiomers of phenylsulfoxyacetic acid give rise to six rotamers which exist as three pairs of mirror-image conformers (see Figure VI). Theoretically, the methylene protons of each of the conformers are nonequivalent, even under conditions of rapid rotation and equal population (91, 92). Hence, the expected n.m.r. spectrum for the methylene protons of the three conformers would be three AB quartets. However, observed n.m.r. spectra of phenylsulfoxyacetic acid in various solvents show only a single AB quartet for the methylene protons of the three conformers (see Table V), and may be classified according to the following possibilities (93):

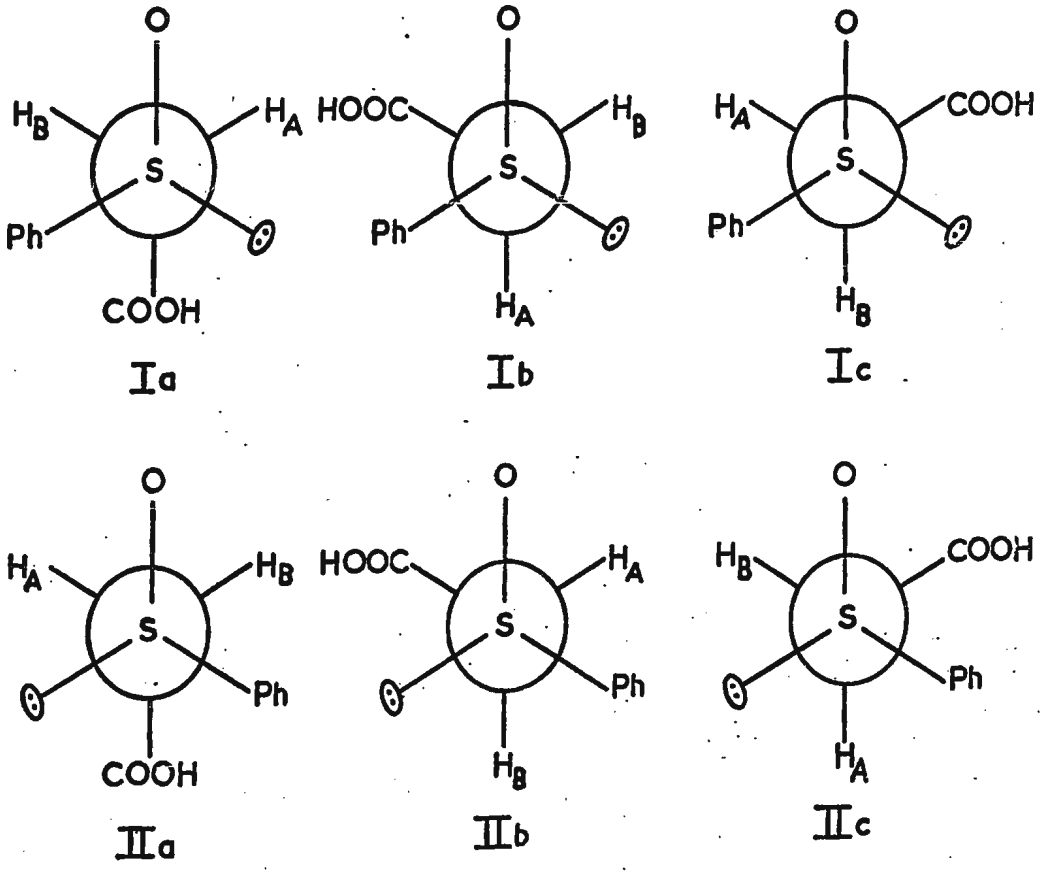
(i) The energy difference between the conformers of long lifetime may be so large that only the most stable is present.

(ii) There may be a mixture of conformers in equilibrium each sufficiently long-lived and abundant to give its own n.m.r. spectrum. The observed spectrum will then be a superposition of these components.

FIGURE VI

NEWMAN DIAGRAMS (VIEWED ALONG THE S-C BOND) OF THE THREE PAIRS OF MIRROR-IMAGE CONFORMERS FOR THE TWO PHENYLSULFOXYACETIC ACID ENANTIOMERS

Conformers Ia and IIa, Ib and IIc, Ic and IIb are mirror images. The methylene protons are arbitrarily designated as H_A and H_B.



(iii) Internal rotation may be occurring at a sufficiently rapid rate for the effective chemical shifts (screening) and spin coupling constants to be averaged.

Other intermediate cases could arise, e.g. interconversion could be rapid between two conformers while a third is stable for a longer period.

The effective nonequivalence of the methylene protons of phenylsulfoxyacetic acid in a solvent at a given temperature is a function of the relative populations of the conformers such that

$$\langle \delta H_A \text{ effective} \rangle = p_1 \delta H_{A_1} + p_2 \delta H_{A_2} + p_3 \delta H_{A_3} \qquad (14)$$

$$\langle \delta H_B \text{ effective} \rangle = p_1 \delta H_{B_1} + p_2 \delta H_{B_2} + p_3 \delta H_{B_3} \qquad (15)$$

$$\langle (\delta H_A - \delta H_B) \text{ effective} \rangle = p_1(\delta H_{A_1} - \delta H_{B_1}) + p_2(\delta H_{A_2} - \delta H_{B_2}) + p_3(\delta H_{A_3} - \delta H_{B_3}) \qquad (16)$$

where $\langle (\delta H_A - \delta H_B) \text{ effective} \rangle$ is the observed nonequivalence, and p_1, p_2, and p_3 are the respective fractional populations of the conformers.

The observations of the large effective nonequivalence of the methylene protons in acidic solvents, e.g. trifluoroacetic acid, and in d_6-dimethyl sulfoxide relative to their effective nonequivalence in deuterium oxide and d_6-acetone (see Table V), is not readily explained, but may lie in a consideration of the following possibilities:

(i) The nonequivalence of the methylene protons is a consequence of the adjacent asymmetric sulfoxide group, and could be enhanced by changes in the magnetic anisotropy due to solvation at specific sites.

(ii) The populations of the three conformers in deuterium oxide and d_6-acetone may be such that the effective nonequivalence of H_A and H_B appears small, due to a cancelling effect in the terms of the averaged sum (see Equation (16)). However, the acidic solvents and d_6-dimethyl sulfoxide may favour a particular conformer or two conformers, and hence reduce the cancelling effect exhibited in deuterium oxide and d_6-acetone by changing the relative populations of the conformers.

The suggestion of a preferred conformation for solvated phenylsulfoxyacetic acid is not without precedent (94); but on the basis of the present experimental data no definite explanation can be proposed to account for the change in the effective nonequivalence of H_A and H_B in various solvents.

The n.m.r. spectra of phenylsulfoxyacetamide dissolved in various solvents (see Table VII) are similar to those of phenylsulfoxyacetic acid in deuterium oxide and d_6-acetone. The AB quartet of the methylene protons is unresolved and appears as a singlet, but coupling between H_A and H_B in trifluoroacetic

acid (J_{AB} = 14.1 c.p.s.) and d_6-dimethyl sulfoxide (J_{AB} = 13.8 c.p.s.) is evident.

For the methylene protons of sodium phenylsulfoxyacetate dissolved in deuterium oxide at 40°, the effective nonequivalence is 9.7 c.p.s. (see Table VIII). About 94% of the acid is undissociated * in deuterium oxide, but the sodium salt is completely dissociated. The chemical shifts of the methylene protons in both the acid and the sodium salt are dependent upon the electronic configuration of the solvated species, and the negative charge of the phenylsulfoxyacetate anion will certainly perturb the electronic configuration; hence, any comparison of the nonequivalence of the methylene protons in the acid and sodium salt is not strictly valid. The phenylsulfoxyacetate anion could well be a "structure maker" in aqueous solution, analogous to the acetate ion (95) which has a Bingham** value of -21.4. This implies that the phenylsulfoxyacetate anion is bound by a more rigid solvent shell in deuterium oxide than the undissociated acid.

The temperature dependence of the chemical shifts for H_A and H_B of sodium phenylsulfoxyacetate in deuterium

* Based on pK_a = 2.66 in H_2O (56)

** A measure of molal fluidity elevations of ions proposed by E.C. Bingham (96)

oxide was examined to provide additional information about the solvation of the anion (see Table IX and Figure VII). If rotation is rapid, the chemical shifts for H_A and H_B will be averaged as shown by equations (14), (15) and (16); and if the conformers have different energies, the ratio of p_1: p_2: p_3 will be given by

$$p_1 : p_2 : p_3 = a_1 e^{-E_1/kT} : a_2 e^{-E_2/kT} : a_3 e^{-E_3/kT} \qquad (17)$$

where a_1, a_2 and a_3 are usually different for each of the conformers, and will be only slightly temperature dependent. Thus, since the effective chemical shifts of H_A and H_B are temperature dependent, i.e. nonequivalence changes with temperature, then rapid rotation of the conformers is indicated (93).*

The preparation of methyl phenylsulfoxyacetate, which is previously unrecorded, warrants some comment prior to the discussion of its n.m.r. spectra. Synthesis was attempted by the following methods (see Figure VIII):

(i) Phenylsulfoxyacetic acid was treated with thionyl chloride, and the resulting product was reacted with absolute methanol.

* More detailed analyses of solvent effects on analogous systems have been discussed by Rauk, Buncel, Wolfe, et al. (97, 98, 99) and Nishio (100, 101).

FIGURE VII

THE VARIATION OF $|\delta H_A - \delta H_B|$ WITH TEMPERATURE IN A DEUTERIUM OXIDE SOLUTION OF $Ph\text{-}SO\text{-}CH_2\text{-}COO^{(-)}\ Na^{(+)}$

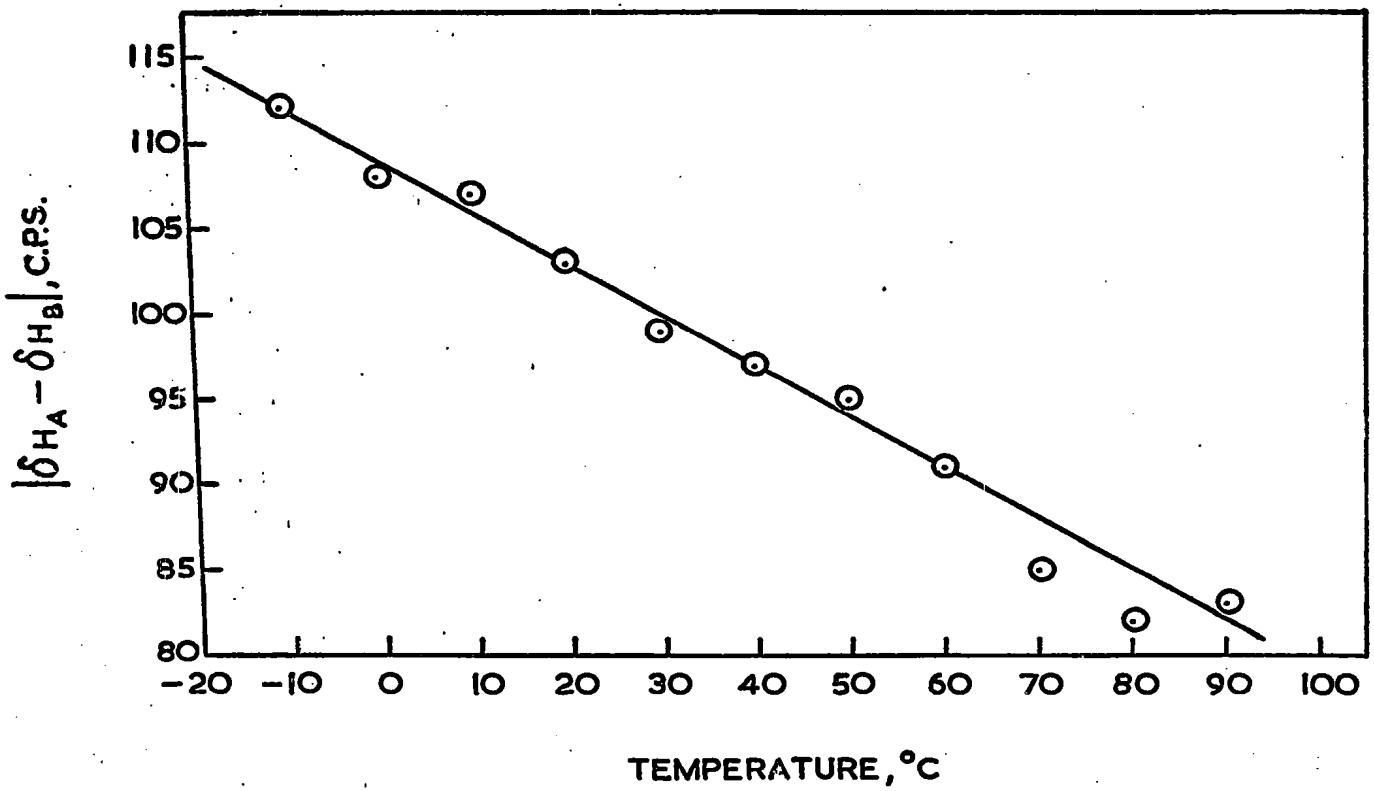
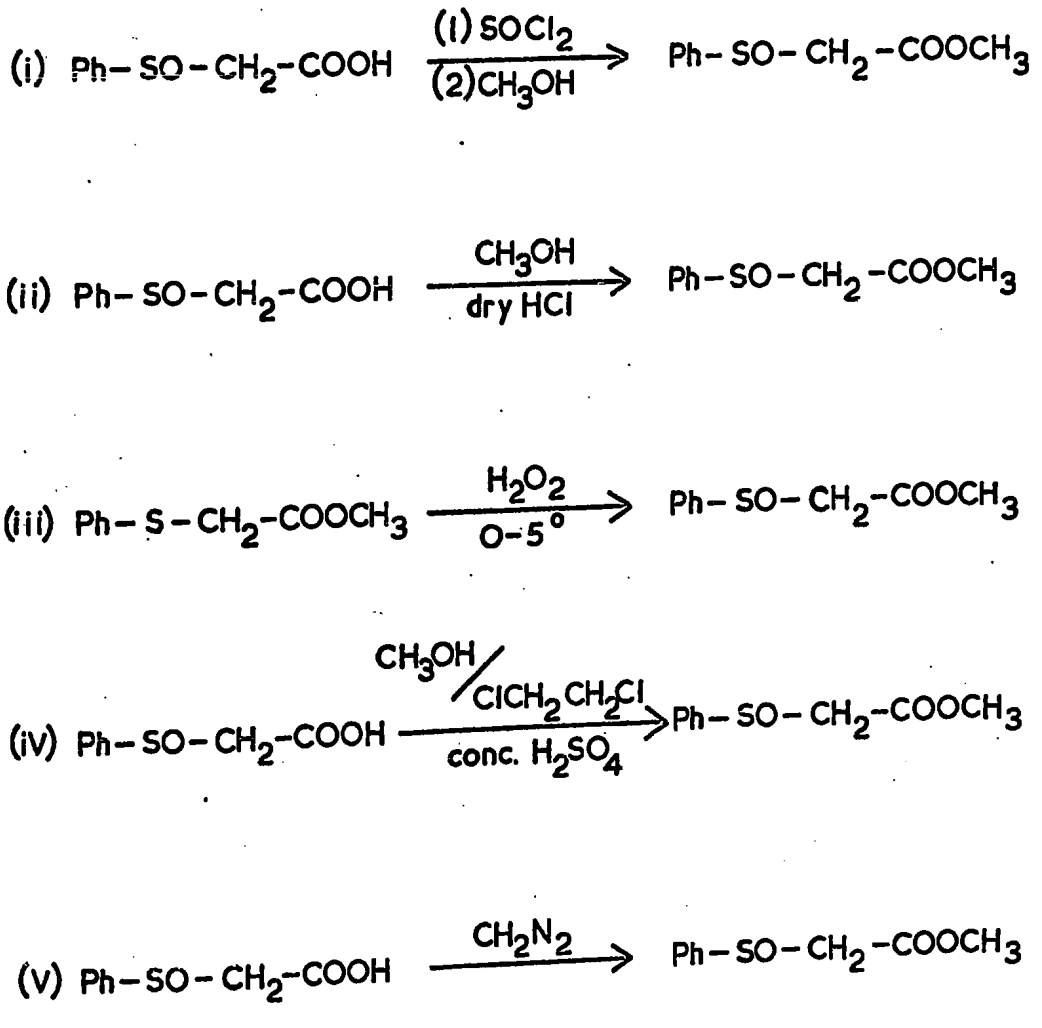


FIGURE VIII

THE ATTEMPTED SYNTHESES OF METHYL PHENYLSULFOXYACETATE



(ii) Phenylsulfoxyacetic acid was refluxed with absolute methanol saturated with dry HCl.

(iii) Methyl phenylthioglycollate was oxidized with hydrogen peroxide.

(iv) A solution of phenylsulfoxyacetic acid and ethylene dichloride was refluxed with absolute methanol in the presence of conc. H_2SO_4.

(v) Phenylsulfoxyacetic acid was treated with diazomethane in anhydrous ethyl ether.

The first four synthetic routes were unsuccessful, but treatment of phenylsulfoxyacetic acid with diazomethane produced methyl phenylsulfoxyacetate in good yield. When phenylsulfoxyacetic acid was refluxed with absolute methanol saturated with dry HCl the product appeared to be $PhSCH(OCH_3)$-$COOCH_3$. The formation of this unusual product certainly merits further investigation. The third and fourth reactions both gave some methyl phenylsulfoxyacetate, but it could not be isolated. In both of these reactions the acid-catalyzed decomposition of phenylsulfoxyacetic acid was evident, as demonstrated by the presence of diphenyl disulfide in the reaction product (103, 104, 105).

Purification of methyl phenylsulfoxyacetate was

achieved by recrystallization from various solvent mixtures of which benzene-petroleum ether (b.p. 40 - 60°; ca. 1 : 9 by volume) was the best. The ester decomposed when distilled, and the main product appeared to be diphenyl disulfide. An unusual elimination and rearrangement of the ester occurred on a chromatographic column of neutral alumina. The only product retrieved from the column was phenyl methyl sulfone.

N.m.r. spectra of methyl phenylsulfoxyacetate dissolved in various solvents were recorded (see Table VI). An outstanding feature of these spectra was a resonance centered between the chemical shifts of H_A and H_B. N.m.r. measurements of the ester in d_4-acetic acid were examined at different temperatures (see Table XI). In each spectrum the "center peak" was clearly apparent. Similar studies of the ester in pivalic acid were carried out over a wide temperature and concentration range (see Tables XII to XVI). Qualitative inspection of the "center peak" showed that its relative intensity was dependent on both temperature and concentration, but more so on the latter than on the former. As an explanation for the existence and behaviour of the "center peak" was not immediately evident, further investigation was attempted, but the experimental results were not reproducible. Since the validity of the observations is in some doubt, further comment is unwarranted. However, from the investigation

of solvation by pivalic acid, it is evident that the mole ratio of pivalic acid to methyl phenylsulfoxyacetate must be greater than 2 : 1 before obvious nonequivalence is exhibited by the methylene protons of the ester (see Tables XII - XVI). This behaviour is similar to that of phenylsulfoxyacetic acid in solutions of trifluoroacetic acid and d_6-dimethyl sulfoxide.

The preparation of methyl α-d-phenylsulfoxyacetate was attempted via the two reactions outlined in Figure IX. Thenn.m.r. spectra of this compound would be less complex than that of the protium ester in the region of the methylene proton resonances. Hence, a more facile observation of the emergence of the "center peak" would be possible. The attempts to prepare methyl α-d-phenylsulfoxyacetate were, however, unsuccessful.

An attempt to prepare phenylselenoxyacetic acid for purposes of n.m.r. examination and comparison with spectra of phenylsulfoxyacetic acid was also unsuccessful. Oxidation of phenylselenoacetic acid with hydrogen peroxide yielded diphenyl diselenide, which appears to be a thermochrome; at room temperature it is yellow, but on heating it becomes a deep red. Potassium phenylselenoxyacetate is stable however, and its n.m.r. spectrum has been recorded in deuterium oxide (see

FIGURE IX

TWO ATTEMPTED SYNTHESES OF METHYL α-d-PHENYLSULFOXYACETATE

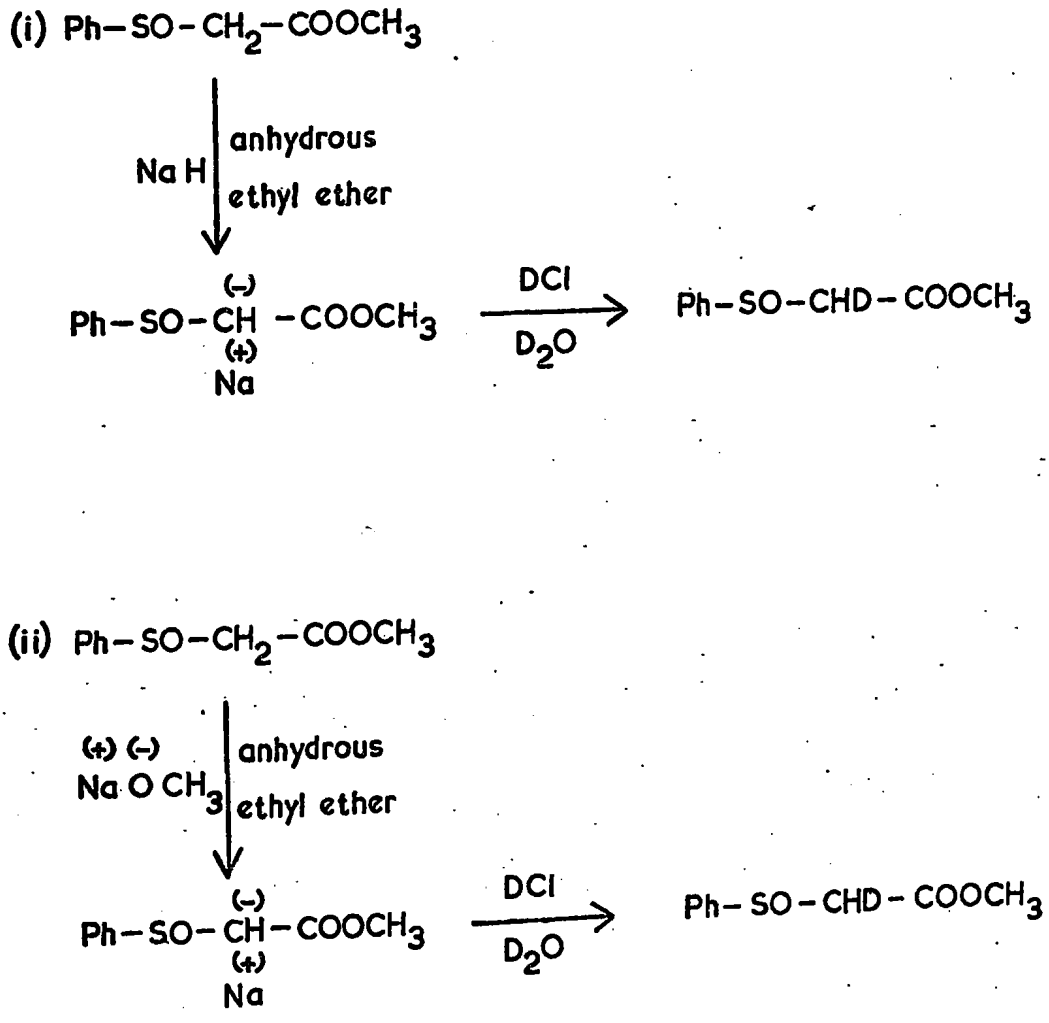


Table VIII). The spectrum presents a case similar to that of sodium phenylsulfoxyacetate, but the aqueous solvation of selenoxy compounds is thought to be different from that of sulfoxy compounds (c.f. Ōki and Iwamura (102)).

Proton - deuteron exchange reactions of phenylsulfoxyacetic acid

α,α-d_2-Phenylsulfoxyacetic acid was prepared by direct proton-deuteron exchange at the methylene position of the protium acid in deuterium oxide. During the exchange the temperature was not raised above 50° to ensure that decomposition of phenylsulfoxyacetic acid would be small. The acid-catalyzed cleavage of phenylsulfoxyacetic acid in acidic media has been investigated by a number of workers (103, 104, 105), but no definitive work has been presented (106).

Since phenylsulfoxyacetic acid undergoes relatively facile proton-deuteron exchange, re-exchange of α,α-d_2-phenylsulfoxyacetic acid may occur in aqueous (H_2O) media and seriously affect the validity of the pK_a measurements. Scott and Benson (107) have shown that isotope effect data are valid if the deuterium content of the isotopically substituted acid is above 90%.* Hence, as the proposed conductivity measurements

* Incomplete deuteration results from either partial deuteration during preparation or re-exchange during measurement, and it leads to a mixture of X-CH_2COOH, X-CHDCOOH, and X-CD_2COOH. Scott and Benson assumed that K_a(HD) is equal to the geometric mean of $K_a(H_2)$ and $K_a(D_2)$ in their calculations and treated the problem classically, i.e. neglected interionic effects on both the mobility and activity of the ions involved in the equilibria.

will be carried out on an aqueous (H_2O) solution of α,α-d_2-phenylsulfoxyacetic acid, it is necessary to investigate the re-exchange process, i.e. the reverse of the preparative method, to establish that the latter limit of 10% re-exchange will not be exceeded during the time associated with a conductance run.

A qualitative kinetic investigation of the re-exchange process was undertaken by examining n.m.r. spectra of samples of deuterated acid which had been left in contact with pure water for various periods of time at room temperature (see Figure X). Samples of the partially exchanged acid were isolated from the solvent by freeze-drying to minimize further exchange during recovery. Examination of the n.m.r. spectra of the recovered samples in moist trifluoroacetic acid/benzene and d_6-dimethyl sulfoxide (see Table XVII) revealed the four peaks appropriate to the methylene protons of the protium acid together with two further relatively broad singlets close to, but which did not exactly correspond with, the shifts of the methylene protons of the protium acid. The intensity of the two broad peaks varied with time reaching a maximum and then diminishing as the conversion of the deuterated acid to the protium acid progressed (see Figure X). The two broad absorptions were assigned to the six rotamers of the two diastereoisomers (see Figure XI) formed in the exchange.

FIGURE X

N.M.R. SPECTRA OF PARTIALLY EXCHANGED

α,α-d_2-PHENYLSULFOXYACETIC ACID AT VARIOUS TIMES

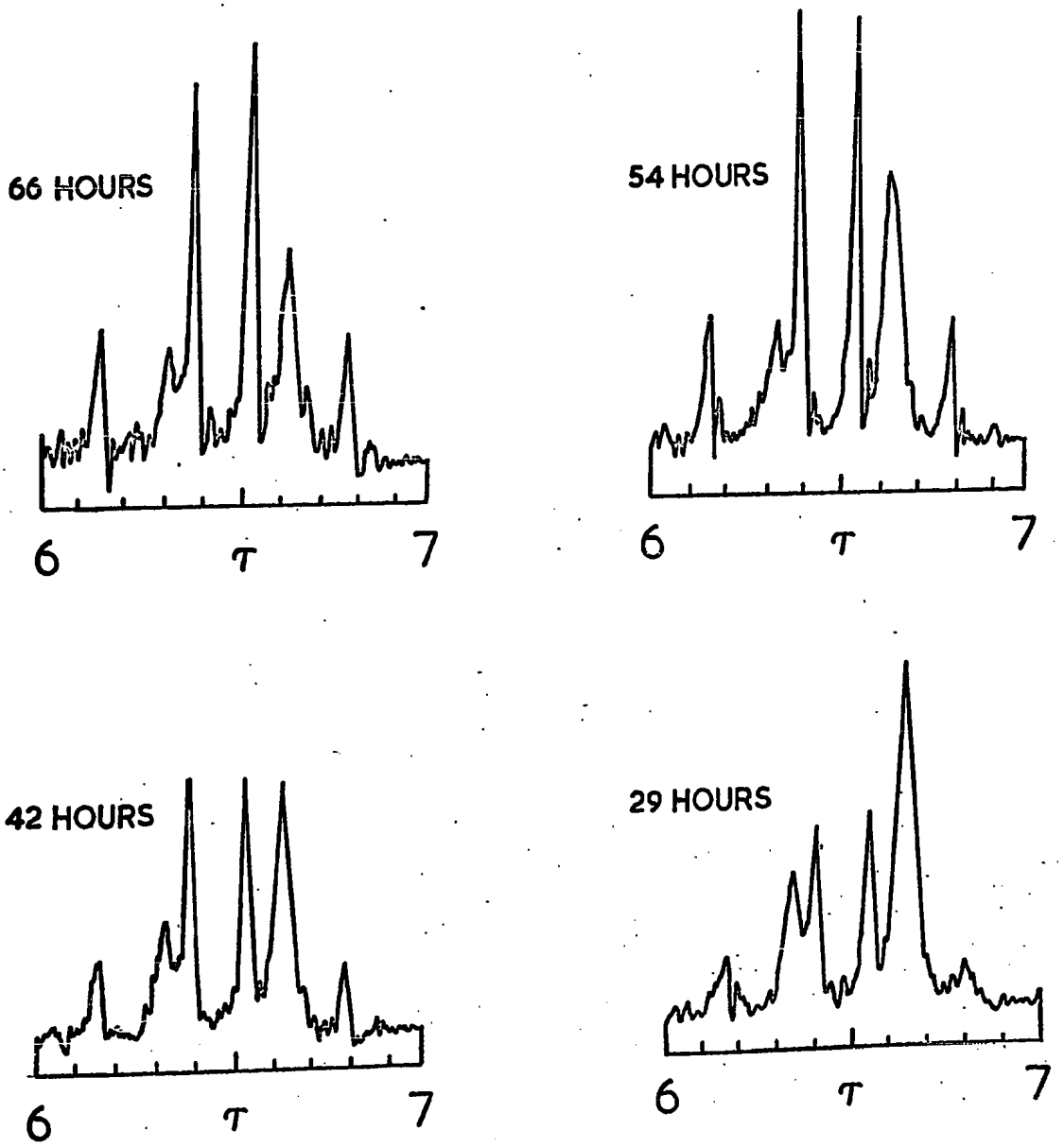


FIGURE XIa

H→D EXCHANGE IN THE TWO ENANTIOMERS OF PHENYLSULFOXYACETIC ACID (Ia AND Ib)

This reaction gives rise to two α-d-phenylsulfoxyacetic acid diastereoisomers (two pairs of mirror-image conformers; IIa and IId, IIb and IIc.).

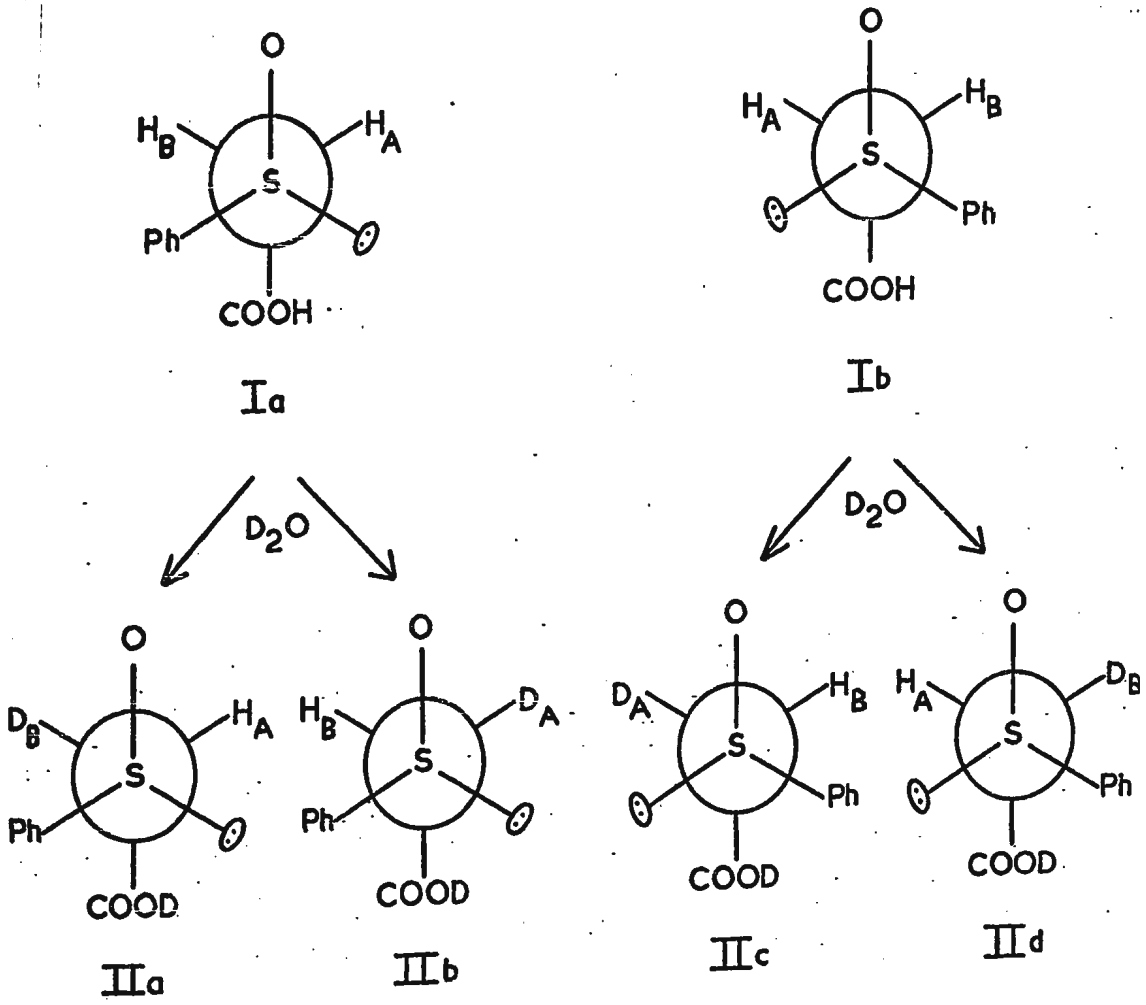
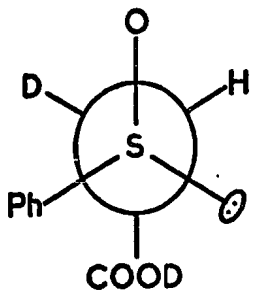


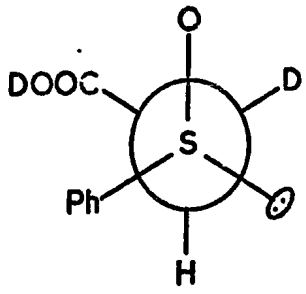
FIGURE XIb

SIX DIFFERENT ROTOMERS OF THE TWO

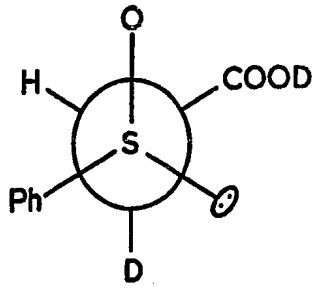
α-d-PHENYLSULFOXYACETIC ACID DIASTEREOISOMERS



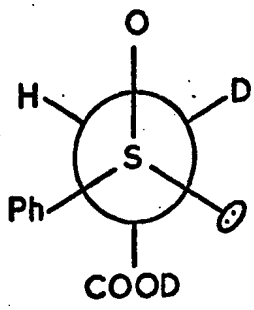
IIIa



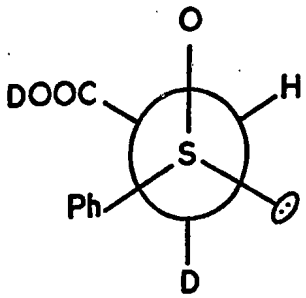
IIIb



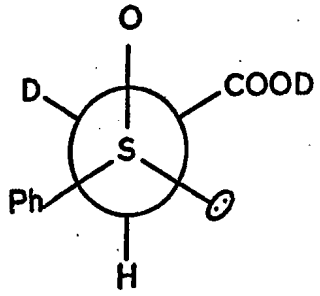
IIIc



IVa



IVb



IVc

Theoretically, six different absorptions should appear for the rotamers, but only two peaks were observed. This observation is similar to that for the solvated protium acid. The two observed peaks are broadened presumably by unresolved (triplet) coupling to deuterium in eachhcase, and the unequal intensity is a consequence of differing exchange rates for the two methylene deuterons (108).

Rauk, Wolfe, Buncel, and Moir (97, 98) have reported similar observations concerning the reactivity of the methylene protons of benzyl methyl sulfoxide towards isotopic exchange in 1M - $NaOD/D_2O$, and have shown that the methylene protons in this compound differ in reactivity by about a factor of fourteen. It may be concluded that the difference in reactivity of the methylene protons of phenylsulfoxyacetic acid is less than in benzyl methyl sulfoxide. The differences in the chemical shifts and the coupling constants for the methylene protons are similar in phenylsulfoxyacetic acid and benzyl methyl sulfoxide, and the only factor which can influence the observation of the diastereoisomers by n.m.r. is the relative rates of exchange of the two protons or deuterons (108). However, a comparison of the exchange rates for benzyl methyl sulfoxide in basic media and for phenylsulfoxyacetic acid in acidic solution is not strictly valid as the latter exchange is almost certainly pH dependent.

The most favourable situation for the observation of both CHD absorptions is when the protons or deuterons are of equal reactivity, since this implies that the diastereoisomers will be formed and removed (neglecting secondary isotope effects on the exchange of the second proton or deuteron) at equal rates. As the difference in reactivity of the methylene protons or deuterons increases, the diastereoisomer formed by the "fast-slow" sequence will be the only isomer detected by proton resonance experiments, irrespective of whether the exchange is from D to H or vice versa.

Hence, the methylene protons of phenylsulfoxyacetic acid in acidic aqueous media are closer in reactivity than those of benzyl methyl sulfoxide in 1M - $NaOD/D_2O$, since both the diastereoisomers were observed with the former compound, whereas only one absorption representing the diastereoisomeric proton was observed in the base of benzyl methyl sulfoxide.

A conformational analysis of the exchange process (see (97), (100), and (108)) suggests that the following factors may be important in determining the relative reactivity of the methylene deuterons in α,α-d_2-phenylsulfoxyacetic acid:

(i) incipient carbanion - sulfur lone pair interactions;

(ii) the relative orientation of the phenyl and carboxyl groups;

(iii) hydrogen bonding between the carboxyl proton and the sulfoxide group.

Any further discussion of the mechanism of the exchange requires a structural assignment of the "fast" and "slow" deuterons, which is unwarranted on the basis of the present experimental data. Rauk, Buncel, Moir, and Wolfe (97) have speculated that the proton which is exchanged preferentially in the methylene group of benzyl methyl sulfoxide is trans to the unshared pair of electrons on the sulfur atom. Nishio (101) has reported that in compounds of the type $R\text{-}C_6H_4\text{-}SO\text{-}CH_2\text{-}C_6H_4\text{-}R'$ the proton which is trans to the sulfur lone pair, i.e. gauche to the sulfoxide oxygen, is less sensitive to change in the electronegativity of the R′ substituent than the proton which is cis to the sulfur lone pair. The chemical shift of trans proton (H_B) is more sensitive to acidic solvation, as shown in Figure XIIa. Nishio (101) has also concluded from a study of proton-deuteron exchange in a compound of this series that the proton gauche to the sulfoxide oxygen and trans to the unshared pair of electrons on the sulfur atom (H_B) is preferentially exchanged in basic media (see Figure XIIb). By examining the stereochemistry and n.m.r. spectra of the two types of compounds shown in Figure XIIc, Nishio hopes to unambiguously assign the methylene protons and predict which

FIGURE XIIa

A NEWMAN DIAGRAM (VIEWED ALONG THE C-S BOND)

OF R-C_6H_4-SO-CH_2-C_6H_4-R′ SOLVATED BY TRIFLUOROACETIC ACID

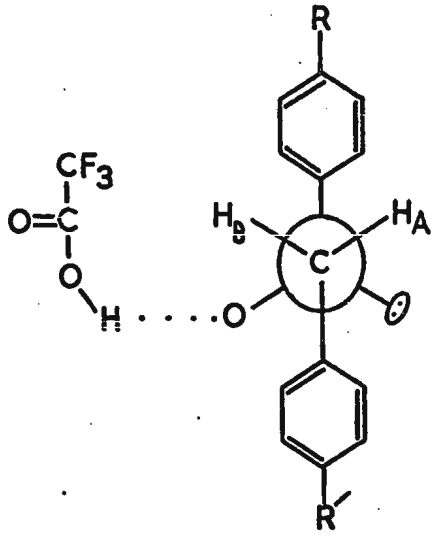


FIGURE XIIb

H→D EXCHANGE AT THE METHYLENE POSITION OF R-C_6H_4-SO-CH_2-C_6H_4-R′

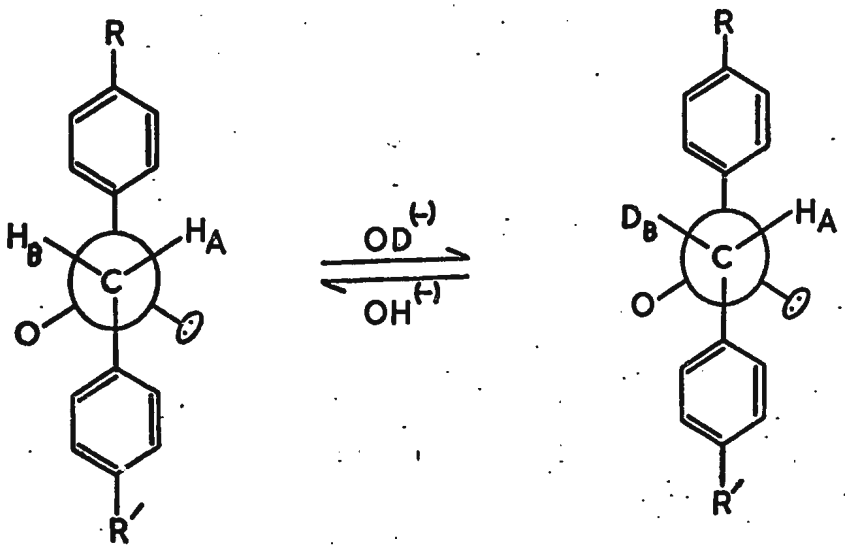
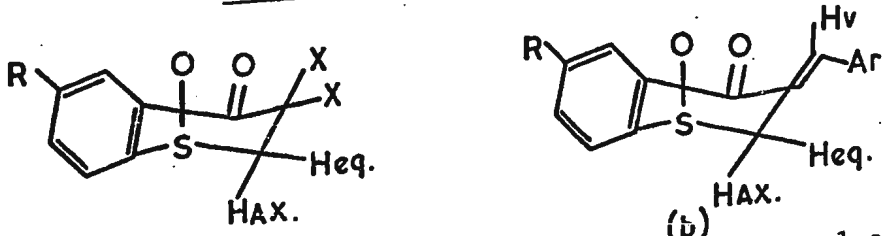


FIGURE XIIc



3,3-dihalothiochromanone-1-oxides

3-benzalthiochromanone-1-oxides

proton will be preferentially exchanged.

A quantitative kinetic analysis of the exchange process (schematically illustrated in Figure XIII) was not attempted. As the exchange process is presumably pH dependent a series of buffer solutions could be examined by proton magnetic resonance after dissolution in deuterium oxide for various periods of time. With the appropriate assumptions the resulting data could then be fitted to the integrated rate equations, and the experimental rate constants determined. However, the inherent difficulty of the exact determination of the various species present by n.m.r. and the recovery of the acid after the exchange would introduce considerable experimental error in any results obtained.

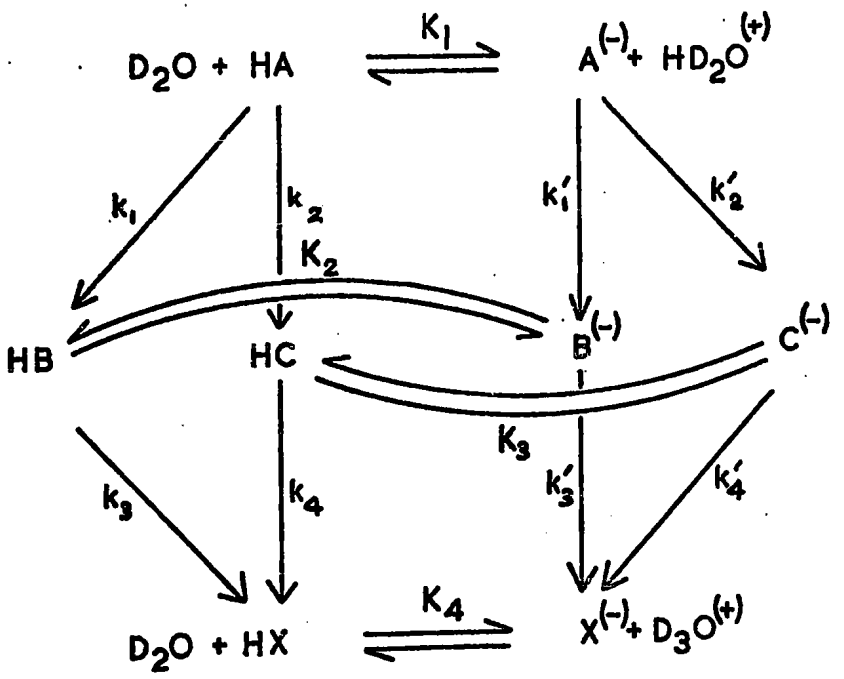
A qualitative experiment was undertaken to determine the point at which 90% phenylsulfoxyacetic acid remained during exchange with deuterium oxide (see Table XVIII). From this preliminary experiment, conductivity measurements of α,α -d_2-phenylsulfoxyacetic acid in aqueous (H_2O) media at 25^o appear feasible.

N.m.r. spectra of partially exchanged phenylsulfoxyacetic acid

In the n.m.r. examination of partially exchanged phenylsulfoxyacetic acid, the shifts of the two broad peaks representing the α-d-phenylsulfoxyacetic acid diastereoisomers

FIGURE XIII

A KINETICS SCHEME REPRESENTING PROTON-DEUTERON EXCHANGE AT THE METHYLENE POSITION OF PHENYLSULFOXYACETIC ACID IN DEUTERIUM OXIDE



HA = Ph-SO-CH_2-COOH

$A^{(-)}$ = Ph-SO-CH_2-$COO^{(-)}$

HB = Ph-SO-CHD-COOD

$B^{(-)}$ = Ph-SO-CHD-$COO^{(-)}$

HC = Ph-SO-CDH-COOD

$C^{(-)}$ = Ph-SO-CDH-$COO^{(-)}$

HX = Ph-SO-CD_2-COOD

$X^{(-)}$ = Ph-SO-CD_2-$COO^{(-)}$

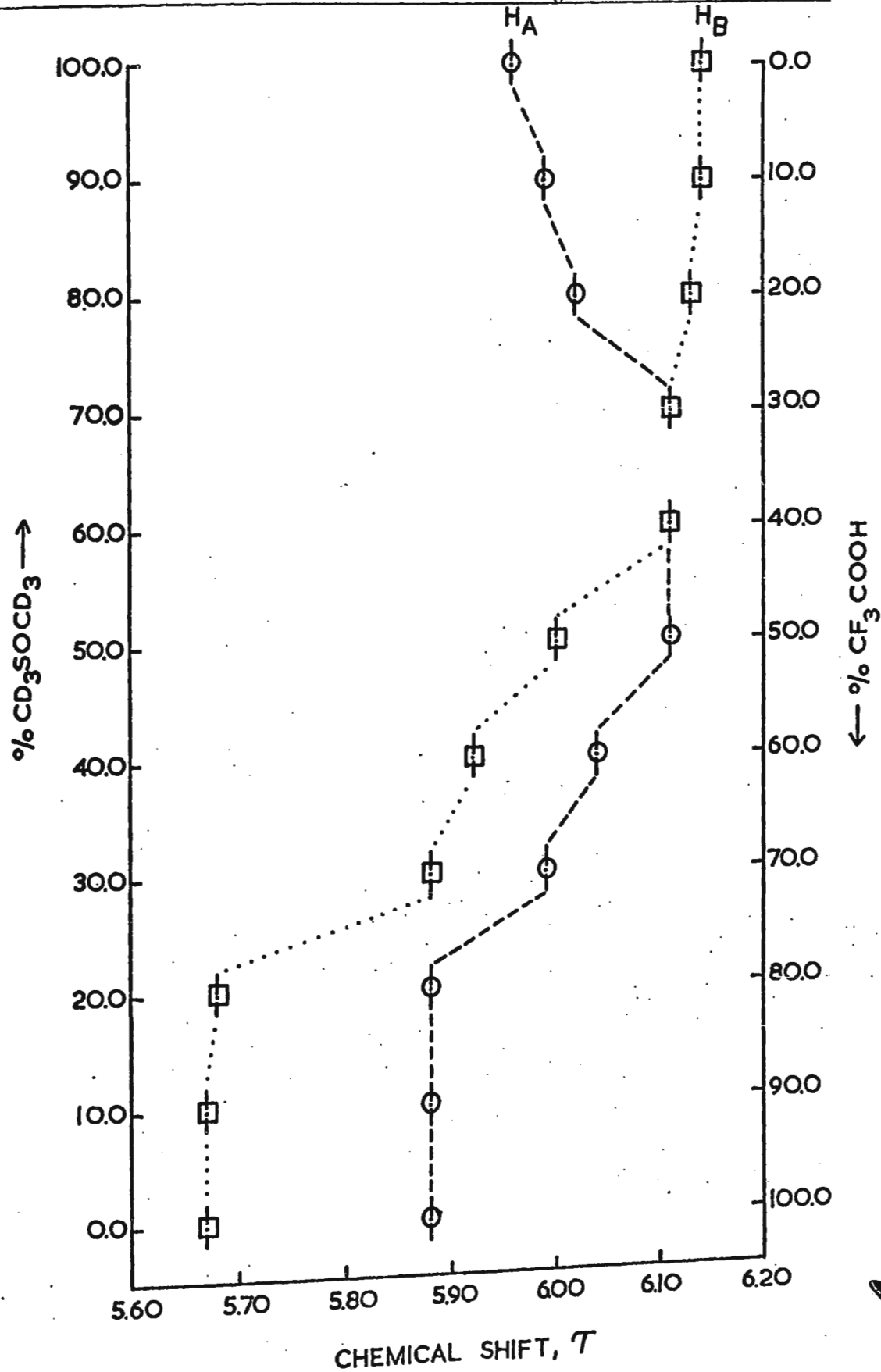
appeared to be exactly reversed when dissolved in d_6-dimethyl sulfoxide relative to their positions in trifluoroacetic acid (see Table XVII). This change in position was evident since the shifts were of unequal intensity, a consequence of unequal reactivity (see above). N.m.r. measurements on solutions of phenylsulfoxyacetic acid in varying amounts of trifluoroacetic acid and d_6-dimethyl sulfoxide were recorded (see Table X and Figure XIV), and the resulting data may be rationalized by the following:

(i) The chemical shifts of H_A and H_B actually coalesce, cross, and then reverse positions as the amount of one solvent (trifluoroacetic acid) increases relative to the amount of the other (d_6-dimethyl sulfoxide). This "crossing" of chemical shifts would involve coincidental equivalence of H_A and H_B due to solvation, but, unless solvation destroys the asymmetry of the sulfoxide group or changes the magnetic anisotropy of the system, equivalence of H_A and H_B is theoretically impossible.

(ii) The chemical shifts of H_A and H_B are reversed in trifluoroacetic acid relative to their positions in d_6-dimethyl sulfoxide because specific solvation is different in each solvent. Assuming d_6-dimethyl sulfoxide is more "basic" than phenylsulfoxyacetic acid, as the concentration of trifluoroacetic acid is increased in a solution of phenylsulfoxyacetic acid and d_6-dimethyl sulfoxide, it does not solvate phenylsulfoxyacetic acid but removes d_6-dimethyl sulfoxide from the sphere of solvation. As this occurs the

FIGURE XIV

THE CHEMICAL SHIFTS FOR THE METHYLENE PROTONS OF Ph-SO-CH_2-COOH IN MIXTURES OF TRIFLUOROACETIC ACID AND d_6-DIMETHYL SULFOXIDE



difference in the chemical shifts of H_A and H_B decreases until coalescence is observed. At this point phenylsulfoxyacetic acid presumably is solvated by a trifluoroacetic acid/d_6-dimethyl sulfoxide complex, which is quite different in magnetic susceptibility and dipole moment from either d_6-dimethyl sulfoxide or trifluoroacetic acid. As trifluoroacetic acid becomes more abundant than d_6-dimethyl sulfoxide, the chemical shifts of H_A and H_B quickly separate, exhibiting nonequivalence relevant to solvation with trifluoroacetic acid. In this sequence coincidental equivalence of H_A and H_B due to solvation does not necessarily occur.

The latter possibility seems to be the best explanation of the phenomenon since coincidental equivalence of H_A and H_B due to solvation is unlikely.

α-d-Phenylsulfoxyacetic acid

In an effort to simplify the n.m.r. spectrum, preparation of α-d-phenylsulfoxyacetic acid by three different syntheses was attempted. As a preliminary experiment to the first snythesis, the preparation of ethyl-2,4-dinitrophenylthiomalonate from sodium diethyl malonate and 2,4-dinitrophenylsulfenyl chloride was examined. The initial reaction was carried out in absolute ethanol, and the resulting product was ethyl-2,4-dinitrophenylsulfenate, not ethyl-2,4-dinitrophenylthiomalonate (see Figure XVa). In the second reaction anhydrous toluene was used as a solvent, but

FIGURE XVa

TWO ATTEMPTED SYNTHESES OF

DIETHYL-2,4-DINITROPHENYLTHIOMALONATE

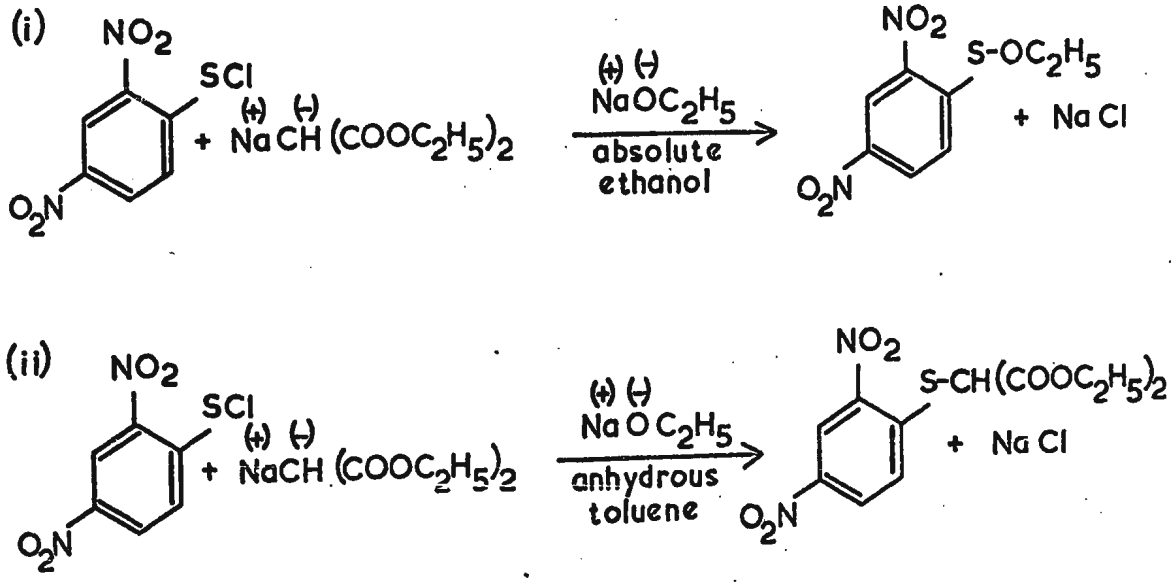
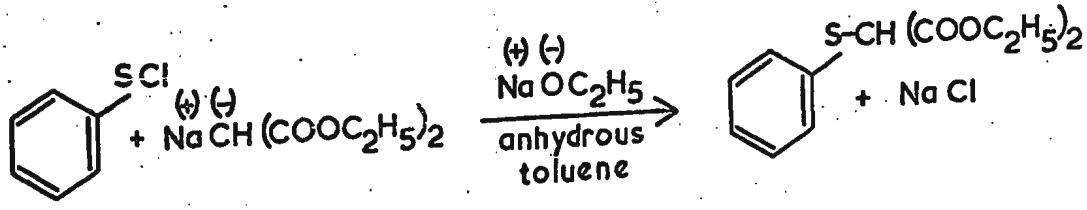


FIGURE XVb

AN UNSUCCESSFUL SYNTHESIS OF

DIETHYL PHENYLTHIOMALONATE



ethyl-2,4-dinitrophenylthiomalonate could not be isolated from the reaction mixture. When this synthesis (see Figure XVb) was used to prepare α-d-phenylsulfoxyacetic acid from phenylsulfenyl chloride and sodium diethyl malonate, diphenyl disulfide was the only product isolated from the reaction mixture.

The second proposed synthesis of α-d-phenylsulfoxyacetic acid (see Figure XVI) involved the preparation of diethyl phenylthiomalonate from diethyl oxalate and ethyl phenylthioglycollate. The diethyl phenylthiomalonate was converted to the dipotassium salt which, in turn, was acidified with DCl and decarboxylated to yield a mixture of α-d-phenylthioglycollic acid and α,α-d_2-phenylthioglycollic acid. However, after oxidation with hydrogen peroxide in anhydrous acetone, about 40% of the product was phenylsulfoxyacetic acid.

The third synthesis of α-d-phenylsulfoxyacetic acid (see Figure XVII) involved the preparation of α-d-chloroacetic acid by the catalytic reduction of glyoxylic acid with deuterium to give α-d-glycollic acid which could be converted into α-d-chloroacetic acid by treatment with thionyl chloride. Potassium α-d-chloroacetate then could be reacted with phenylthiocyanate in aqueous methanol at -50° to give α-d-phenylthioglycollic acid, which could be oxidized to α-d-phenylsulfoxyacetic

FIGURE XVI

THE PREPARATION OF α-d-PHENYLSULFOXYACETIC ACID FROM ETHYL PHENYLTHIOGLYCOLLATE, DIETHYL OXALATE, AND SODIUM ETHOXIDE

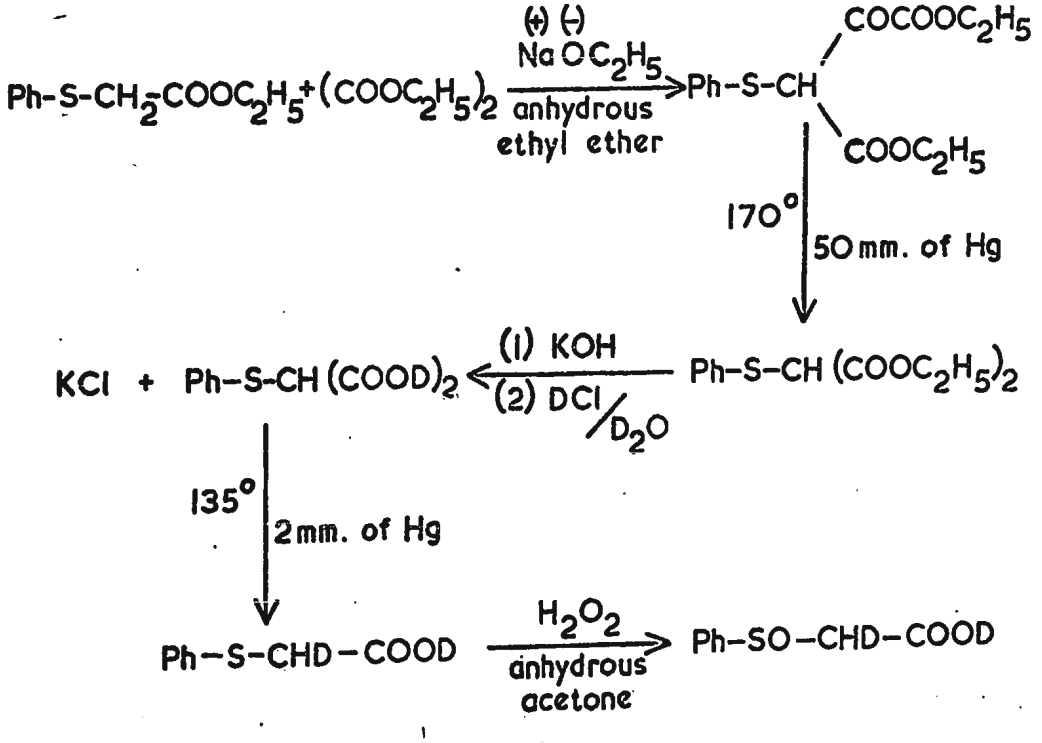
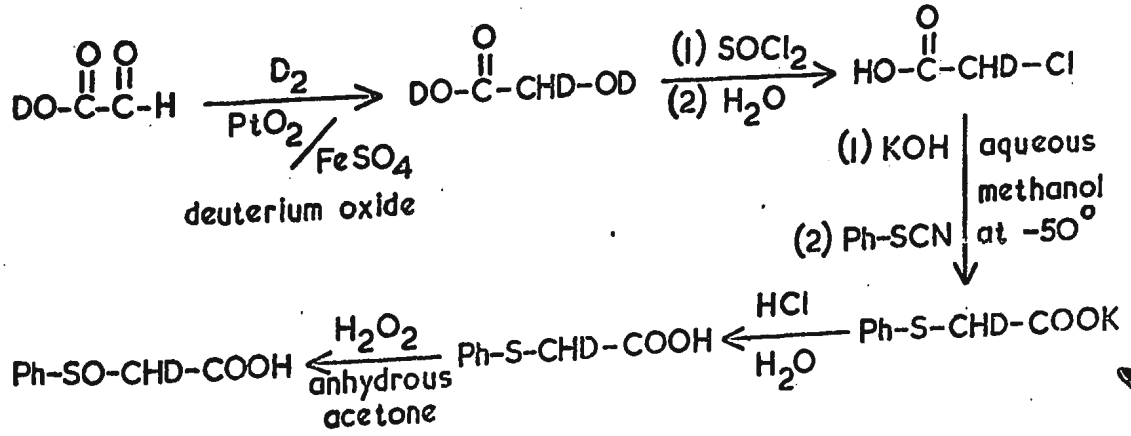


FIGURE XVII

THE PREPARATION OF α-d-PHENYLSULFOXYACETIC ACID FROM α-d-CHLOROACETIC ACID



acid. However, the isolation of α-d-glycollic acid and its conversion to α-d-chloroacetic acid could not be achieved, although the remainder of the reaction sequence was successful.

The oxidation of α-d-phenylthioglycollic acid to α-d-phenylsulfoxyacetic acid with hydrogen peroxide appeared to induce proton-deuteron exchange at the methylene position even in anhydrous media. This presumably occurred because the residual water molecule after the oxidation was well situated for exchange at the methylene position of the newly formed α-d-phenylsulfoxyacetic acid. This problem of re-exchange could be circumvented by an anhydrous oxidation of α-d-phenylthioglycollic acid, e.g. with chromate in anhydrous acetone.

Phenylsulfonylacetic acid and some derivatives

Phenylsulfonylacetic acid was prepared by oxidation of sodium phenylthioglycollate with potassium permanganate. The ethyl ester was prepared by refluxing a solution of phenylsulfonylacetic acid and ethylene dichloride with absolute ethanol in the presence of conc. H_2SO_4; and the amide was prepared by oxidation of phenylthioacetamide with excess hydrogen peroxide in acetone. A qualitative inspection (via n.m.r. measurements) of proton-deuteron exchange at the methylene position of phenylsulfonylacetic acid indicated that exchange occurs in (acidic) deuterium oxide. The exchange appears to

be slightly more rapid than with phenylsulfoxyacetic acid, although more measurements are clearly needed to establish whether re-exchange of α,α-d_2-phenylsulfonyl-acetic acid in water will be sufficiently slow to permit accurate conductivity measurements of the deuterated acid.

SUMMARY

The salient points arising from this investigation are summarized by the following observations:

(i) The chemical shifts of the methylene protons of phenylsulfoxyacetic acid, sodium phenylsulfoxyacetate, and methyl phenylsulfoxyacetate are extremely solvent dependent, whereas those of phenylsulfoxyacetamide do not appear to be solvent dependent at the temperatures considered. As the empirical parameters are inseparable on the basis of the current data, no explanation of solvent effects is offered.

(ii) The methylene protons of phenylsulfoxyacetic acid differ in reactivity, and the exchange process, whether H to D or <u>vice versa</u>, is stereoselective.

(iii) Chloroacetic acid and α,α-d_2-chloroacetic acid may be prepared with sufficient purity to allow the accurate determination of the secondary isotope effect.

(iv) The preparation of α,α-d_2-phenylsulfoxyacetic acid and α,α-d_2-phenylsulfonylacetic acid may be accomplished through direct H → D exchange by dissolution of the corresponding protium acids in deuterium oxide.

(v) Conductivity measurements on α,α-d_2-phenylsulfoxyacetic acid and α,α-d_2-phenylsulfonylacetic acid in aqueous (H_2O) media appear feasible, but more investigation of each D → H exchange process is necessary.

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APPENDIX

FIGURE XVIII

N.M.R. SPECTRUM OF PHENYLSULFOXYACETIC ACID DISSOLVED IN TRIFLUOROACETIC ACID

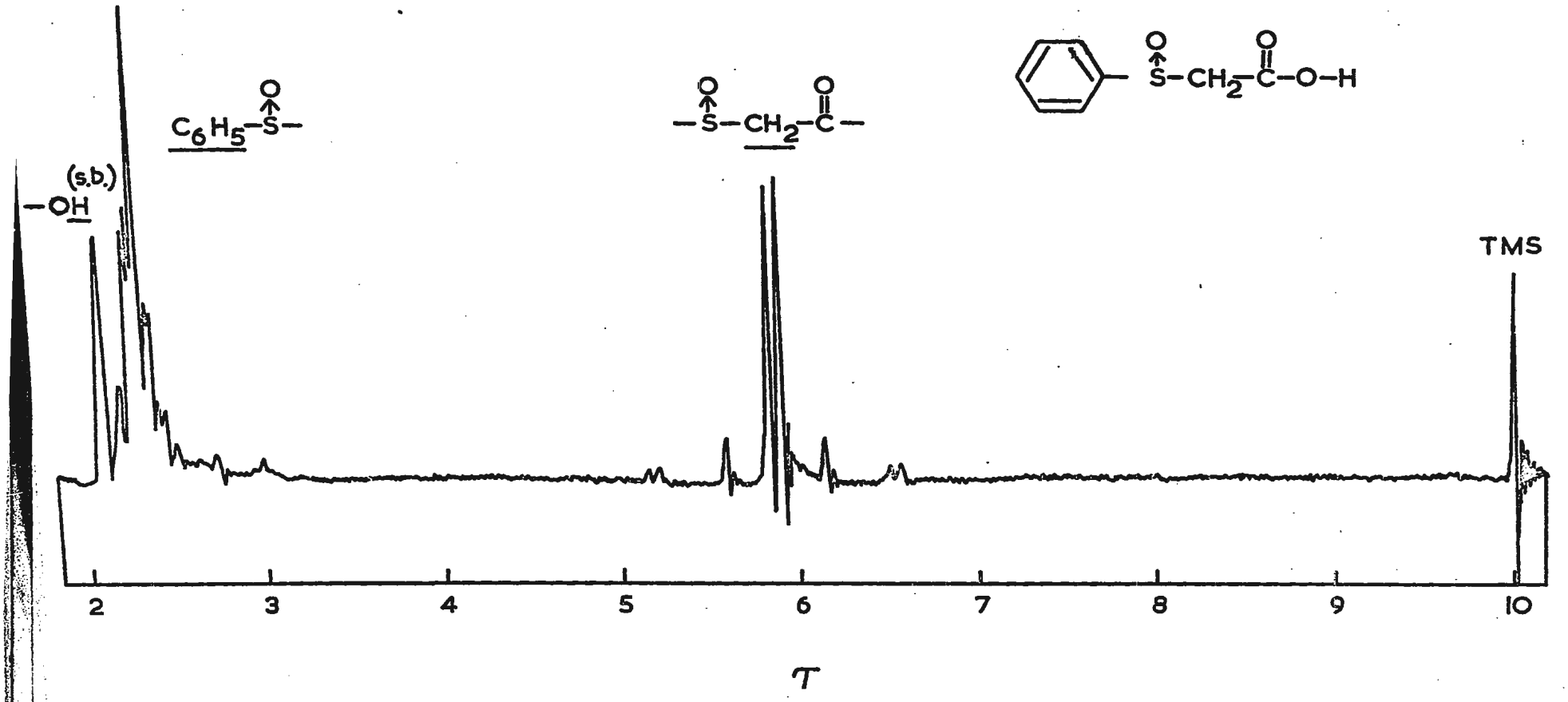


FIGURE XIX

N.M.R. SPECTRUM OF METHYL PHENYLSULFOXYACETATE DISSOLVED IN TRIFLUOROACETIC ACID

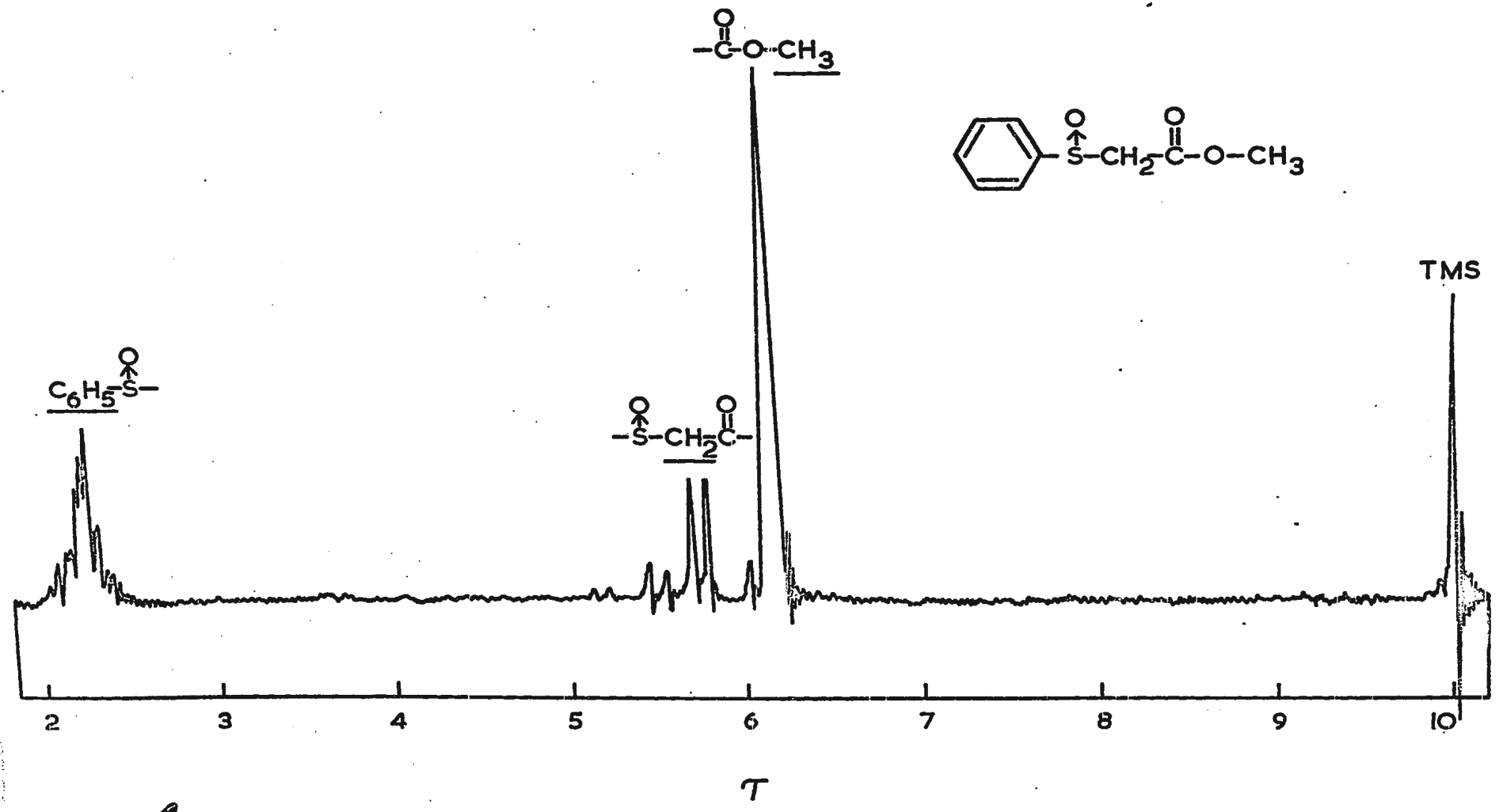


FIGURE XX

N.M.R. SPECTRUM OF PHENYLSULFOXYACETAMIDE DISSOLVED IN TRIFLUOROACETIC ACID

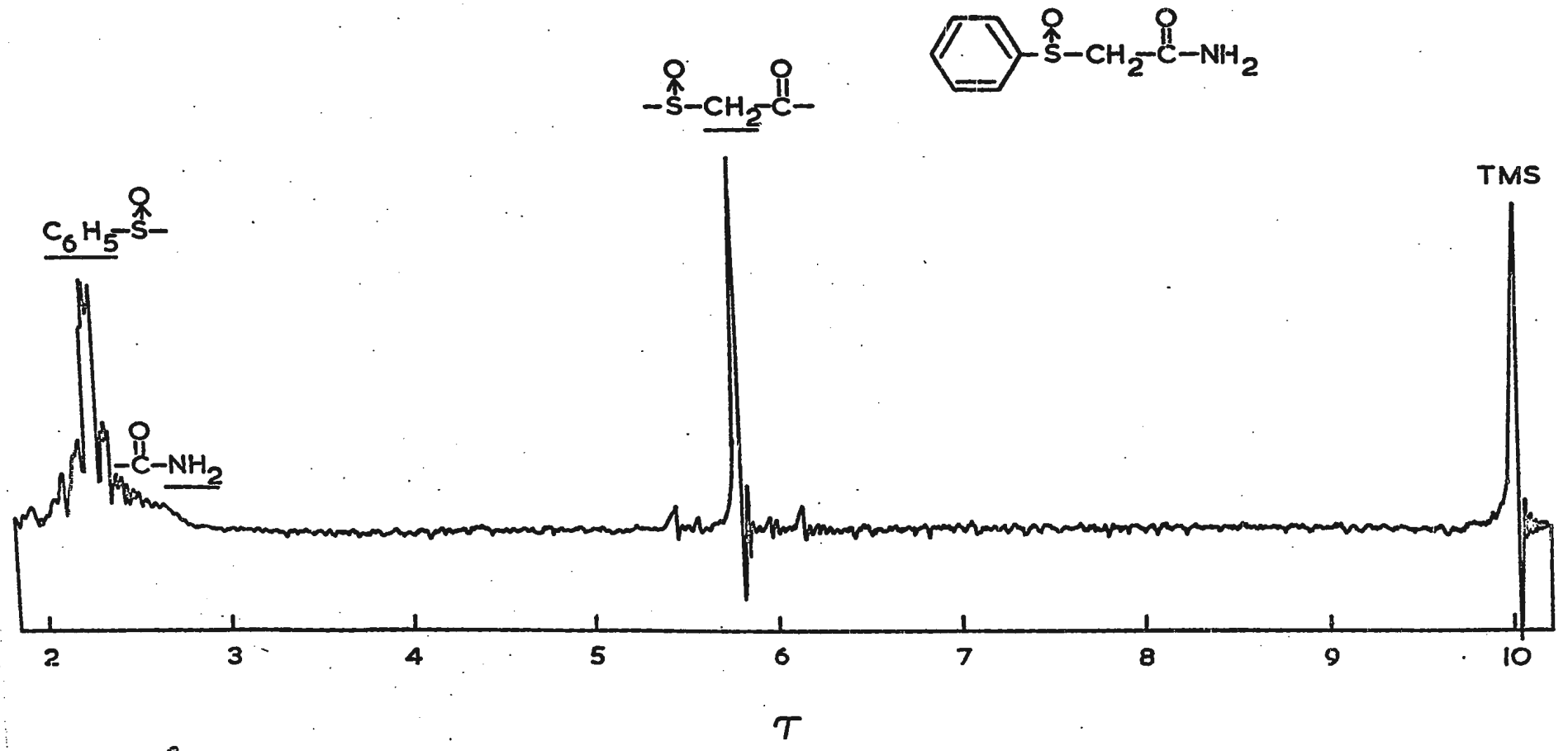


FIGURE XXI

N.M.R. SPECTRUM OF SODIUM PHENYLSULFOXYACETATE DISSOLVED IN D_2O

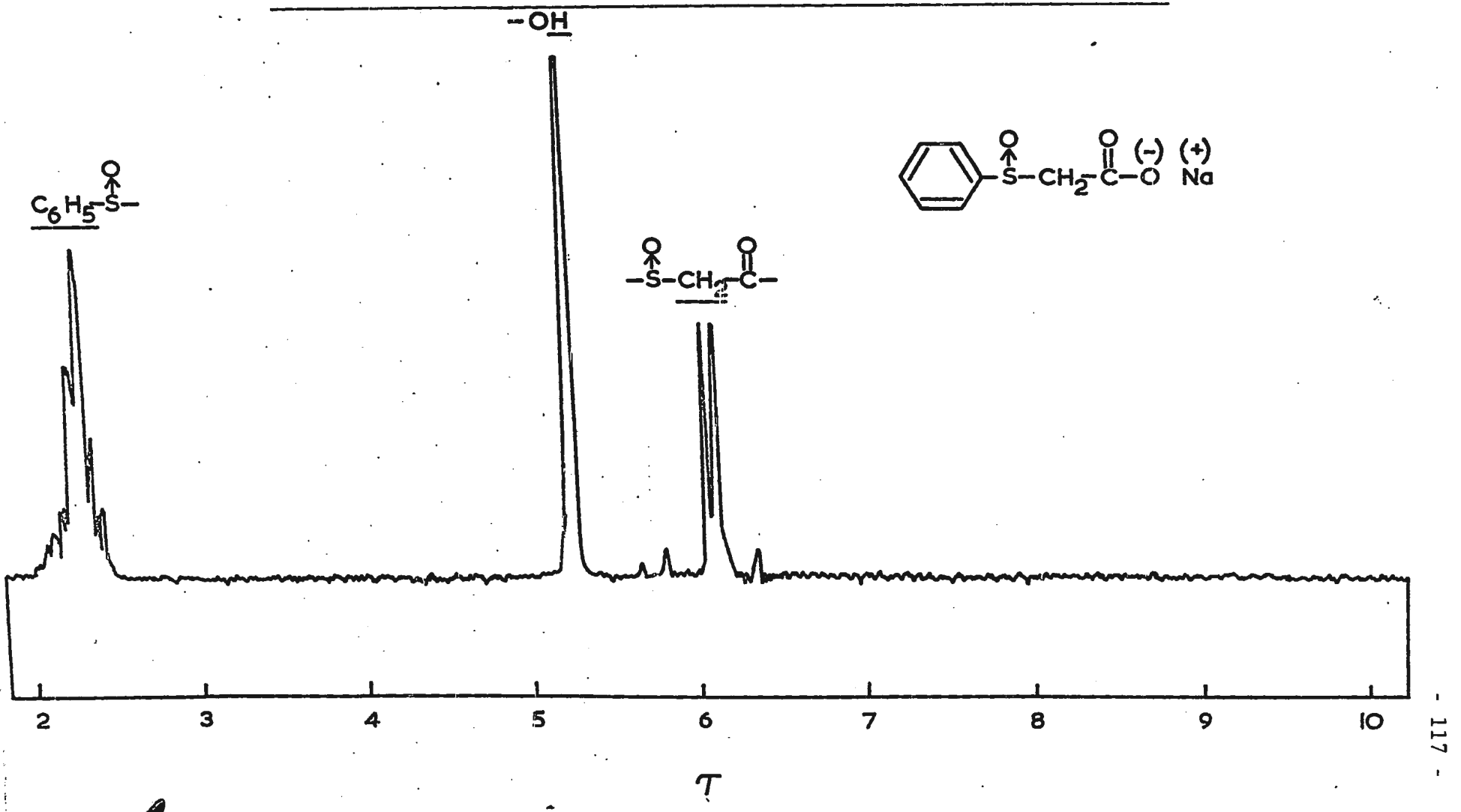
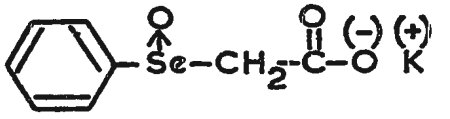
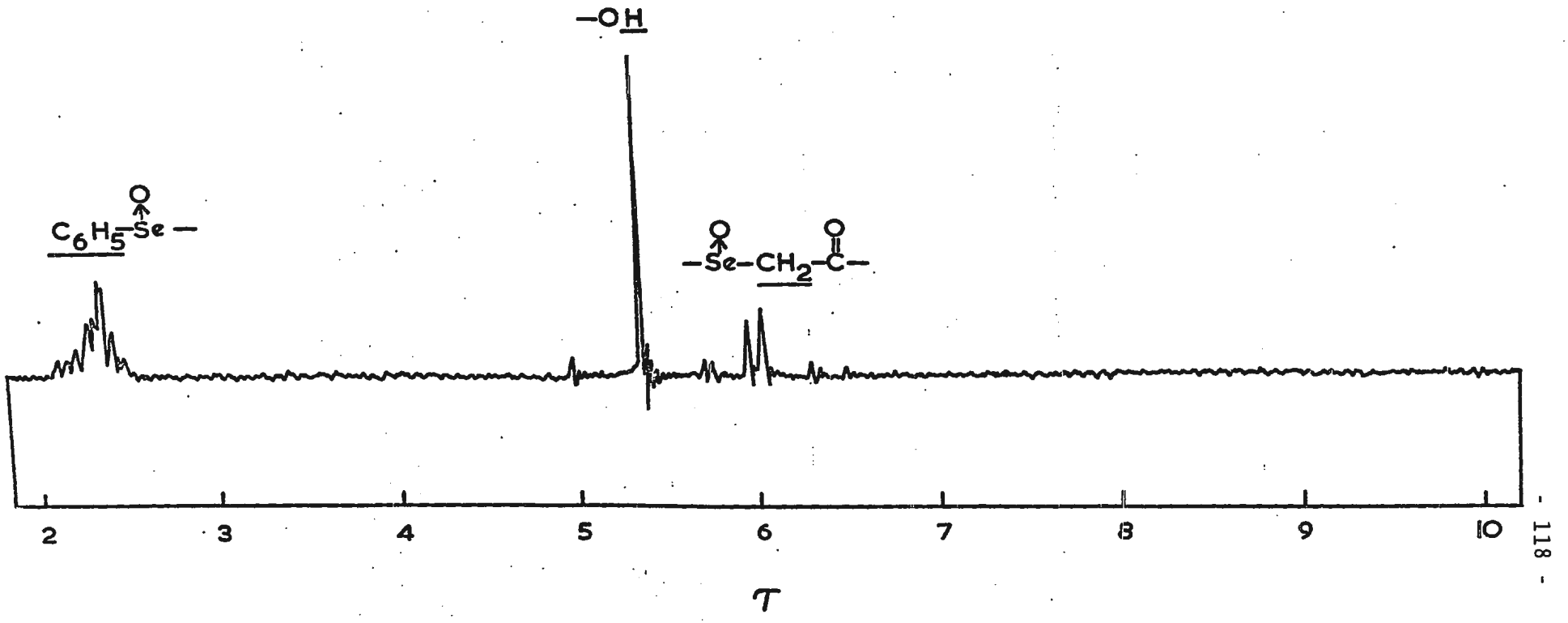


FIGURE XXII

N.M.R. SPECTRUM OF POTASSIUM PHENYLSELENOXYACETATE DISSOLVED IN D_2O





ERRATA

Pg. 27

The purity of chloroacetic acid was obtained by comparing the respective integrations of the $Cl\text{-}\underline{CH_2}\text{-}COOH$ and $Cl_2\text{-}\underline{CH}\text{-}COOH$ absorption peaks. The inherent instrumental error of a single integration is about ± 2%, but the error in the measurement of the percent purity is considerably smaller from the following considerations.

Let "x" represent the integration value of the chloroacetic acid absorption peak and "y" represent the integration value of the dichloroacetic acid absorption peak, then the percent purity is given by

$$\% \text{ purity} = \frac{x(100)}{x + y} = \frac{1}{1 + \frac{y}{x}} \cdot 100$$

Let Δx equal the error in x, i.e. $\Delta x = \pm 0.02x$, and Δy equal the error in y, i.e. $\Delta y = \pm 0.02y$. Then the percent purity is given by

$$\% \text{ purity} = \frac{1}{1 + \frac{y + \Delta y}{x + \Delta x}} \cdot 100$$

However, in all cases considered in the thesis $x >> y$. Hence, $x + \Delta x >> y + \Delta y$. This implies that as x becomes greater than y, i.e. as the purity of the chloroacetic acid increases, the error in the measurement of the percent purity decreases. In

fact, when the chloroacetic acid is ca. 95% pure, the error in the measurement is about ± 0.15%.

Pg. 57

The absorption peaks of all solutes in D_2O are not directly related to the τ-scale. The major peaks of the phenyl proton absorptions were used to calibrate these spectra, and each absorption was then given an approximate τ value. These calibrations assume that absorption peaks do not change position with change in solvent but this assumption may not be justified.

Pg. 79

The term "chemical shift" is misused throughout the thesis. Chemical shift (δ) is given by

$$\delta = \frac{H - H_r}{H_r}$$

where "H" is the resonant field of the signal being measured at a fixed frequency and "H_r" is the corresponding resonant field for a second proton signal chosen as a reference signal. Hence, the values quoted in the thesis are wrongly designated as "chemical shifts" and should be termed "absorption peaks".