INDOLE 3-DIMETHYLSULFONIUM YLIDS:

A STUDY OF THEIR CHEMICAL AND PHYSICAL PROPERTIES

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Abstract

Synthesis of sulfonium ylids, 3-dimethylsulfonioindolide, 3-dimethylsulfonio-2-methylindolide and 3-dimethylsulfonio-2-phenylindolide were accomplished. Carbon-13 and ^1H nmr of ylids and the related thioethers and sulfonium salts were studied in an attempt to describe the electronic changes occurring within the indole system to accommodate ylid stabilization. In a study of their physical properties, it was discovered that the sulfonium salt $\rightleftharpoons$ ylid system displayed a hysteresis during acid - base titration. The cause for the hysteresis was shown to be a result of covalent hydration (probably of the indole C_2-C_3 double bond). The uv spectra of the ylid and its analogs differed in aqueous and nonaqueous solvents suggesting that a chemical reaction occurred in protic solution. The ^1H nmr of sulfonium salts in protic solvents revealed the formation of a new species in the solution. This new species, upon acid - base titration exhibited a titration hysteresis identical to that previously observed in titration of either sulfonium salt or ylid. The mass spectra of the sulfonium salts and ylids by different techniques (EI, EI with rapid sample heating and FD) were obtained; by the newly developed technique of electron ionization with rapid heating and photoplate ion recording, indole sulfonium salt "hydrates" exhibit ions assignable as sulfonium salt hydrate species.

TO MY MOTHER AND MY FATHER

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I want to express my deepest thanks to Dr. G. Doyle Daves, Jr., for his patient and understanding guidance both in and out of science throughout my graduate study at the Oregon Graduate Center.

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Chapter 1. Introduction

Ylids are a class of organic compounds of considerable theoretical and synthetic importance which have the general formula $R_2\overset{+}{A}\bar{C}XY$ or $R_3\overset{+}{B}\bar{C}XY$, where A is a group VI element, e.g. sulfur, and B is a group V element, e.g. nitrogen and phosphorus.

Phosphorus ylids, which undergo the Wittig reaction (Eq. 1), are considerably more stable than their nitrogen analogs due to an ability to expand their valence shell (see, however, Wolfe[2] and the discussion below) and have been widely used in the synthesis of long chain alkenes and heterocyclic compounds from carbonyl compounds.

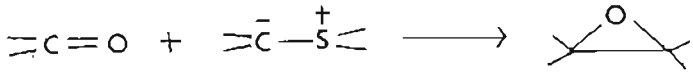
$$\rangle C=O \; + \; Ph_3P=\overset{R'}{\overset{|}{C}}-R \longrightarrow -\overset{|}{C}=\overset{R'}{\overset{|}{C}}-R \qquad \text{Eq. 1}$$

Nitrogen and sulfur ylids, which are generally less stable, readily undergo a variety of rearrangements.

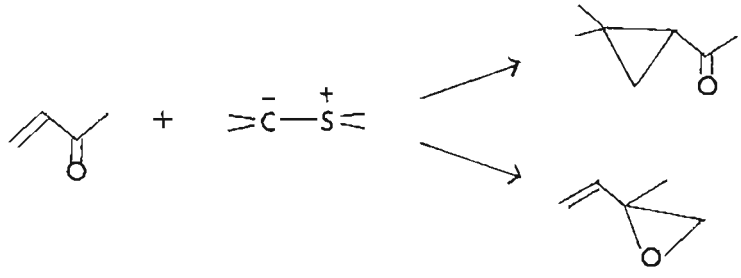
Sulfur ylids are good nucleophilic alkylidene transfer reagents because the sulfonium center stabilizes an adjacent negative charge. This unusual stabilization was observed in the study by Doering[1] who noted that trimethylsulfonium iodide undergoes 98 % deuterium incorporation at 62°C after three hours with deuteroxide catalysis, while tetramethylammonium iodide shows no noticeable incorporation after 504 hours under the same conditions. Tetramethylphosphonium iodide shows 73.9 % deuterium exchange in 3 hours. Doering interpreted these data to indicate that one factor operating in this stabilization is d-orbital resonance in sulfur and phosphorus atoms, which is absent in nitrogen.

Contrary to this interpretation, using ab initio SCF-MO computations performed on the model ylids $\overset{+}{P}H_3\bar{C}H_2$, $\overset{+}{N}H_3\bar{C}H_2$, $\overset{+}{S}H_2\bar{C}H_2$ and $\overset{+}{O}H_2\bar{C}H_2$, Wolfe[2] et. al. found that $\overset{+}{A}$-$\bar{C}$ ($\overset{+}{B}$-$\bar{C}$) bonds are longer than the A-C (B-C) bonds of the stable tautomers for the first row ammonium and oxonium ylids, whereas for the second row ylids, $\overset{+}{A}$-$\bar{C}$ ($\overset{+}{B}$-$\bar{C}$) bonds are shorter than the A-C (B-C) bonds of the tautomers. Also $\overset{+}{A}$-$\bar{C}$ ($\overset{+}{B}$-$\bar{C}$) bonds of the second row ylids were shown to be stronger than those of the first row ylids upon examination of charge distributions and overlap populations. The carbanionic centers of the second row ylids are more nearly planar and more flexible than those of corresponding first row ylids. Wolfe rationalized these various different characteristics of first and second row ylids in terms of group orbital diagrams, which focus upon the stabilizing and destabilizing interactions between a carbanion lone pair and π and π^* AH_n (BH_n) group orbitals. The destabilizing interaction dominates when A (B) is a second row atom.

Sulfur ylids react with electron deficient functional groups, such as carbonyls and Michael acceptors (Eq. 2 and Eq. 3), resulting either in carbonyl addition forming an epoxide or in cyclopropanation.

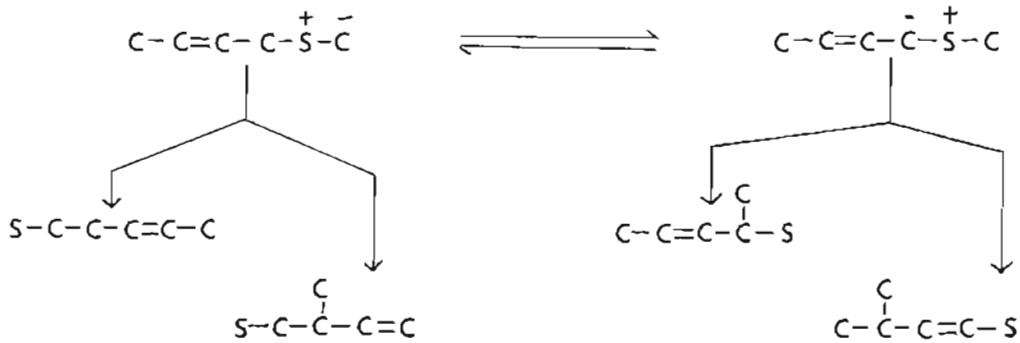


Eq.2

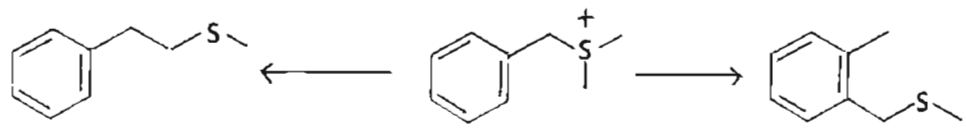


Eq. 3

Allyl- and benzyl sulfonium alkylides undergo isomerization reactions with formation of new carbon-carbon bonds as in the three-centered Stevens rearrangement (symmetry forbidden according to the Woodward-Hofmann rules) and five-centered Sommelet-Hauser rearrangements (symmetry allowed)[3-7]. (Eq. 4 and Eq. 5) The ability to desulfurize products readily either by elimination using Na/liq.NH_3 or Li/CH_3NH_2 or reduction using excess Raney nickel catalyst also makes this reaction a valuable synthetic transformation in which sulfur is used as a template[8-10]. Thus the versatile character of sulfur ylids has prompted much interest in their applications as synthetic intermediates.



Eq. 4

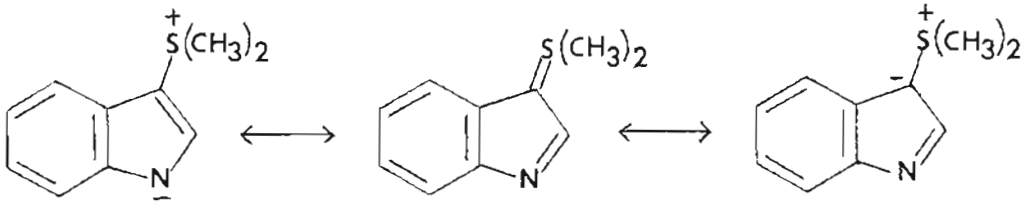


Eq. 5

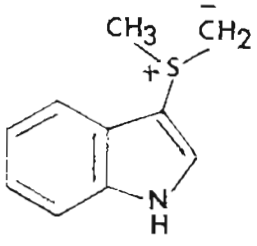
Sulfur ylids can be generated from corresponding sulfonium salts by use of appropriate bases. Ylids possessing only alkyl, vinyl or aryl substituents are unstable and generally must be generated at low temperature, and be utilized in a very short time. In contrast, ylids possessing electron-withdrawing substituents, i.e. carbonyl, cyano, sulfonyl and nitro groups, have enough stabilization so that they are

isolable, storable and often crystalline[11-13]. The shelf life of these ylids depends on the nature and number of anion-stabilizing groups. Also the stability of ylids increases as the substituent at the alpha carbon atom has more capability to delocalize negative charge[12].

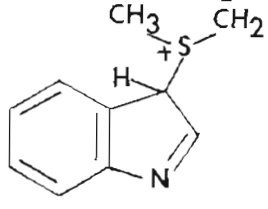
In sulfur ylids, the groups which stabilize the positive charge on sulfur increase the basicity of the corresponding ylids, thus lowering the stability of the carbanion adjacent to sulfur. The stabilization involves delocalization of the positive charge, thus increasing the extent of adjacent negative charge by reducing inductive electron withdrawal and decreasing p_π-d_π overlap with positive sulfur. Electron delocalization by an attached group at any point in the molecule leads to decreased basicity[1,12,14].



1a



1d



1e

In connection with a search for new ways of making carbon-carbon bonds for C-nucleoside synthesis[15], a new stable, crystalline ylid, 3-dimethylsulfonioindolide (1a) was synthesized[16]. When this ylid was

dissolved in deuteriochloroform or deuteriomethanol, the deuterium of the solvent exchanged with hydrogen in the ylid methyl groups at or near room temperature. This requires (a) the intermediacy of a methylidene ylid (1d and 1e) which must be present in equilibrium with ylid 1a and (b) that the ylid be sufficiently basic to remove a proton (deuteron) from the solvent (in this case $CDCl_3$ or CD_3OD). During the exchange reaction in CD_3OD, no ylid decomposition was observed indicating that the intermediate formed is probably 1d rather than 1e since 1e would be expected to undergo rapid Sommelet-Hauser rearrangement to produce 4-methylthiomethylindole[14].

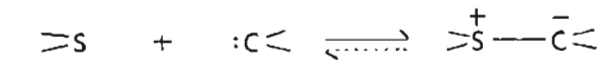
It is unique that a stable, crystalline ylid has such a high basicity; the pKa of the conjugate acid of 1a is 11.1. Thus 1a is at least three pKa units more basic than any carbonyl stabilized sulfonium ylid for which data are available[11,12,17,18].

This unusual property of 3-dimethylsulfonioindolide prompted a further study which includes synthesis of analogous ylids and the study of their spectroscopic and other unique physical properties.

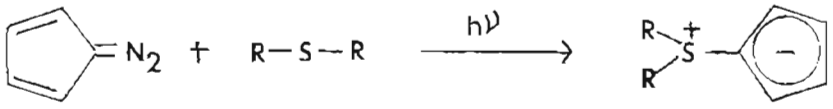
Chapter 2. Synthesis of 3-Dimethylsulfonioindolide and Its Analogs

The general method of ylid synthesis is the removal of a proton from the corresponding sulfonium salt by use of an appropriate base. Choice of the exact base depends largely on the basicity and structure of the ylid being generated. For stabilized sulfonium ylids, alkoxide bases in the corresponding alcohol or sodium hydroxide in anhydrous solvent are frequently used. For nonstabilized ylids, irreversible ylid generation requires the use of an anhydrous strong base, e.g. an organolithium, after which usually follow prompt use of the ylid generated *in situ*[10].

Another useful approach involves the direct formation of ylids by the addition of a carbene to a sulfide (Eq. 6)[19].



Eq. 6a



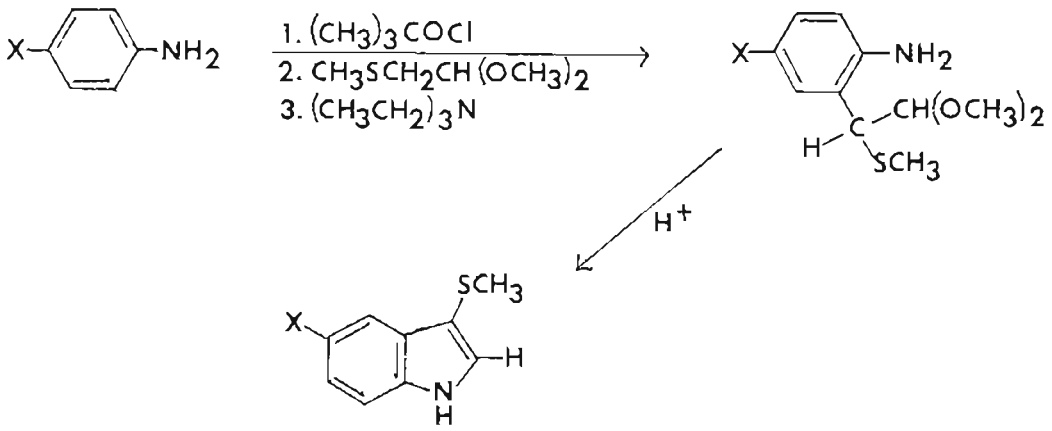
R: $-CH_3$, $-CH_2CH_3$

Eq. 6b

Since the most common method involves base treatment of sulfonium salt, the availability of salts and their precursors are of great importance. Generation of sulfonium salts are frequently carried out by direct alkylation of alkyl thioethers using active alkylating agents such as primary[8,20], allyl[20,21], and benzyl halides[7,20] or α-halocarbonyl[11,22] compounds. Methylations utilizing trimethyloxonium tetrafluoroborate, methylfluorosulfate or dimethoxycarbonium fluoroborate also have often been used[10].

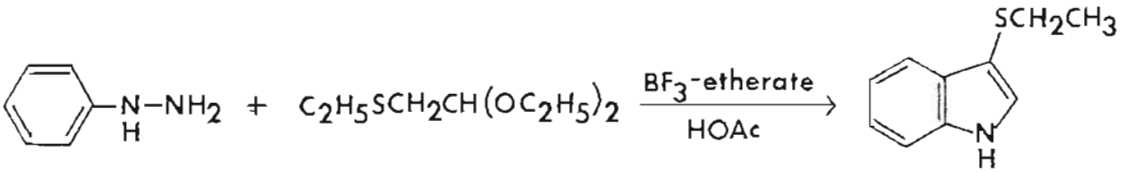
In some instances, the presence of silver salt, i.e. silver fluoroborate or silver perchlorate, helps to eliminate the side reaction (disproportionation) by removing the halide or to otherwise facilitate the reaction[23].

Only a few methods for the preparation of 3-alkylthioindoles, the precursors of indole sulfonium salts, are available. Recently, Gassman[24] introduced a new method for converting aniline and p-substituted anilines into 2-H and 2-substituted indoles by utilizing methylthioacetaldehyde (Scheme 1).



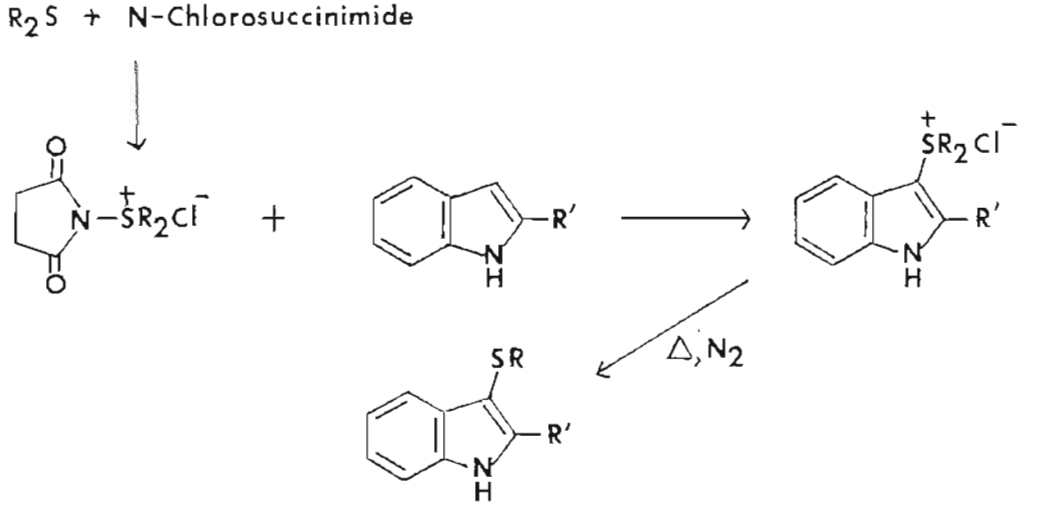
Scheme 1. Gassman Synthesis of 3-Methylthioindoles

Before this method was developed, a modification of the classical Fisher indole synthesis, in which phenylhydrazine in acetic acid was condensed with ethylthioacetaldehyde diethylacetal in the presence of boron trifluoride etherate, yielded 3-ethylthioindoles[25](Scheme 2). The utility of these two related reaction which produce 3-alkylthioindoles largely depend upon the availability of the appropriate alkylthioacetaldehyde diethylacetal.



Scheme 2. Modified Fisher Synthesis of 3-Ethylthioindoles

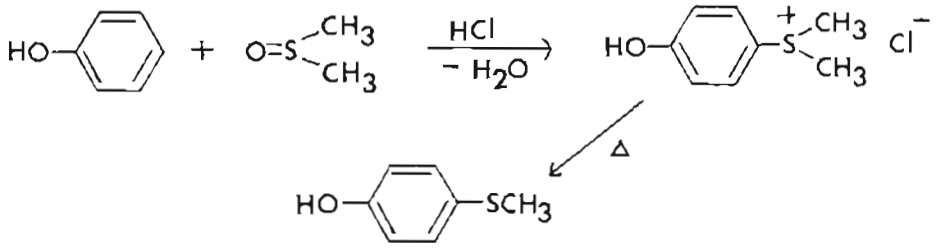
For the preparation of 3-dialkylsulfonium salts of indole, Tomita[26] reacted indoles with succinimidodiethylsulfonium chloride in dichloromethane or chloroform at -20°C under nitrogen. From this reaction 3-diethylsulfonioindole chloride was obtained, and subsequent heating of the sulfonium iodide at 150°C in nitrogen produced 3-ethylthioindole (Scheme 3).



Scheme 3. Reaction of Indole with Succinimidodiethylsulfonium Chloride

Another direct approach for sulfonium salt synthesis is illustrated by the condensation of dimethylsulfoxide with phenol in the pre-

sence of hydrogen chloride gas which produces dimethyl-(4-hydroxyphenyl)-sulfonium chloride which can be subsequently converted to 4-hydroxyphenylthiomethyl ether by heating[27] (Scheme 4).



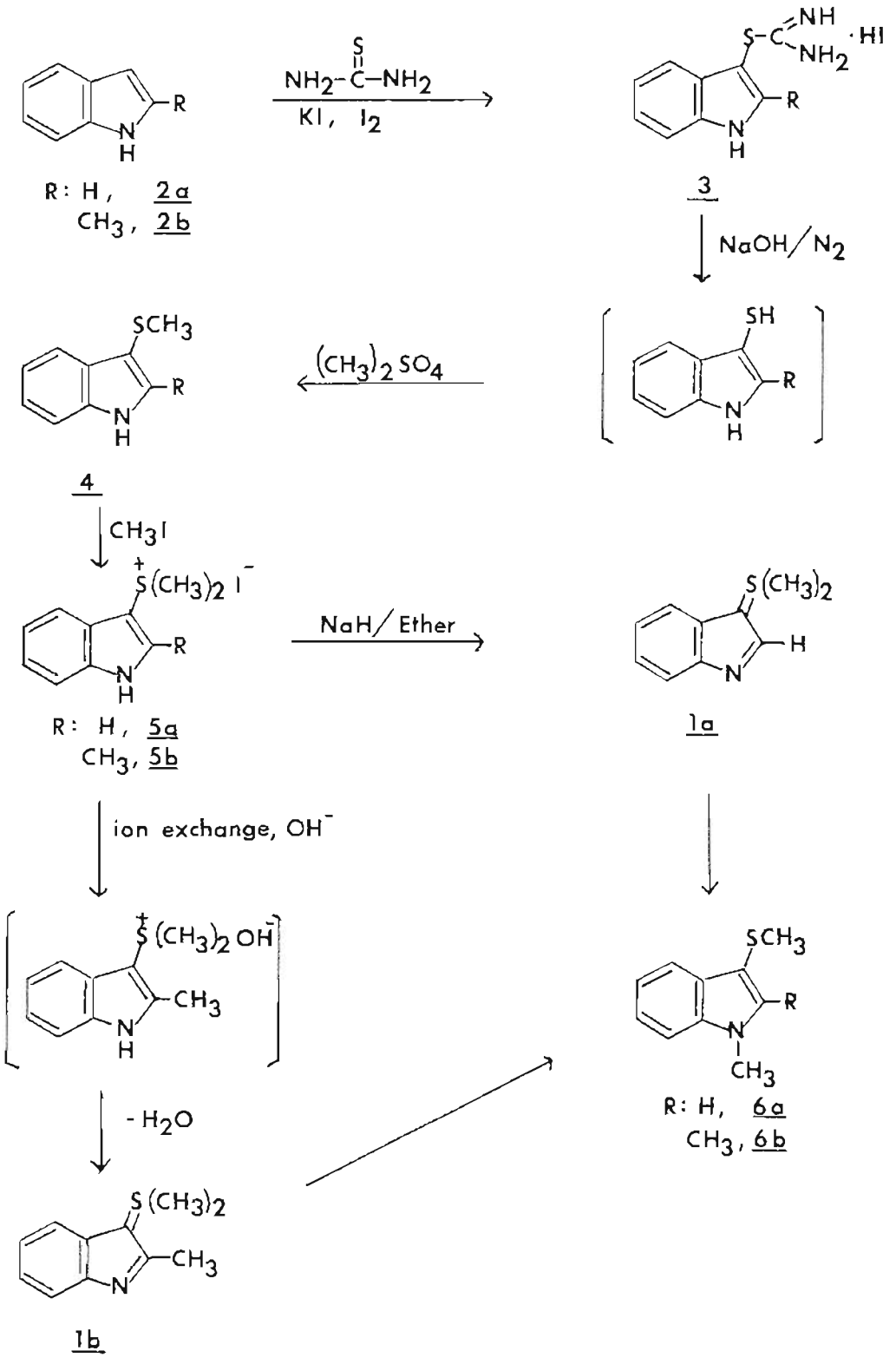
Scheme 4. Condensation of Dimethylsulfoxide and Phenol

We opted to use the method designed by Harris[28] to prepare 3-alkylthioindoles because of easy availability of its starting materials and mild reaction conditions. The prepared 3-alkylthioindole was then further alkylated to produce a 3-dialkylsulfonioindole halide, which subsequently was treated with either sodium hydride in ether or an appropriate ion exchange resin to produce the corresponding ylid (Scheme 5).

Indole and thiourea were treated with one equivalent of iodine-potassium iodide reagent at room temperature to give S-(3-indolyl)-isothiouronium iodide (3a) as light pink crystals. Treatment of 3a with aqueous sodium hydroxide at 80 - 100°C under nitrogen followed by alkylation of the intermediate thiolate anion using dimethyl sulfate produced 3-methylthioindole (4a) which was purified by vacuum distillation. 3-Methylthioindole (4a) was identified by its ^{1}H nmr spectrum in $CDCl_3$ which showed an S-CH_3 resonance signal at δ 2.24 and H-2 as a singlet at δ 6.82. The success of hydrolysis-methylation largely

depended on the protection of the thiol produced by hydrolysis from the air and/or other oxidizing agents such as iodine. Reacting 4a with an equivalent of methyl iodide gave a quantitative yield of white needle-shaped crystalline 3-dimethylsulfonio-1H-indole iodide (5a). The nmr of 5a in DMSO-d_6/$CDCl_3$ showed downfield shifts of the S-CH_3 resonance to δ 3.47 and H-2 to δ 8.45. Treatment of 5a with aqueous base to form the ylid 1a was not satisfactory since 1a underwent facile rearrangement to 6a during the removal of water. Alternatively, treating 5a in dimethylformamide with sodium hydride in ether at $0^{o}C$ with work-up of the reaction mixture at or below room temperature produced white crystalline ylid (1a) in good yield. The product 1a was characterized by its nmr spectrum which exhibited characteristic signals at δ 3.07 (6H, s, S-Me_2) and δ 8.02 (1H, s, H-2), and its mass spectrum which showed a molecular ion at m/e 177. This ylid 1a was stable for a period of months if kept in a freezer and protected from oxygen and water.

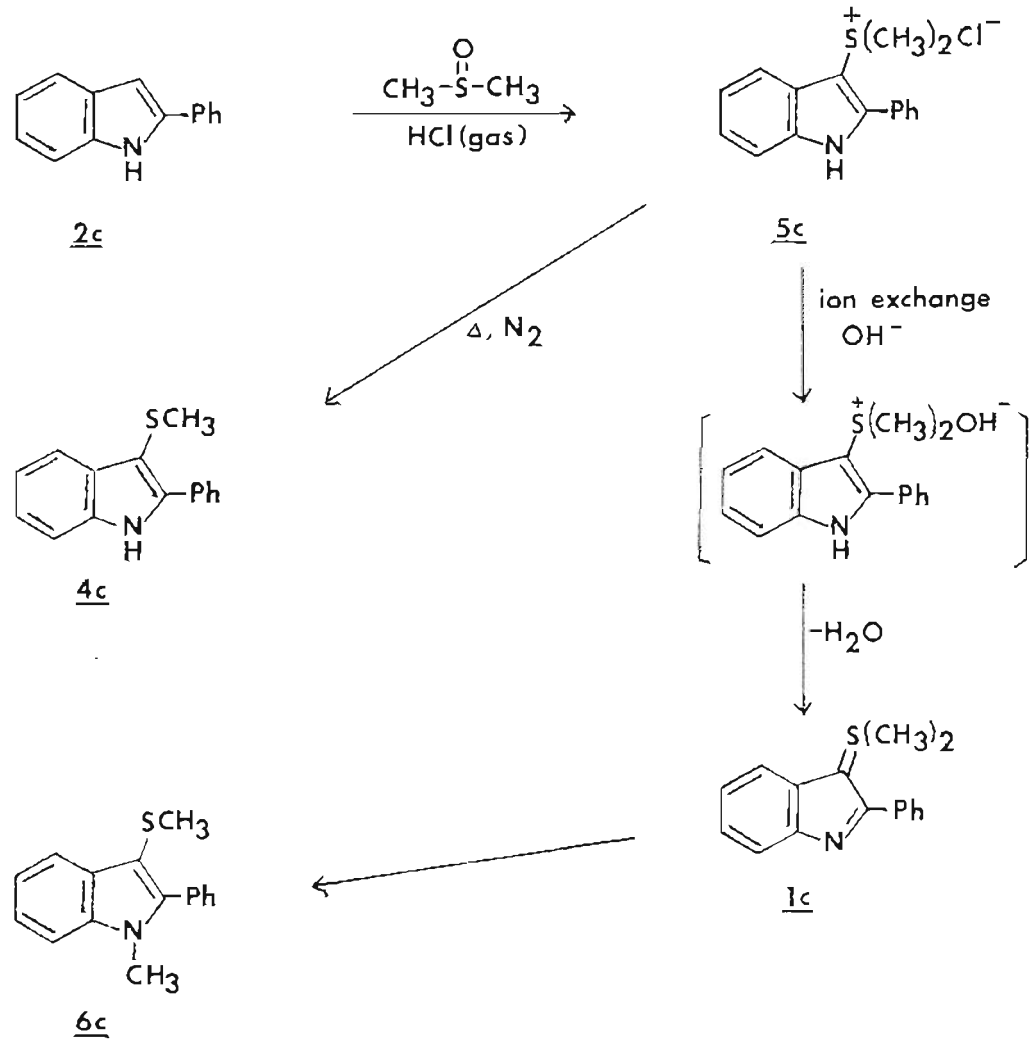
For the series of compounds derived from 2-methylindole (2b), the same procedure as used in the indole (2a) series was applied to obtain 3-methylthio-2-methylindole (4b) with ^1H nmr ($CDCl_3$) showing δ 2.04 (C_2-CH_3) and δ 2.15 (S-CH_3) for its methyl groups and 3-dimethylsulfonio-2-methylindole iodide (5b) with methyl signals in ^1H nmr spectra (DMSO-d_6/$CDCl_3$) at δ 2.65 (C_2-CH_3) and δ 3.40 (S-CH_3). Treatment of 5b with either aqueous base or sodium hydride in anhydrous solvents produced a dark mixture containing ylid 1b. However, attempts at purification caused the ylid to undergo rearrangement to 6b. Therefore, the problem was overcome by using minimum amount of work-up at a relatively low temperature. When sulfonium salt 5b was shaken with ion exchange



Scheme 5. Synthesis of Methylthioether, Sulfonium Salt and Ylid in Indole and 2-Methylindole Series

resin (Bio-Rad AG1-X8, OH^- form, in methanol), 3-dimethylsulfonio-2-methylindolide, 1b, was produced in quantitative yield (Scheme 5). This ylid was characterized by its nmr spectrum ($CDCl_3$) which showed δ 2.53 for C_2-CH_3 and δ 2.92 for S-Me_2 and a mass spectrum with a molecular ion at m/e 191.

Application of the method used in the indole (2a) and 2-methylindole (2b) series for the preparation of derivatives of 2-phenylindole (2c) was not satisfactory since 2-phenylindole (2c) seemed to be more susceptible to the oxidation. A direct route for the preparation of 3-dimethylsulfonio-2-phenylindole halide (5c) in which 2-phenylindole (2c) was allowed to react with dimethylsulfoxide in the presence of anhydrous hydrogen chloride has been reported[29] and was successfully used (Scheme 6). The resulting 3-dimethylsulfonio-2-phenylindole chloride (5c) exhibited an ^1H nmr chemical shift for the S-methyl resonance at δ 3.52 (DMSO-d_6/$CDCl_3$). Sulfonium chloride 5c was shaken up with ion-exchange resin (Bio-Rad AG1-X8, OH^- form) to produce 3-dimethylsulfonio-2-phenylindolide (1c) obtained as a light yellow powder. The S-methyl groups of this ylid appear at δ 3.02 in the ^1H nmr ($CDCl_3$). A mass spectrum showed a molecular ion at m/e 253. The ylid 1c rearranged to 6c when exposed to the atmosphere for a prolonged period. 3-Methylthio-2-phenylindolide (4c) was produced as yellow crystals upon heating the sulfonium chloride, 5c, under nitrogen. The S-methyl group of thioether 4c was observed at δ 2.20 in the ^1H nmr spectrum ($CDCl_3$).



Scheme 6. Synthesis of Methylthioether, Sulfonium Salt and Ylid in 2-Phenylindole Series

Chapter 3. Carbon-13 and Hydrogen-1 Nuclear Magnetic Resonance Study of 3-Dimethylsulfonioindolide and Related Analogs

A number of nuclear magnetic resonance (nmr) studies of phosphorus ylids[30-37] and corresponding phosphonium salts[31,33-35] have been undertaken with the goal of improving the description of bonding and electron distribution of these systems[30-40]. Similar, although less extensive, studies have been made of arsonium ylid systems[32,38,41]. Surprisingly, few nmr data (^{1}H [40,42-44] or ^{13}C [40,45]) for sulfonium ylids are available. The present experiments, while undertaken to improve our understanding of the indole sulfonium ylids[16,29], provide useful information relevant to the more fundamental problem of correlating experimental measurements, i.e. ^{1}H and ^{13}C nuclear magnetic resonance chemical shifts, with chemical bonding and electron distribution description of ylids[30-45].

Results

Tables 1 and 2 contain the ^{1}H and ^{13}C chemical shifts respectively for ylids (1), thioether (4) and sulfonium salts (5). The methyl carbon shift in 2-methylindole (Table 2) is sufficiently shielded to clearly separate 2-methyl and S-methyl derivatives, and allow methyl assignment by inspection. Linewidth, intensity and off-resonance data identified the non-protonated carbons. Carbon-7a in 4a was assigned in view of its similarity to C-7a in 3-methylindole (Table 2), as was C-3a, leaving C-3 assigned to the highly shielded (108 ppm) resonance. Protonated C-7 and C-5 give shifts again similar

Table 1

'H Nuclear Magnetic Resonance Chemical Shifts for 3-Dimethylsulfonio-indolides (1), 3-Methylthio-1H-indoles (4) and Dimethyl 1H-Indole-3-ylsulfonium Salts (5)

Compound	Resonance (δ)[a]			
	H-2	2-Me	S-Me	Aromatic
1a	8.02		3.07	7.08-7.20, 7.57, 7.80
1b		2.53	2.92	6.98-7.10, 7,41, 7.65
1c			3.02	7.08-7.20, 7.32-7.68, 7.80
4a	6.82		2.24	7.03-7.10, 7.62
4b		2.04	2.15	6.89-7.01, 7.51, 7.82
4c			2.20	7.07-7.14, 7.30-7.46, 7.68-7.80, 7.98
5a	8.45		3.47	7.27-7.44, 7.66, 8.01
5b		2.65	3.40	7.20-7.32, 7.53, 8.06
5c			3.52	7.36, 7.56-7.76, 8.02

[a]For 1 and 2 $CDCl_3$ was used as solvent; for 3 $CDCl_3$-$(D_3C)_2SO$ was used.

Table 2

^{13}C Nuclear Magnetic Resonance Chemical Shifts for 3-Dimethylsulfonioindolides (1), 3-Methylthio-1H-indoles (4), Dimethyl 1H-Indol-3-ylsulfonium Salts (5) and Related Indoles

Compound	Resonance (δ)[a]										
	C-2	C-3	C-3_a	C-4	C-5	C-6	C-7	C-7a	S-Me	2-Me	2-Ph
Indole[c]	124.1	102.1	127.6	120.5	121.7	119.6	111.0	135.5			
2-methylindole[b]	135.4	100.1	129.6	119.8	120.8	119.6	110.6	136.8		13.1	
2-phenylindole[d]	137.4	98.5	128.2	119.7	121.2	119.1	110.9	136.8			
3-methylindole[b]	121.6	110.9	128.0	118.6	121.6	118.9	110.9	136.0		9.4(3-Me)	
1a	119.91	109.61	132.47	(120.31)	122.31	(119.57)	115.82	146.16	31.30		
1b	119.96	108.94	150.64	(119.40)	(120.15)	(118.96)	114.92	156.70	30.50	15.75	
1c	127.92	79.78	145.84	(119.33)	(120.60)	(117.43)	(117.23)	153.32	28.79		C-1' 134.25 o 129.49 m 128.14 p 128.11
4a	127.7	108.0	128.70	119.18	122.7	120.30	111.57	136.3	20.1		
4b	139.10	103.95	129.96	118.51	121.72	120.17	110.74	135.12	19.63	11.78	
4c	139.67	104.87	(130.94)	119.56	122.94	120.59	111.14	135.59	19.57		C-1'(131.86) o 128.07 m 128.55 p 128.19
5a	133.74	92.62	124.06	118.35	123.58	121.72	113.34	136.51	29.29		
5b	145.89	87.31	124.03	117.73	123.29	121.98	113.04	136.68	29.06	12.74	
5c	146.81	88.13	124.55	118.69	124.01	122.25	113.80	137.19	28.86		C-1' 130.16 o 129.83 m 128.84 p 128.18

[a]P.p.m. downfield from Me_4Si; solvents used were $CDCl_3$ for 1 and $CDCl_3$-$(D_3C)_2SO$ for 4 and 5. Solvents for reference spectra were dioxane for 2-methylindole and $CDCl_3$ for indole and 2-phenylindole.

[b]Data taken from L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," J. Wiley & Sons, Inc., New York, 1972.

[c]Data taken from R. G. Parker and J. D. Roberts, J. Org. Chem. 35, 996 (1970).

[d]Data taken from T. L. Gilchrist, C. W. Rees and C. Thomas, J. Chem. Soc., Perkin I, 8 (1975).

to 3-methylindole. C-4 and C-6 were too close in shift to assign accurately using only their shifts. When their coupled spectra were considered, however, the aromatic coupling patterns had enough symmetry that patterns for C-4 and C-7 (also C-5 and C-6) were of similar character. This allowed assignment of C-4 and C-6 in 4a[46]. Confirmation for the C-2 assignment was present in its coupled spectrum where C-2 exhibited a one-bond J_{CH} of ~183 Hz, well outside the range of typical aromatic coupling of ~160 Hz exhibited by C-4, -5, -6, and -7. Apart from the expected deshielding of C-2 upon substitution (~12 ppm from indole - 2-methylindole or 2-phenylindole) 4b and 4c have shifts similar to 4a. In the coupled spectrum of 4b C-2 shows a quartet of doublets while C-3a and C-7a are featureless broad multiplets. C-5 and C-6 in 4b were identified from their coupling patterns and ordered similarly to their order in 2-methylindole, 3-methylindole and indole. Methylation of 4a results in the salt 5a. C-2 was again confirmed in the coupled spectrum of 5a through a $^1J_{CH}$= 191.4 Hz. C-7a in 5a was assigned based on intensity and expected line position relative to 4a. C-3a was easily distinguished by intensity (longer T_1, smaller intensity in the time-averaged FT experiment). Hence, the effect of methylation was, as expected, felt at C-3, resulting in a 15 ppm shielding.

C-5, C-6 and C-4 in 5a were assigned based on the pattern characteristics in the coupled spectrum. Compounds 5b and 5c were assigned similarly. Phenyl resonances in 4c and 5c were assigned based on intensity and expected proximity of the meta resonances to 128.5 ppm.

The ylids exhibited large enough changes that assignment of C-4, C-5 and C-6 is tenuous. C-3 stands out in all three ylids as well as

the methyls. C-7 was assigned as the most shielded protonated aromatic resonance. Low solubility made detailed coupled spectra impractical to obtain, resulting in the uncertainty in aromatic assignments. The quartenary carbons were sufficiently spread out in shift to allow assignment by inspection.

Discussion

Nuclear magnetic resonance (nmr) chemical shifts for heteroatomic (particularly heterocyclic) compounds are characterized by multiple and complex effects[47,48]. Currently, methods (theoretical and empirical) for rationalizing and/or predicting chemical shifts of such compounds are of only limited utility. Although chemical shifts are influenced by electronic charge densities, efforts to define this relationship adequately to permit correlation of chemical shifts with electron densities at specific nuclei of complex molecules or ions have been particularly disappointing[48,49]. As a result, systematic studies involving chemical shift assignments within series of closely related compounds are important.

S-methyl resonances - The reasonable assumption that the electron demand of the sulfur nucleus and the resulting electron donation by the S-methyl substituents increases in the order thioether (4), sulfonium ylid (1), sulfonium salt (5) is supported by the chemical shifts of the S-methyl hydrogens which exhibit stepwise increases in nuclear shielding according to this ordering (Table 1). The relatively small chemical shift differences (0.4 - 0.5 ppm) between S-methyl hydrogen resonances of ylids 1a - 1c and corresponding sulfonium salts 5a - 5c

suggest an ylid structure in which negative charge distribution minimally involves the dimethylsulfonium center.

The ^{13}C chemical shifts (Table 2) for the various S-methyl substituents do not correlate directly with corresponding hydrogen shifts (Table 1). The S-methyl ^{13}C resonances for thioethers 4a - 4c appear at higher field than the corresponding resonances for the ylids (1a - 1c) in accord with the behavior of the respective hydrogen resonance shifts. However, although the differences are small (1 - 2 ppm), the ^{13}C resonances of ylid (1) S-methyls occur downfield of sulfonium salt (5) S-methyl resonances in both the C-2H (a) and C-2 Me (b) series.

C-2 Substituents - The ^{1}H chemical shifts for C-2H (compounds, 1a, 4a and 5a) and for C-2 Me (compounds, 1b, 4b and 5b) exhibit the same order of shielding, 4 < 1 < 5, seen for the S-methyl ^{1}H resonances. And as with the S-methyl resonances, the ^{13}C resonances for C-2 methyl shows an inverted order, i.e. 4b < 5b < 1b, in which the ylid substituent is most shielded. The C-1' carbon of the C-2 phenyl substituent shows still a different order of nuclear shielding (5c < 4c < 1c) emphasizing the complexity of factors determining chemical shifts in these compounds.

Effects on C-2 and C-3 of substitution at these sites - It is well established that C-2 of indole is relatively electron deficient whereas C-3 is the site of highest carbon electron density[49]. As shown by the reference data in Table 2, the chemical shifts for these carbons reflect this property with C-2 of indole exhibiting a chemical shift of δ 124.1 and C-3 appearing at higher field, δ 102. Methyl or phenyl substitution at C-2 causes a substantial (11 - 13 ppm) downfield shift

of the C-2 resonance and an upfield shift of smaller magnitude (2 - 4 ppm) of the C-3 resonance. Introduction of an S-methyl group at C-3 results in an additional small (3 - 4 ppm) downfield shift of the C-2 ^{13}C resonance. Substitution at C-3 of S-methyl increases the shielding at C-3 by 4 - 6 ppm. Addition of a second methyl group at sulfur forming sulfonium salts, 5a - 5c, causes the ^{13}C resonance of C-2 to move downfield an additional 4 - 7 ppm and C-3 to experience a large upfield shift (~16 ppm). Thus, substitution at C-2 (methyl or phenyl) and/or at C-3 (methylthio or dimethylsulfonium) causes, in every instance, increased shielding at C-2 and (except for substitution of methylthio at C-3) decreased shielding at C-3. These effects are summarized in Figures 1 - 3.

Effects of ylid formation on ^{13}C shifts of pyrrole ring carbons - Perhaps the most striking result of the present study is the fact that all four carbons of the indole pyrrole ring (C-2, C-3, C-3a and C-7a) experience substantially equal changes in nuclear shielding as a result of the transformation from sulfonium salt to ylid. Figure 1 shows these changes diagramatically for the 2-methylindole pair 1b and 5b. In this pair, C-2 of ylid 1b is deshielded 26 ppm with respect to C-2 of sulfonium salt 5b. The corresponding changes in chemical shifts for C-3, C-3a and C-7a are 22, 27 and 20 ppm respectively; however, in each of these cases the ylid carbons experience more shielding than the corresponding sulfonium salt carbons. The pyrrole ring carbon resonances of the C-2H ylid-sulfonium salt pair (1a and 5a) exhibit similar behavior (Fig. 2), although the magnitudes of the chemical shift diffe-

rences are smaller than in the C-2 methyl compounds. The C-2 phenyl pair (1c and 5c) show a significantly different behavior (Fig. 3) in that C-3 as well as C-2 is deshielded in ylid 1c ; C-3a and C-7a are shielded in comparison with corresponding carbons of sulfonium salt 5c as was observed in the other series.

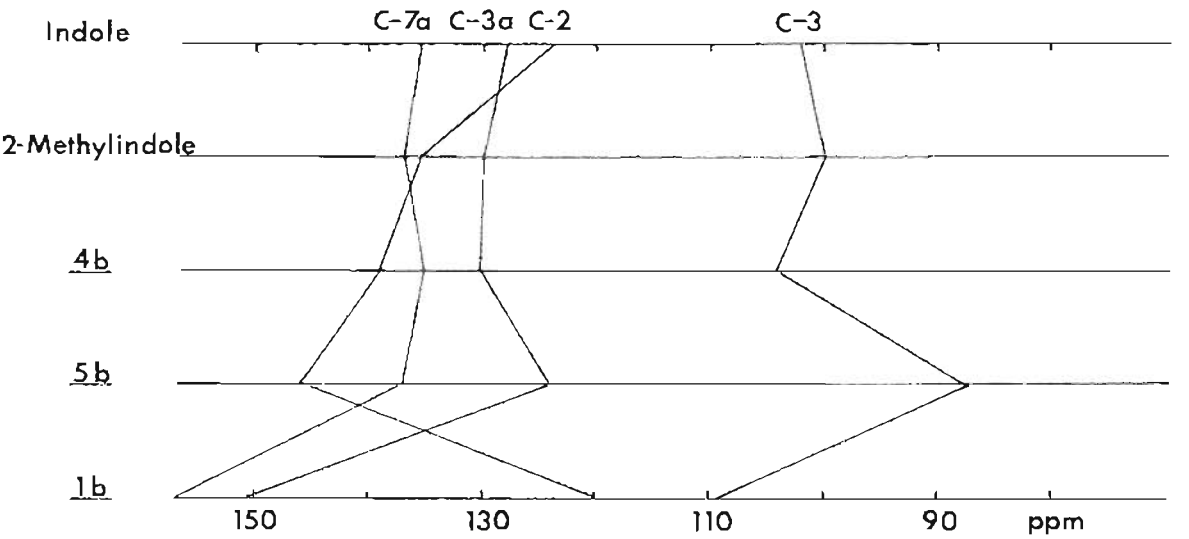


Fig. 1. Comparison of ^{13}C Chemical Shift in 2-Methylindole Series

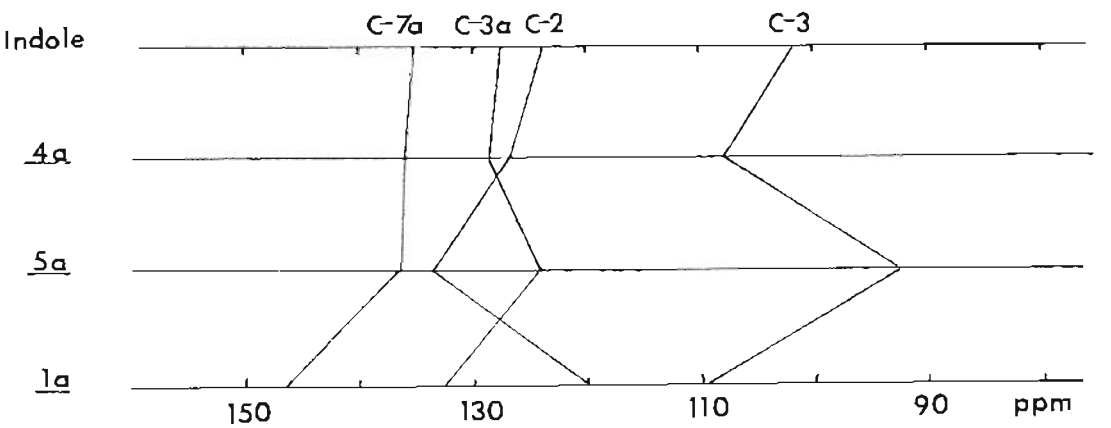


Fig. 2. Comparison of ^{13}C Chemical Shift in Indole Series

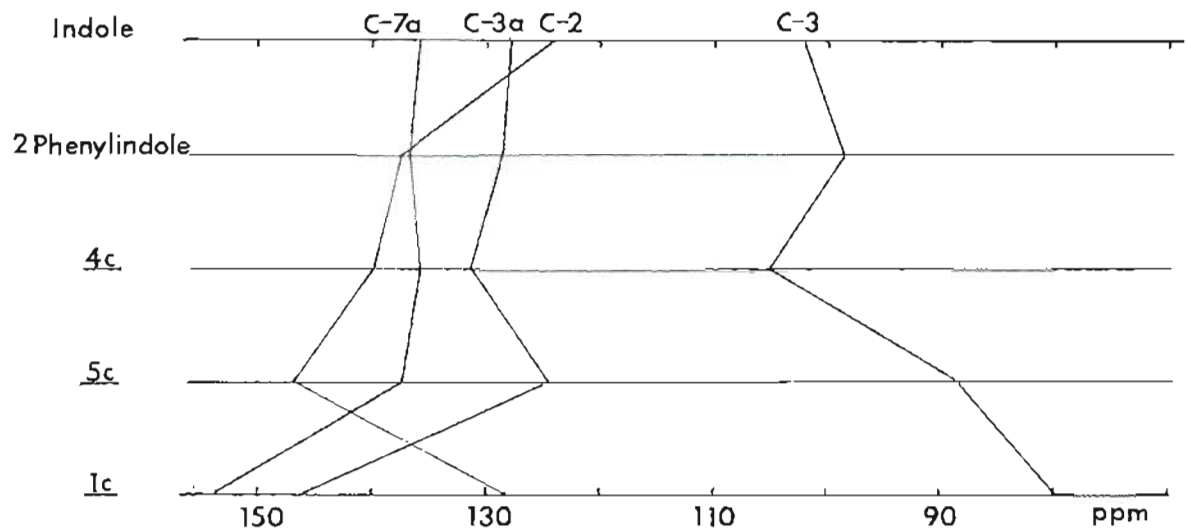


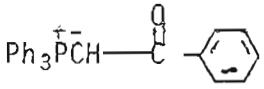
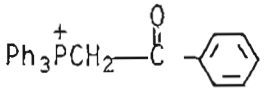
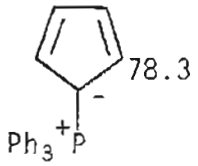
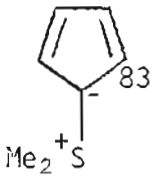
Fig. 3. Comparison of ^{13}C Chemical Shift in 2-Phenylindole Series

While the other carbons of the carbocyclic ring (C-4, C-5, C-6 and C-7) are only slightly shifted as result of ylid formation, the large shielding changes experienced by the bridgehead carbons C-3a and C-7a are indicative that the significant electron density change associated with the transformation (sulfonium salt $\rightleftharpoons$ sulfonium ylid) affects not only the 'annelated' enamine system (i.e. N-1, C-2 and C-3) but the aromatic benzene ring system as well.

Comparison with phosphonium salt - phosphonium ylid systems - There is a dearth of ^{13}C chemical shift data for other sulfonium salt - sulfonium ylid pairs[40,45]; as a result it is useful to use data for selected phosphonium salts and phosphonium ylids as models in considering the present results. In Table 3 are representative data from phosphorus ylid studies and, in addition, ^{13}C chemical shift data for two sulfur ylids, dimethyloxosulfonium methylide[40,51] and dimethylsulfonium cyclopentadiene[45], previously studied.

Table 3

^{13}C Chemical Shifts for Selected Model Compounds

A	$Me_3\overset{+}{P}\overset{-}{C}H_2$ -2.3	$Me_3\overset{+}{P}CH_3$ 11.3	Ref. 32,35,36
B	$Ph_3\overset{+}{P}\overset{-}{C}H_2$ -4.1	$Ph_3\overset{+}{P}CH_3$ 11.4	Ref. 33
C	$Me_2\overset{+}{S}\overset{-}{C}H_2$ 32.8	$Me_2\overset{+}{S}CH_3$ 5.9	Ref. 40,51
D	 50.5 184.8	 38.7 196.5	Ref. 31,37
E			Ref. 31,36
F			Ref. 45

Entries A and B in Table 3, trimethyl- and triphenylphosphonium methylides and corresponding phosphonium salts, show the expected deshielding of the carbanionic carbons as compared with the protonated forms[32,33,35,36]. However, in sharp contrast, the carbanionic carbons of the "stabilized" triphenylphosphonium phenacylide[31,37](entry D) appears 12 ppm downfield of the corresponding carbon of the phosphonium salt. In this phosphonium ylid - phosphonium salt pair, it is the carbonyl carbon which is deshielded as a result of converting the phosphonium salt to ylid. Thus, changes in carbon shielding associated with the transformation from phosphonium salt to ylid (or vice versa) parallel those observed in the present study for the 3-dimethylsulfonium indole salt - ylid system (1 - 5), i.e. increased shielding of the carbanionic carbon (C-3 in the indole series) and decreased shielding of the "carbonyl" carbon (C-2 in the indole series). That the two systems are comparable is indicated by the close similarity of chemical shifts in the cyclopentadiene ylids (Table 3, E and F)

Conclusion - While the hydrogen chemical shifts for compounds 1 - 3 are qualitatively consistent with a simple model associating changes in hydrogen nuclear shielding with corresponding changes in molecular electron densities and/or distribution, the failure of corresponding ^{13}C chemical shifts to correlate similarly is evidence that much more complex relationships are involved. The relatively small effects observed for S-methyl resonances suggests limited involvement of sulfur in delocalizing the ylid anionic charge while the significant chemical shift changes observed for each of the four carbons of the indole pyrrole ring are consistent with electron delocalization throughout

this system. The striking differences in ^{13}C magnetic resonance behavior of the C-2 phenyl series as compared with the C-2H and C-2 methyl compounds, especially in view of the general similarity of other properties, is further evidence of the complex interplay of factors which determine ^{13}C chemical shifts[47,48].

Chapter 4. Titration of 3-Dimethylsulfonioindolide and Its Analogs with Acids and Bases

Since 3-dimethylsulfonioindolide, 1a, displayed a highly basic character by exchanging deuterium from solvent, e.g. $CDCl_3$ or CD_3OD, with its S-methyl protons[16], a titration was carried out to measure the pKa of its conjugate acid. The sulfonium ylid (1a) was dissolved in methanol, and first titrated with 0.10 N hydrochloric acid, then back titrated with 0.10 N sodium hydroxide[52] and the procedure was repeated establishing the stability of the system and the reversible ylid $\rightleftharpoons$ sulfonium salt formation.

Surprisingly, a "hysteresis" was observed during this titration (Fig. 4); that is, back titration (i.e. titration of the sulfonium salt with base) gave a different set of pH values from the forward titration (titration of the ylid with acid), whereupon a second forward titration retraced the pH value of the first. When other related sulfonium salts, i.e. 3-dimethylsulfonio-2-methylindole iodide (5b), 3-dimethylsulfonio-2-phenylindole chloride (5c) and 3-diethylsulfonioindole iodide (7)[53] were titrated in the same manner, a hysteresis was observed in all cases (Fig. 5 - 7). Within these hysteresis 'loops', pH drifted toward the middle of the loop in the cases of both forward and backward titrations, indicating that if enough time was allowed to equilibriate the system, a single titration curve may be traced. Calculations of pKa's from the sodium hydroxide titration curves gave pKa's for the conjugate acids (i.e. for sulfonium salts) of ylids in the range of 10.88 - 11.28 (Table 4). This pKa is an overall equili-

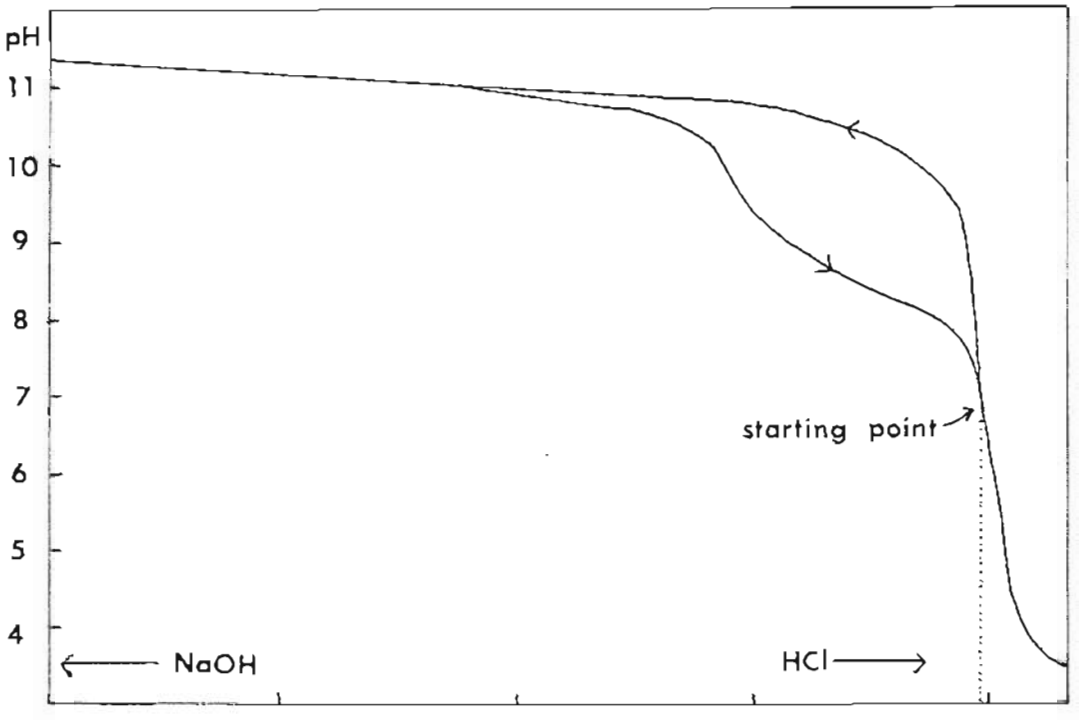


Fig. 4. Titration of Indole Sulfonium Salt (5a) $\rightleftharpoons$ Ylid (1a)

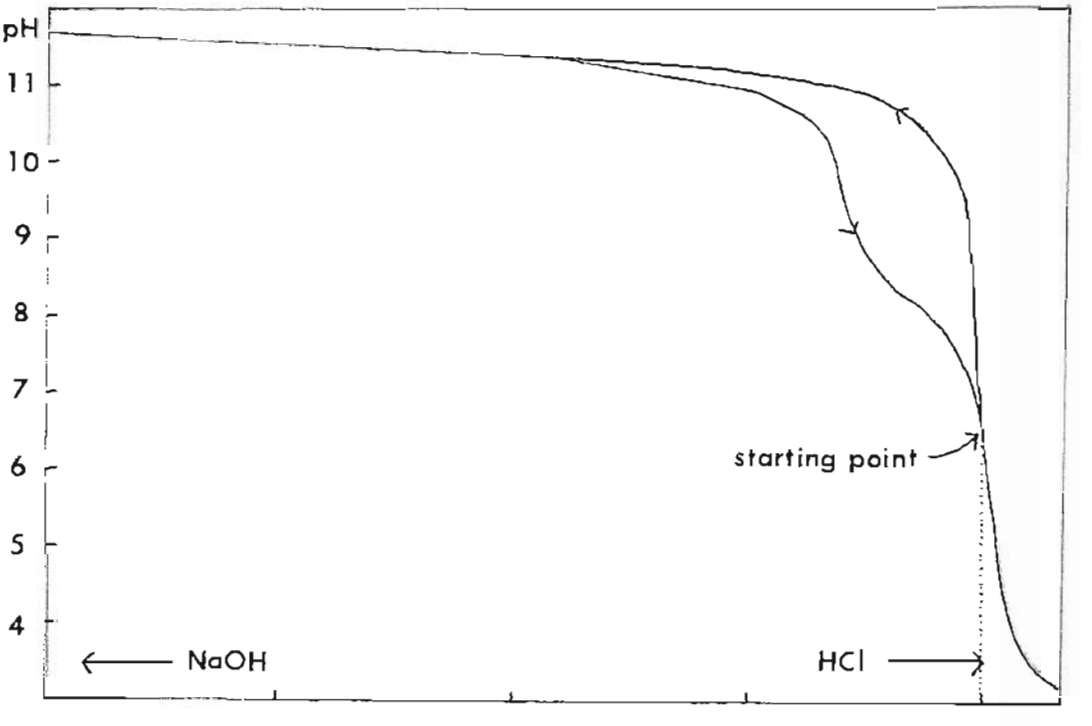


Fig. 5. Titration 2-Methylindole Sulfonium Salt (5b) $\rightleftharpoons$ Ylid (1b)

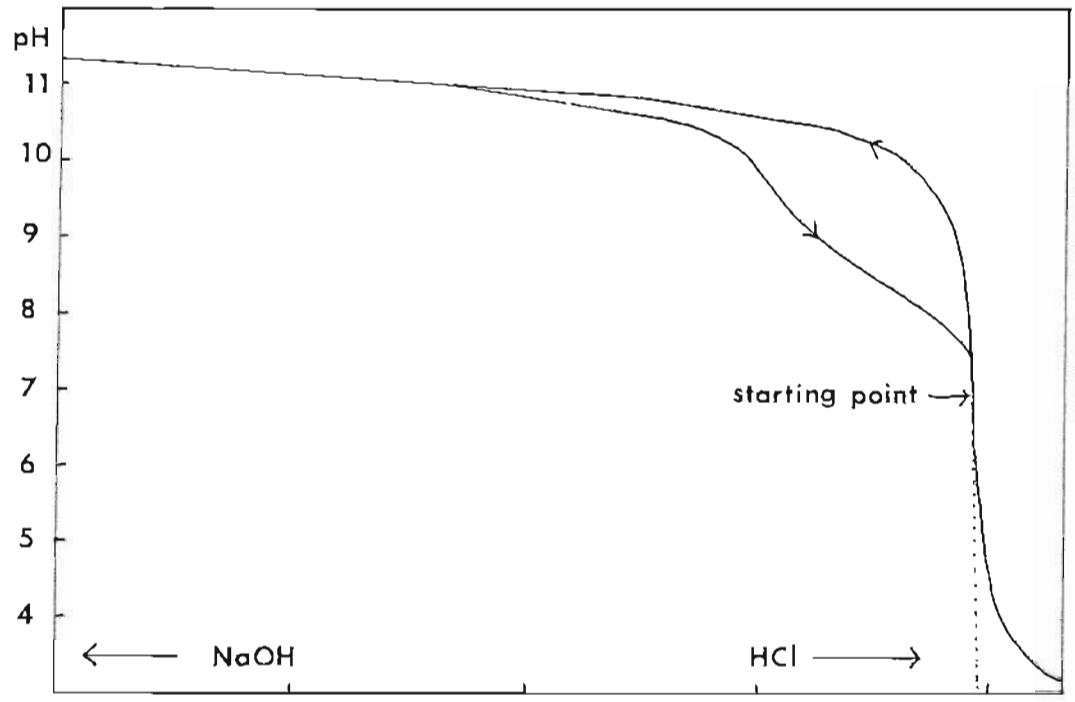


Fig. 6. Titration of 2-Phenylindole Sulfonium Salt (5c) $\rightleftharpoons$ Ylid (1c)

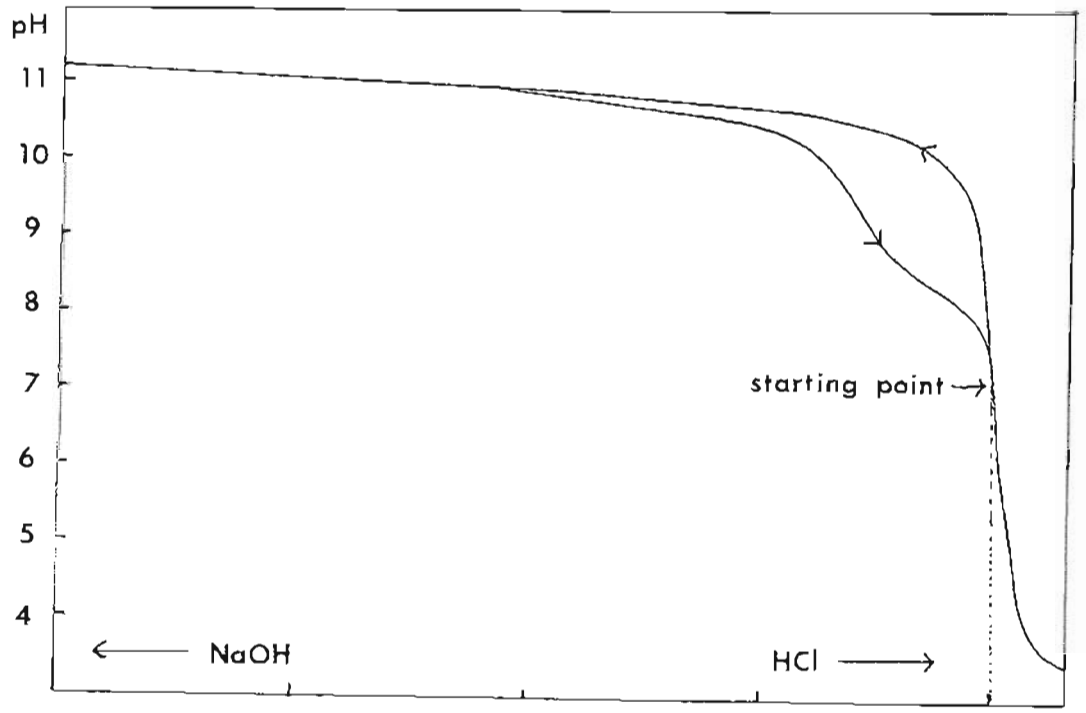


Fig. 7. Titration of Diethylsulfonium Salt (7) $\rightleftharpoons$ Ylid

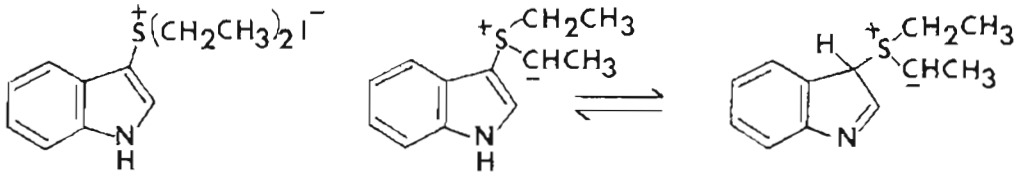
brium value which is a composite of pKa's involved in the titration[57]. This value is considerably higher than the carbonyl stabilized sulfonium ylids which are in the range of 6.46 to 8.13 [11,12,17,18].

Table 4. pKa for Deprotonation of Indole Sulfonium salts

compounds	pKa
5a	11.09
5b	11.28
5c	10.88
7	11.02

The observation of hysteresis upon acid-base titration indicates that a slow and quantitative interconversion of two or more substances occurs. These substances may be (a) the products of ring-opening and closing reactions, (b) tautomers, or (c) a compound and its covalent hydrates[54]. On the basis of the structures of the sulfonium salts, 5a - 5c, and ylids, 1a - 1c, the first-noted possibility involving an equilibrium ring-chain relationship appears to be ruled out.

Examination of tautomerization as a cause of hysteresis - 3-Diethylsulfonioindole iodide 7, also displayed a hysteresis (Fig. 7)

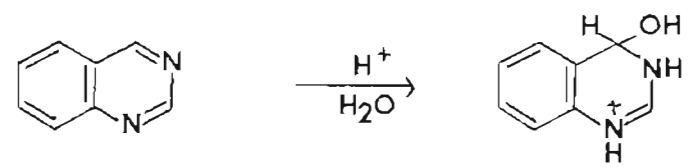


7 8a 8b

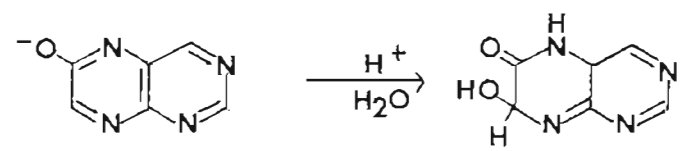
and highly basic pKa, 11.02. If slow equilibriation of tautomers, such as 1a, 1d and 1e, were the source of the hysteresis, it was expected that diethylsulfonium iodide would not display the effect since the possibility of an ethyl carbanion as 8a or 8b existing in a relatively free state is very small when compared to that of a methyl carbanion[55].

Although the deuterium exchange with protons of S-methyl groups had been observed for indole sulfonium ylid[16], 1a, and 2-phenylindole sulfonium ylid[29], 1c, in $CDCl_3$ and CD_3OD, the contribution of tautomers 1d and 1e to the hysteresis does not seem to be important.

Examination of covalent hydration in sulfonium salts and ylids - Covalent hydration is a phenomenon whereby one molecule of water adds across C=C, C=N or C=O bond of a dissolved molecule. Albert first reported the phenomenon[56]. The observation that quinazoline (Eq. 7a), and some pteridines (eg. Eq. 7b), had ultraviolet spectra and ionization constants that were absolutely incompatible with the orthodox formulation of these molecules, led him to conclude (in 1955) that in solution, water was being added across the C=N bond of at least one ionic species in each case[56]. Indication of covalent hydrations are anomalous ionization constants (pKa), ultraviolet spectra, infrared spectra and/or nuclear magnetic resonance spectra. Of these, the



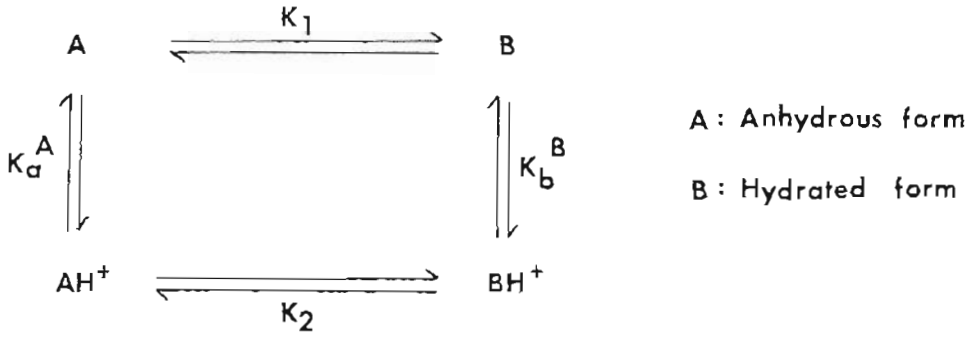
Eq. 7a



Eq. 7b

first two are initially the most useful. Quite different from non-covalent retention of water in an analytical specimen, covalent hydration is often unrecognized in elemental analysis because the hydrated anionic (cationic) species is seldom subjected to analysis[57].

The complex equilibria involved in hydration can be the cause of anomalous ionization constant (pKa)[57], such as the pKa's observed in the present study (Scheme 7).



Scheme 7. Equilibria Involved in Covalent Hydration

When pKa is determined from potentiometric titration measurements in which the solution is allowed to come to equilibrium before reading, an overall $pKa^{equil.}$, which is the composite of pKa^{A}, pKa^{B}, pK_1 and pK_2 of the system, can be obtained. Usually A and BH^+ are found to be stable species, while B and AH^+ rapidly lose and gain water respectively[57]. Hydration should always be suspected when potentiometric readings, made during determination of pKa values show a drift[58].

When addition of water occurs across a double bond (C=C, C=N and C=O), the ultraviolet spectrum of the hydrate in water can be vastly different from the spectrum of the anhydrous substance in nonaqueous solvent, such as cyclohexane, piperidine and dioxane[58,59]. Therefore, comparison of ultraviolet spectra in water and in anhydrous solvent is a useful method to detect covalent hydration.

To determine the site of the covalent hydration, use of analogs of the original compound is valuable. For example, insertion of a methyl group at the site where nucleophilic attack (by OH^- or H_2O) occurs during hydration considerably hinders the addition of water, thus lowering the percentage of the hydrated species present at equilibrium and also decreasing the rate of hydration[58,59]. This effect, although partly electronic, has been shown to be largely steric and apparently is caused by steric acceleration of the elimination of the hydroxyl group. The effect of such a methyl group on the pKa value is also revealing because a decrease in the amount of the hydrated species causes a decrease in pKa value, whereas a methyl group is otherwise base-strengthening. But, so far, no example is known with certainty in which a methyl group suppresses hydration entirely[58].

In order to determine the cause for the hysteresis exhibited upon acid-base titration of indole sulfonium ylid, 1a, the possibility of covalent hydration was investigated. It seems that one feature necessary for hydration is the presence of an electron-withdrawing center (e.g. $-\overset{+}{S}Me_2$ as in the present case) which causes the π-electron layer to be depleted[57]. As a result, a highly polarized double-bond becomes isolated from Kekule-type conjugation, and reaction typical of

such a bond can take place. The C_2-C_3 double bond of sulfonium salt 5 is polarized as a result of the electron demand of the charged sulfur at carbon-3.

For the purpose of sterically blocking C-2, the most probable site of covalent hydration, an analog of 1a, 3-dimethylsulfonio-2-methylindolide (1b) was prepared and titrated potentiometrically, and its pKa was determined (Fig. 5 and Table 4). Surprisingly, the titration curve was essentially the same as that observed for the 2-H analog, 1a, and pKa, 11.28, was very similar. The slight increase is probably due to the base-strengthening effect of the 2-methyl group. This result indicated that the phenomenon causing the hysteresis is not affected by the steric (or electronic) effect of methyl group substitution at carbon-2. The minimal effect of a C-2 substituent was confirmed by the observation of the same hysteresis and highly basic pKa (10.88) of 2-phenylindole sulfonium salt 5c (Fig. 6). The lower pKa of 5c compared to those of 2-H and 2-methyl analogs is due to the electron-withdrawing character of 2-phenyl substituent.

The observation of a titration hysteresis in each of these three cases (1a - 1c), failed to provide evidence concerning the possibility of covalent hydration; certainly the phenomenon underlying the hysteresis effect shows little sensitivity to steric crowding at C-2.

In related ^{1}H nmr experiments (see Chapter 6), evidence for a new species, prepared by heating aqueous or acidic aqueous solutions of sulfonium salts, 5b, 5c and 7, was obtained. Isolation of these new species -termed "hydrates"- was achieved. Titration of these "hydrates" of 5b and 7 produced the results shown in Figures 8 and 9.

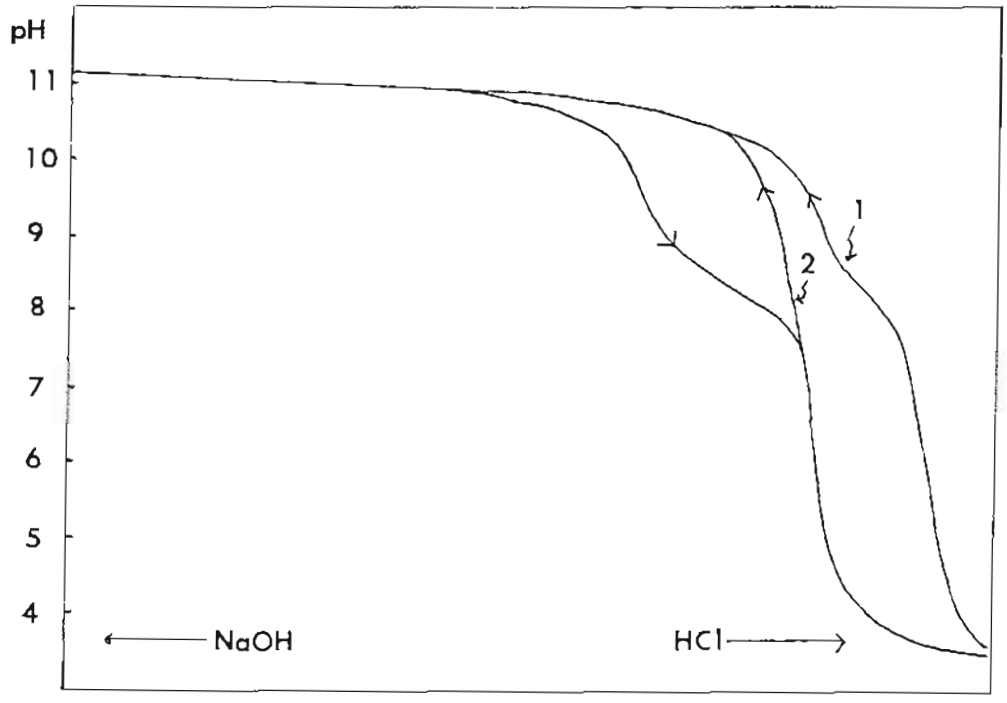


Fig. 8. Titration of 2-Methylindole Sulfonium Salt (5b) hydrate
1. first base titration, 2. second base titration

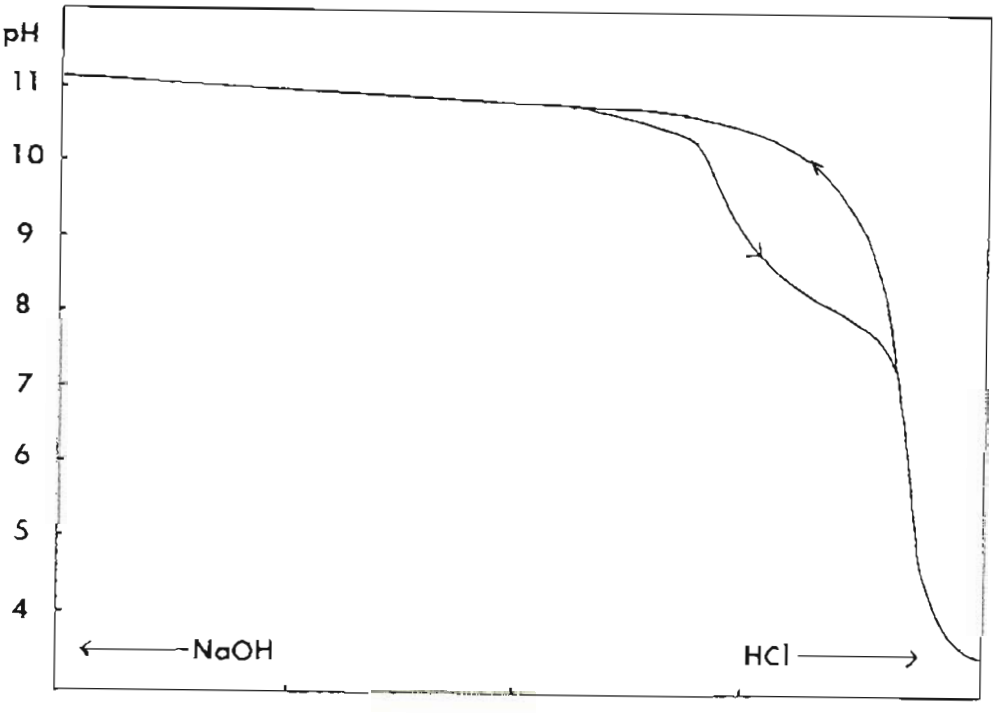


Fig. 9. Titration of Diethylsulfonium Salt (7) hydrate

The near identity of the titration behavior of these species with that of the sulfonium salts (5b and 7) from which they were derived establishes that no important structural changes (e.g. methyl group rearrangements or oxidation) had occurred and strongly suggest that this new species is directly related to the hysteresis phenomenon.

Chapter 5. Ultraviolet Spectra of Methylthioethers, Sulfonium Salts and Ylids

The ultraviolet (uv) spectra of sulfonium salts, 5a - 5c, and sulfonium ylids, 1a - 1c, in aqueous (water) and nonaqueous (dioxane) solvents were obtained to investigate (a) differences of the chromophoric systems and (b) possible effects of protic solvents in the spectra of the sulfonium salts and ylids (Table 5 and Figures 10 - 12).

Spectra of the corresponding 3-methylthioindoles, 4a - 4c, were obtained for comparison. The uv spectra of methylthioethers in dioxane are characterized by broad bands at 272 nm (4a and 4b) and 301 nm (4c) (Table 5). This is similar to the uv spectra of 2,3-dimethylindole, λ_{max}(EtOH) 280 nm[60]. In 4c, the coplanar 2-phenyl group causes the band to shift to the longer wavelength.

Comparison of the spectra of methylthioethers, 4a - 4c, with those of sulfonium salts, 5a - 5c (Table 5), establishes that, in aprotic solvents, the chromophoric systems of the two compound classes are very similar. The uv spectra of 2-H and 2-methylindole sulfonium ylids, 1a and 1b, display an additional absorption maximum (or shoulder) at longer wavelengths when compared to their analogous methylthioethers, 4a and 4b, while the spectrum of 2-phenylindole sulfonium ylid, 1c, was essentially the same as that of the corresponding methylthioether (4c).

2-Methyl and 2-phenylindole sulfonium salts, 5b and 5c, gave uv spectra in dioxane similar to those of the corresponding ylids 1b and

Table 5

UV Spectra of Methylthioethers, Sulfonium Salts and Ylids

Compounds	H_2O, λ_{max}, nm (ε)	Dioxane, λ_{max}, nm (ε)
4a		273 (5510)
5a	223(s) (18900) 260(5520) 275(s) (4570)	279 (5640)
1a	261(6090), 282(s) (2930)	262(7170), 280(5750)
4b		272 (9030)
5b	225(s) (7820) 276(s) (1760) 283(s) (960)	276 (8540)
1b	276(s) (3340) 284(s) (1900)	273(6910) 291(s) (5530)
4c		237(14300), 301(12500)
5c	235(14200), 288(10100)	236(13800), 301(10300)
1c	236(9240), 289(5820)	237(17200), 301(10600)

1c indicating that, in aprotic solvent, the chromophoric systems of the ylids differ little from those of the sulfonium salts (Fig. 11 and 12). In addition, for the 2-phenylindole sulfonium salt, 5c, and ylid, 1c, pair, the maxima in dioxane show shifts of 13 nm to longer wavelength from those in water, in agreement with the expected solvent shift[61] (Fig. 12).

Indole sulfonium ylid, 1a, shows a maximum at 261 nm in both water and dioxane, without the expected solvent shift, suggesting that changes in electron distribution in the ylid system caused by the change in solvents offsets the solvent effect. The sulfonium salt, 5a, shows a 19 nm shift to longer wavelength in dioxane from the spectrum in water, a shift which is larger than the expected solvent shift[61]. This sulfonium salt - ylid pair (5a and 1a) exhibits similar aqueous solution uv spectra, while displaying markedly different spectra in dioxane (Fig. 10).

The most striking effects of solvent change on uv spectra were observed for 2-methylindole sulfonium salt, 5b, and ylid, 1b. For these compounds, while the spectra of the dioxane solutions were comparable to those for other sulfonium salt - ylid pairs (Fig. 11), the aqueous solution spectra indicated the chromophoric system to be radically altered exhibiting only a broad uv absorption envelope with no distinct maxima. These results strongly indicate that water reacts with these compounds in a way which destroys the chromophore giving rise to the long wavelength absorption. The absence of distinct absorption maxima is consistent with the presence of more than one species in the solution.

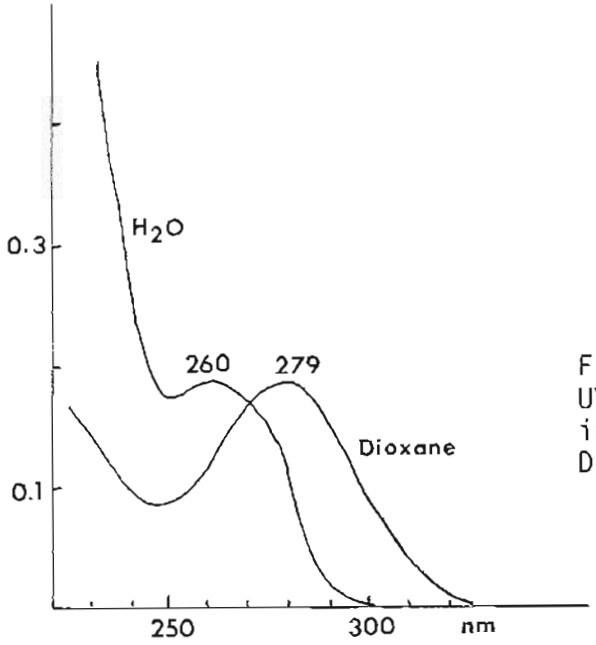


Fig. 10a
UV Spectra of 3-Dimethylsulfonio-indole iodide (5a) in Water and Dioxane

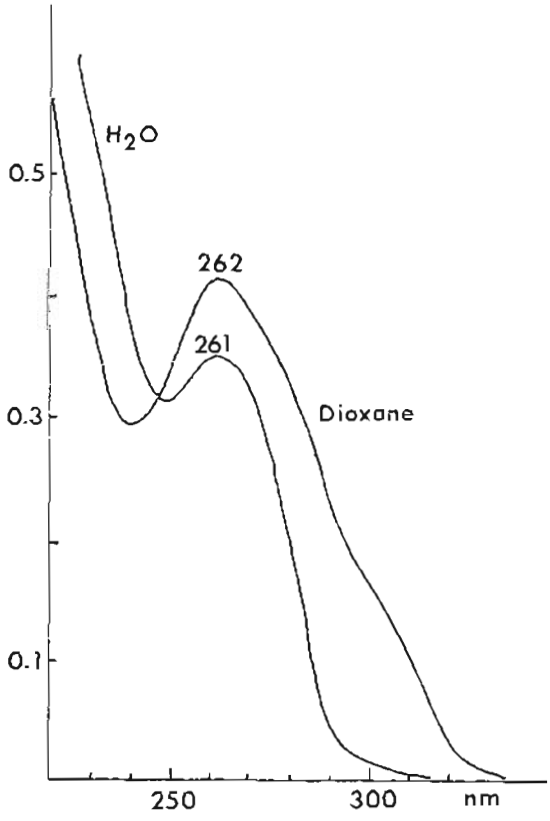


Fig. 10b.
UV Spectra of 3-Dimethylsulfo-nioindolide (1a) in Water and Dioxane

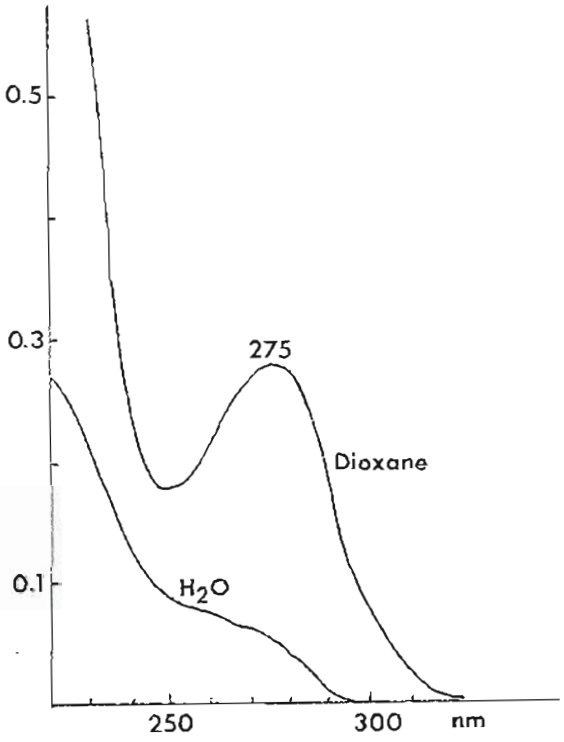


Fig. 11a.
UV Spectra of 3-Dimethylsulfonio-2-methylindole iodide (5b) in Water and Dioxane

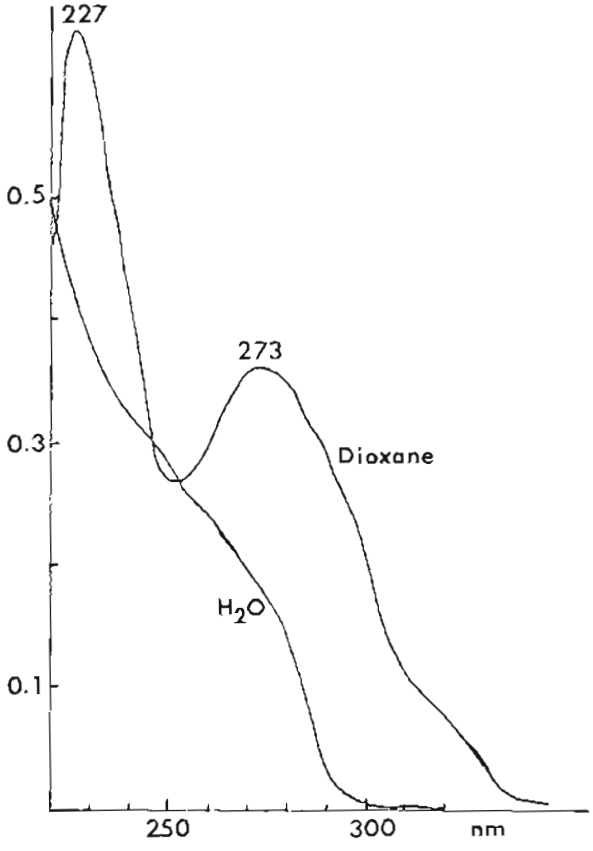


Fig. 11b.
UV Spectra of 3-Dimethylsulfonio-2-methylindolide (1b) in Water and Dioxane

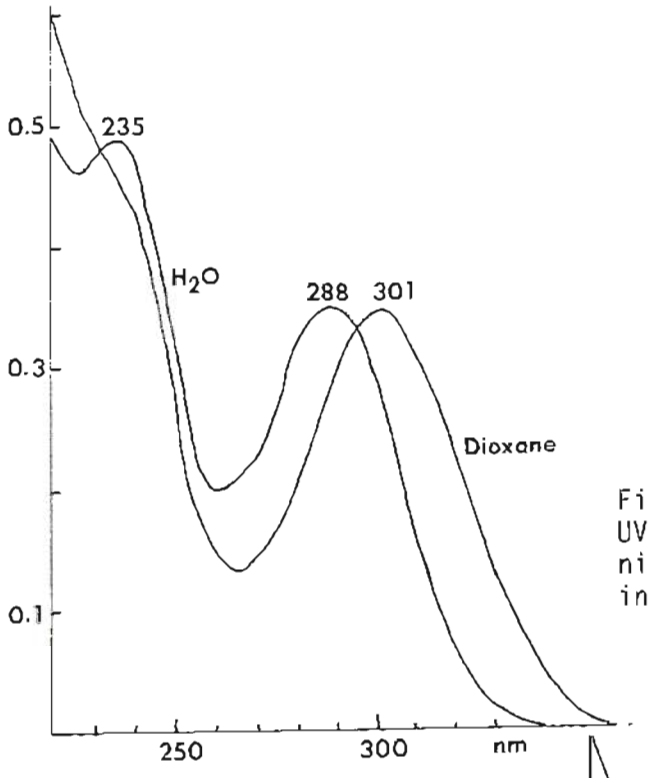


Fig. 12a.
UV Spectra of 3-Dimethylsulfonio-2-phenylindole iodide (5c) in Water and Dioxane

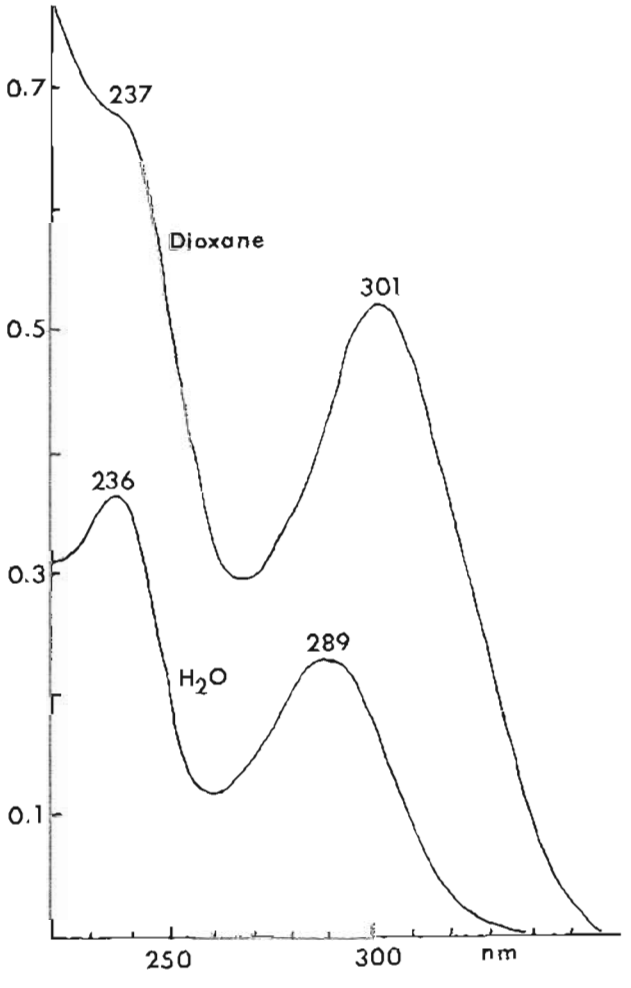


Fig. 12b.
UV Spectra of 3-Dimethylsulfonio-2-phenylindolide (1c) in Water and Dioxane

It is noteworthy that chromophoric systems of these three pairs (1a - 5a, 1b - 5b and 1c - 5c) which possess different C-2 substituents (hydrogen, electron-donating and electron-withdrawing, respectively) are affected differently by solvents.

Chapter 6. ^{1}H Nuclear Magnetic Resonance Study of Sulfonium Salts in Protic Solvents

^{1}H Nuclear magnetic resonance (^{1}H nmr) study of sulfonium salts, 5a - 5c and 7, and sulfonium ylids 1a - 1c in protic solvents was quite revealing (Tables 6 - 9). Although the spectra of ylids in D_2O did not display any important differences from those in aprotic solvents, the nmr spectra of sulfonium salts in D_2O proved to be of special interest. When a solution of 2-methylindole sulfonium salt, 5b, in D_2O was left standing at room temperature for 24 hours, a set of methyl resonances indicating formation of a new species was observed (Fig. 13). The reaction could be facilitated by the addition of trifluoroacetic acid (10 % by volume) and/or by warmimg the solution. Upon cooling such a solution, a reddish oil was observed to separate. Isolation of this material by decantation of the water layer allowed an nmr spectrum to be obtained. The resulting spectrum (Fig. 13c), which showed two methyl resonances at δ 2.42 (3H, s, C_2-Me) and δ 3.09 (6H, s, -SMe_2) and aromatic protons (Table 6) was distinctly different from corresponding spectra of either the sulfonium salt or ylid.

When diethylsulfonium salt, 7 (Table 7) and 2-phenylindole sulfonium salt, 5c (Table 8), were dissolved in D_2O/TFA, the formation of a new species were also observed in both cases. For 2-phenylindole sulfonium salt, the chemical shift for new S-methyl peaks in D_2O/TFA appeared at δ 2.70 and in the case of diethylsulfonium salt, the set of new resonances for S-ethyl groups occurred at δ 1.33 (6H, triplet,

Table 6

'H NMR[a] of 2-methylindole Sulfonium Salt (5b) and its Analogs in Protic Solvent

Condition/Solvent	2-CH_3	-$\overset{+}{S}(CH_3)_2$	Aromatic Protons
CD_3OD	2.66 (3H)	3.36 (6H)	7.28(2H) 7.51(1H) 7.96(1H)
D_2O/2 days, R.T.	2.41[b], 2.62	2.92[b], 3.24	6.98, 7.31-7.54, 7.75
D_2O/TFA	2.62	3.26	7.31(2H) 7.56(1H) 7.79(1H)
D_2O/TFA/Δ	2.39[b], 2.64	2.90[b], 3.28	6.98, 7.20-7.56, 7.80
Separated oily fraction/CD_3OD	2.42	3.09	7.09(2H) 7.30(1H) 7.67(1H)
Ylid/CD_3OD	2.50	3.12	6.99, 7.43, 7.66

[a] Ppm from ext. TMS (D_2O, D_2O/TFA) or int. TMS (CD_3OD).

[b] These peaks increase with heating.

Table 7

'H NMR of Diethylsulfonium Salt (7) and its Analogs in Protic Solvent[a]

Condition/Solvent	H-2	$^{+}S(CH_2\underline{CH_3})_2$	$^{+}S(\underline{CH_2}CH_3)_2$[b]	Aromatic Protons
CD_3OD	8.30	1.28	3.86	7.28-7.40, 7.64, 7.92
D_2O	8.25	1.35	3.83	7.42-7.62, 7.74-8.00
D_2O/TFA (10%)	8.17	0.94[c], 1.33	3.41[c], 3.76	7.01, 7.43, 7.70-7.88
D_2O/30% TFA	8.01	1.18	3.60	7.17-7.31, 7.54-7.67
Separated oily fraction in CD_3OD	8.24	1.33	3.94	7.32-7.46, 7.70, 7.90
Ylid/CD_3OD	7.86	1.19	3.55	7.00-7.11, 7.57-7.68

[a] Ppm from ext. TMS (D_2O, D_2O/TFA) or int. TMS (CD_3OD).

[b] 2 quartets centered at this shift.

[c] These peaks increase with heating.

Table 8

'H NMR of 2-phenylindole Sulfonium Salt (5c) and its Analogs[a]

Condition/Solvent	$\overset{+}{S}(CH_3)_2$	Promatic Protons
TFA	3.42	7.42-7.78(8H), 7.90(1H)
D_2O/TFA	2.70, 3.18	7.03, 7.23-7.29, 7.41, 7.75
D_2O/TFA/Δ, 2 hrs.	2.61, 3.15	7.26-7.58, 7.73
Ylid/$CDCl_3$	3.04	7.08-7.42, 7.60, 7.85

[a] In ppm from ext. TMS (D_2O/TFA) or int. TMS ($CDCl_3$ and TFA).

Table 9

'H NMR of Indole Sulfonium Salt (5a) and its Analogs[a]

Condition/Solvent	H-2	$\overset{+}{S}(CH_3)_2$	Aromatic Protons
D_2O	8.24	3.41	7.53(2H) 7.80(1H) 8.05(1H)
D_2O/TFA	7.95	3.13	7.21(2H) 7.47-7.70(2H)
DMSO-d_6	8.22	3.38	7.30(2H) 7.63(1H) 8.00(1H)
DMSO-d_6/D_2O	8.28	3.35	7.45(2H) 7.75(1H) 8.04(1H)
Ylid/D_2O	8.20	3.34	7.45(2H) 7.87-8.10(2H)

[a] In ppm from ext. TMS (D_2O, D_2O/TFA) or int. TMS (DMSO-d_6).

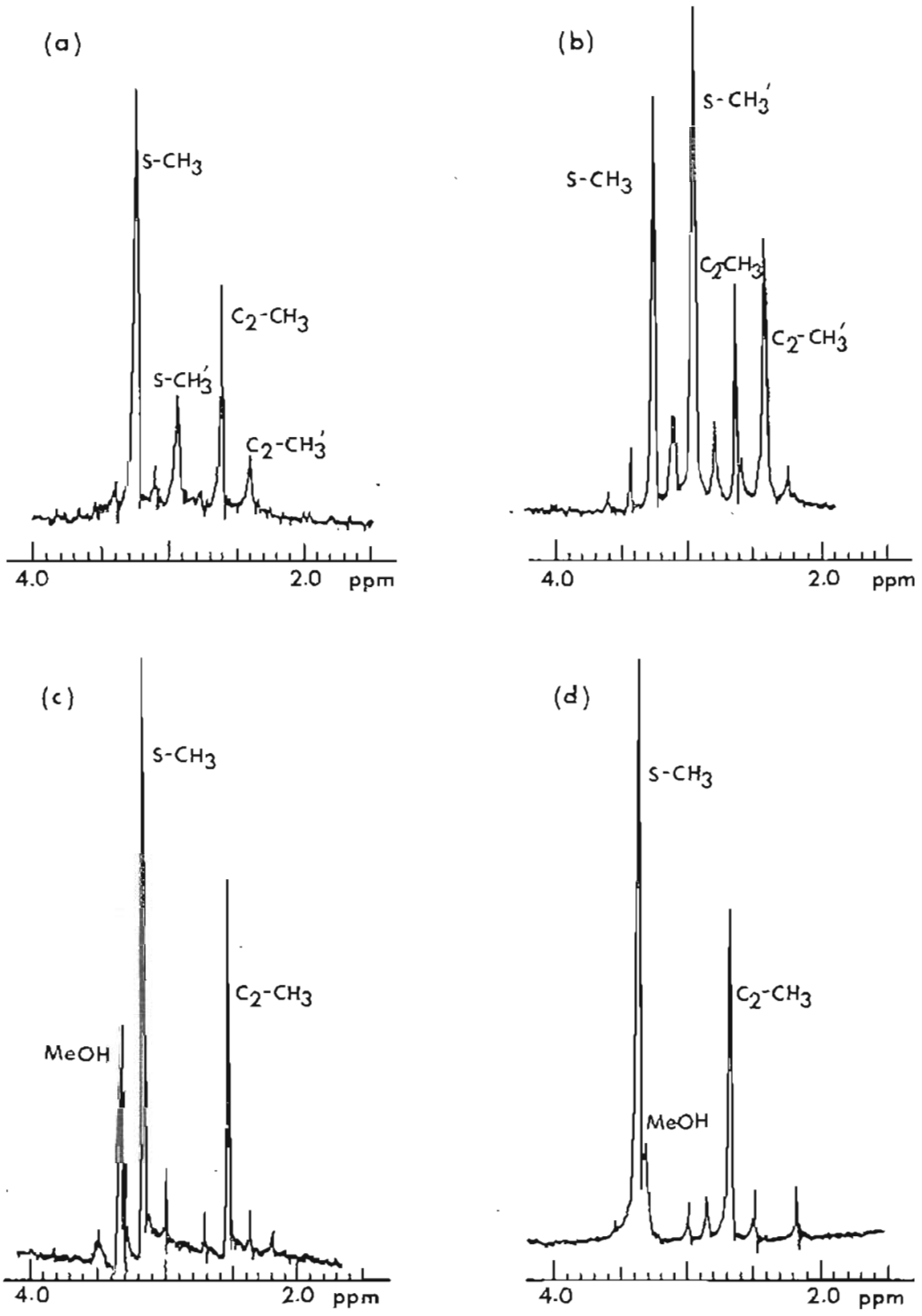


Fig. 13. ^{1}H Nmr of 2-Methylindole Sulfonium Salt in Protic Solvent a) D_2O/TFA, ext.TMS. b) D_2O/TFA/Δ, 1 Hr., ext.TMS. c) Isolated oily fraction in CD_3OD. d) Sulfonium salt, 5b, in CD_3OD

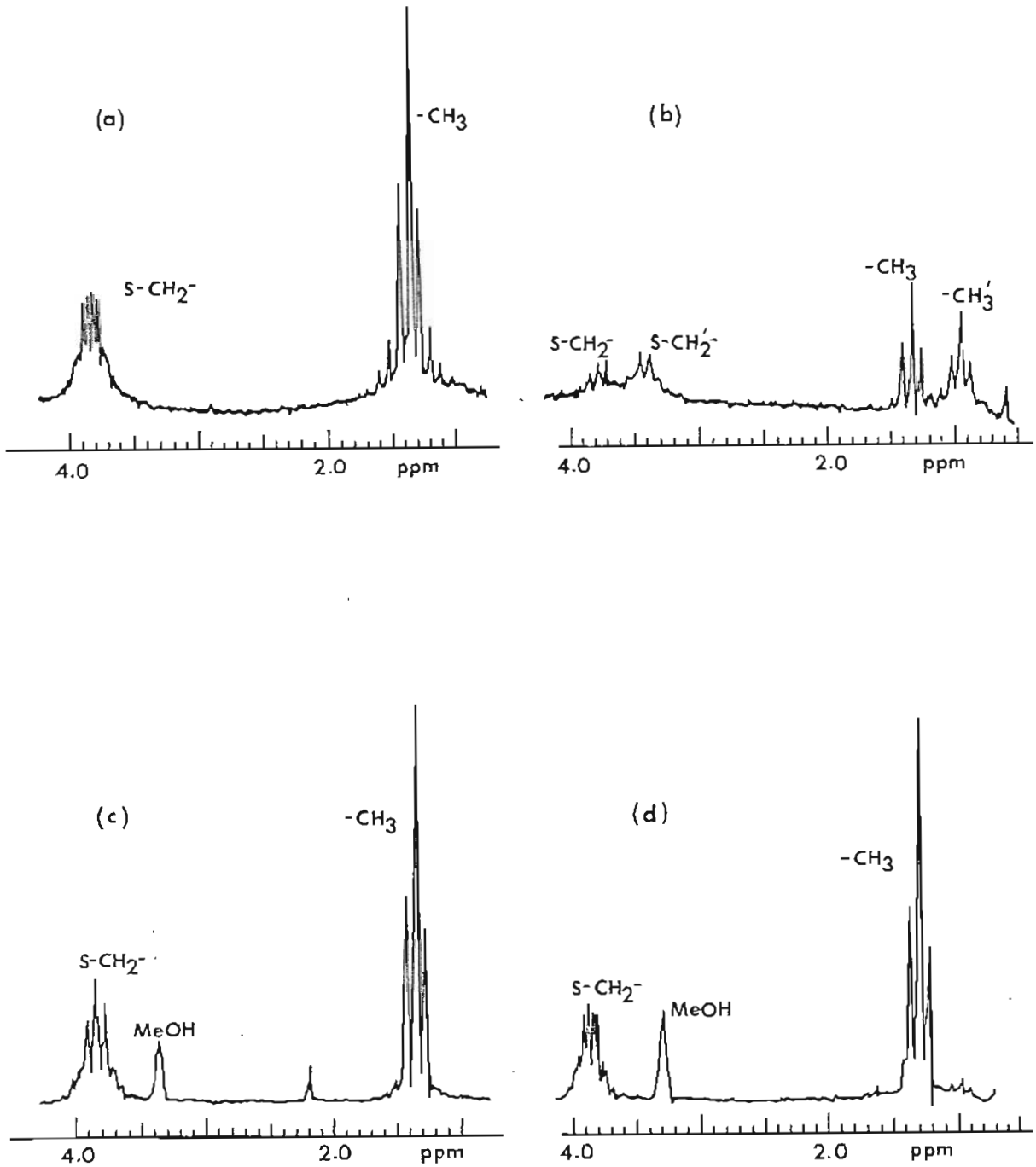


Fig. 14. ^{1}H Nmr of Diethylsulfonium Salt 7 in Protic Solvent a) D_2O, ext.TMS. b) D_2O/TFA, ext.TMS. c) Isolated oily fraction in CD_3OD. d) Sulfonium Salt, 7, in CD_3OD

$-CH_3$) and δ 3.94 (4H, 2qt., $-S-CH_2-$) when the new compounds were isolated and redissolved in CD_3OD (Fig. 14c).

When the same reaction was attempted with 2-H indole sulfonium salt, 5a, using different solvents (D_2O, D_2O/TFA, DMSO-d_6/D_2O), it was not possible to establish definitely the coexistence of two species as in other compounds (Table 9).

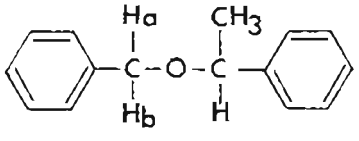
Several interesting observations were made in the nmr spectra of sulfonium salts in protic solvents. In the nmr spectra of 2-H indole sulfonium salt, 5a, and diethylsulfonium salt, 7, in CD_3OD, the chemical shift of 2-H is δ 8.28 and δ 8.30 respectively, i.e. at an unexpectedly low field for this type of proton. The analogs, both ylids and "hydrates", also show such low field chemical shifts (Tables 7 and 9).

Another striking feature of the nmr spectra of the compound 7 was that in the chemical shift of the "hydrate", the methyl resonance shifted 0.4 ppm upfield from that of anhydrous sulfonium salt (Fig. 14b). This difference in chemical shift is the same as that for the methylene group attached to sulfur, i.e. 0.4 ppm upfield. The same magnitude of the change in chemical shift in methylene and methyl group implies that the effect causing these shifts is not a through-bond effect, but a type of a through-space effect.

The nmr spectra of diethylsulfonium salt (Fig. 14d) exhibited magnetic nonequivalence of the methylene protons in protic solvents, i.e. D_2O, D_2O/TFA and CD_3OD. For instance in CD_3OD, two overlapping quartets centered at δ 3.86 were observed for the methylene protons. Magnetic nonequivalence of methylene protons was also observed for the "hydrate" of diethylsulfonium salt 7; when DMSO-d_6 was used as a

solvent, the methylene protons in sulfonium salt, 7, appeared as one quartet.

Magnetic nonequivalence of methylene protons located close to an asymmetric center[62-64] has been frequently observed. In sulfonium salts and sulfonium ylids, magnetic nonequivalence has been noticed even when two of the same alkyl groups are attached to the positively charged sulfur atoms[65-67]. In general, the magnitude of nonequivalence is known to be dependent on the solvent polarity, i.e. the degree of nonequivalence of the geminal protons decreases with increasing dielectric constant of solvent[63,65]. In the case of 1-phenylethylbenzylether (9), the chemical shift differences between the resonances for methylene protons were larger than anticipated in hydrogen-bonding solvents (formic acid, acetic acid, ethanol). Another exception is 10, in which the methyl protons show equivalence in $CDCl_3$, DMSO-d_6 and acetone-d_6, but chemical shift nonequivalence is clearly displayed in trifluoroacetic acid solvent[64]. The nonequivalence of the methylene hydrogens in an asymmetric acyclic compound has been shown by Roberts et. al.[68] to be mainly due to conformational preference.



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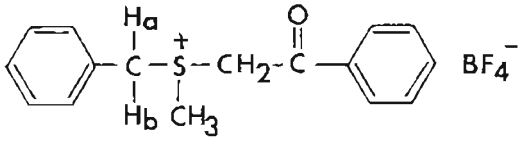

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In the cases of diethylsulfonium salt 7 and its analogs, the nonequivalence originated from the two separate methylene groups in different electron environments. Therefore, an assumption is made that the nonequivalence of methylene groups may be created by the interaction

between the sulfonium center and the protic (polar) solvents; presumably this interaction is absent in less polar solvents.

Chapter 7. Mass Spectra of Indole Sulfonium Salts and Its Ylids

Conventional electron ionization mass spectra of indole sulfonium salts, 5a - 5c, and ylids, 1a - 1c, were obtained as part of compound identification procedures. Sulfonium iodides, 5a and 5b, failed to exhibit molecular ions but did show ions at m/e 163 and 178 respectively, which represent CH_3I loss from the molecular ions. 2-Phenylindole sulfonium chloride, 5c, behaved similarly by displaying at the ion of highest mass, an ion m/e 239, corresponding to the loss of CH_3Cl from the molecular ion. Ylids, 1a - 1c, were characterized by the exhibition of the molecular ions $M^{+\cdot}$, for which symbol $Y^{+\cdot}$ is used, and $M^{+} - CH_3$ ($Y^{+} - CH_3$) ions (Table 10).

When the field desorption (FD) mass spectroscopic method was employed for analysis of the 2-methylindole (b) compound series, ions at m/e 192 (YH^+), 191 ($Y^{+\cdot}$), 177 ($Y^{+} - CH_2$) and 142 (CH_3I) were observed with emitter heating current at 7 - 9 mA for sulfonium salt, 5b. Ylid, 1b, exhibited ions at m/e 192 (YH^+), 191 ($Y^{+\cdot}$) and 177 ($Y^{+} - CH_2$). The prepared "hydrate" of 5b also displayed ions, 192 (YH^+), 191 ($Y^{+\cdot}$) and 177 ($Y^{+} - CH_2$). Upon further heating of these samples, 1b and 5b, to to above 10 mA, an intermolecular rearrangement product, m/e 206 ($YH^+ + CH_2$) was observed.

A conventional electron-ionization mass spectrometer (EI ms) with application of the rapid-heating technique[69] was also applied to obtain mass spectra of sulfonium salts. Sulfonium salts dissolved in dimethylformamide and sulfonium salts dissolved in H_2O/TFA (the condition

wherein the "hydrate" was observed) were applied to the probe tip. The technique used combines sample vaporization from a tungsten wire by rapidly heating a sample to > 1000^{o} with photoplate recording of spectra during the very brief period (~ 0.1 sec.) of ion production. Due to the high abundance of lower mass ions, only ions with mass higher than that of the molecular ions are considered. 2-Methylindole sulfonium salt 5b exhibited ions 191 (Ylid = $Y^{\pm}$), 192 (YH^{+}), 205 ($Y^{\pm}$ + CH_2), 206 (YH^{+} + CH_2), 209 ($Y^{\pm}$ + H_2O), 223 ($Y^{\pm}$ + CH_2 + H_2O) and 339 ($Y^{\pm}$ + YH^{+} + H_2O - SMe_2). Indole sulfonium ylid 1b yielded characteristic ions identified with those observed for sulfonium salt 5b, with exception that ions at m/e 209 and 339 were absent. The "hydrate", i.e. sulfonium salt 5b after treated with H_2O/TFA, exhibited a mass spectrum similar to that of the sulfonium salt (Table 10). Ions at m/e 205, 206 and 223 are produced as a result of thermal rearrangements involving intermolecular transfer of methyl groups[70].

Electron ionization ms with rapid heating was used to obtain mass spectra of other sulfonium salts and of sulfonium salt "hydrates". Ions at m/e 177 ($Y^{\pm}$), 178 (YH^{+}), 191 ($Y^{\pm}$ + H_2O), 196 (YH^{+} + H_2O) and 209 ($Y^{\pm}$ + CH_2 + H_2O) were observed in the spectrum of sulfonium salt, 5a. The "hydrate" prepared from 5a, showed ions at m/e 177, 178, 191, 195, 196, 209, in a spectrum indistinguishable from that of the parent sulfonium salt. Similarly, the "hydrate" of 2-phenylindole sulfonium salt, 5c, displayed ions at m/e 253 ($Y^{\pm}$), 254 (YH^{+}), 268 (YH^{+} + CH_2) and 271 ($Y^{\pm}$ + H_2O). Ions at m/e 205 ($Y^{\pm}$), 206 (YH^{+}), 223 ($Y^{\pm}$ + H_2O) and 224 (YH^{+} + H_2O) were observed for the hydrate of diethylsulfonium salt 7.

Table 10

Selected Ions from the Mass Spectra

of Sulfonium Salts and Their Derivatives

Compounds	Method a	Ions ($^{m}/e$)					
		$Y^{+}\cdot+H_2O+CH_2$	$Y^{+}\cdot+H_2O$	$Y^{+}\cdot+CH_3$	YH^{+}	$Y^{+}\cdot$	$Y^{+}\cdot(YH^{+}\cdot)-CH_3$
1a	EI					177	162
5a	EI						163
5a*[b]	EI$^{\neq}$	209	195	192	178	177	162
1b	EI					191	176
	EI$^{\neq}$	223		206	192	191	177
	FD			206[c]	192	191	177
5b	EI						177
	EI$^{\neq}$	223	209		192	191	177
	FD			206[c]	192	191	177
5b*[b]	EI$^{\neq}$	223	209	206	192	191	177
	FD			206[c]	192	191	177
1c	EI					253	238
5c	EI						239
5c*[b]	EI$^{\neq}$		271	268	254	253	239
7*[b]	EI$^{\neq}$	237	223		206	205	191

[a] EI: Conventional electron ionization mass spectroscopic method (EIms).
EI$^{\neq}$: EIms with fast-heating and photo-late recording technique.
FD: Field desorption (FD) method using carbon micro-emitter with emitter heating current 7-9 mA.

[b] Sulfonium salt dissolved in H_2O/TFA, followed by warming the solution.

[c] These ions appear only with heating current above 10 mA.

Chapter 8. Summary

A stable, crystalline and unusually basic (pKa = 11) sulfonium ylid, 3-dimethylsulfonioindolide (1a) and its 2-methyl (1b) and 2-phenyl (1c) analogs and their precursor, 3-methylthioindoles (4) and 3-dimethylsulfonium salts (5) were prepared.

Carbon-13 and ^{1}H nuclear magnetic resonance data for these compounds have been obtained, and analyzed in terms of the electronic changes associated with the sequential change at sulfur; thioether $\rightleftharpoons$ sulfonium salt $\rightleftharpoons$ sulfonium ylid. Relatively small changes observed for S-methyl resonances suggests limited involvement of sulfur in delocalizing ylid anionic charge. In contrast, the significant ^{13}C chemical shift change observed for each of the four carbons of the indole pyrrole ring are consistent with ylid electron delocalization throughout this system.

The deuterium exchange with protons of S-methyl groups had been observed for these indole sulfonium ylids[16,29], 1a - 1c, in $CDCl_3$ and CD_3OD, indicating highly basic characters. When titration was carried out on these sulfonium ylids, a hysteresis was observed in all cases. Another sulfonium salt, 3-diethylsulfonioindole iodide, 7, also displayed a hysteresis when titrated. The hysteresis occurred regardless of the C_2- (-H, $-CH_3$, -phenyl) and/or C_3- (S-dimethyl, S-diethyl) substituents. Among the possible causes of the hysteresis, a ring-chain relationship and tautomers have been ruled out. The pKa of sulfonium salts, 5a - 5c and 7 (Table 4), ranging from 10.88 - 11.28, are at

least three pKa units higher than those for carbonyl-stabilized sulfonium ylids which have been reported[11,12,17,18]. The unusual basicities of these indole sulfonium salts suggest that the observed pKa's are overall $pKa^{equil.}$, i.e. a composite of pKa's of the two (or more) species in equilibrium which give rise to the observed hysteresis[57,58]. During acid or base titration, the pH drifts rapidly, which is often observed for compounds undergoing covalent hydration[58].

The study of ultraviolet spectra showed that the chromophoric system is different in aqueous and nonaqueous solvents in the cases of both indole sulfonium salt, 5a, and 2-methylindole sulfonium salt, 5b. The same phenomenon was observed with their corresponding ylids, 1a and 1b. These results strongly indicate that water reacts with these compounds in a way which changes the chromophoric system in aqueous solution.

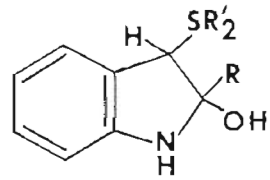
A ^1H nmr study of sulfonium salt, 5a - 5c and 7, in protic solvents was carried out. The appearance of second, new species in solution (D_2O, D_2O/TFA) was observed with 2-methylindole sulfonium salt, 5b, 2-phenylindole sulfonium salt, 5c, and diethylsulfonium salt, 7. The formation of this new species was observed both in acidic medium and under neutral condition. In the case of diethylsulfonium salt, 7, a single species was observed with a higher concentration of TFA (25 - 30 % by volume). This is consistent with the achievement of rapid equilibriation of indole sulfonium salt hydrated and nonhydrated forms. The new compound, isolated in crude form, was termed a "hydrate" of the sulfonium salt.

The electron ionization mass spectra (with fast-heating and photo-

plate ion recording of samples of sulfonium salt, 5b, and the corresponding sulfonium salt "hydrate" exhibited ions assignable as $(Y^{+\cdot} + H_2O)$ ions.

Consideration of these results and the highly polarized nature of the C_2-C_3 bond in the sulfonium salt due to the charged sulfur at C-3 leads us to postulate the addition of a molecule of water across the C_2-C_3 double bond to produce hydrate (11).

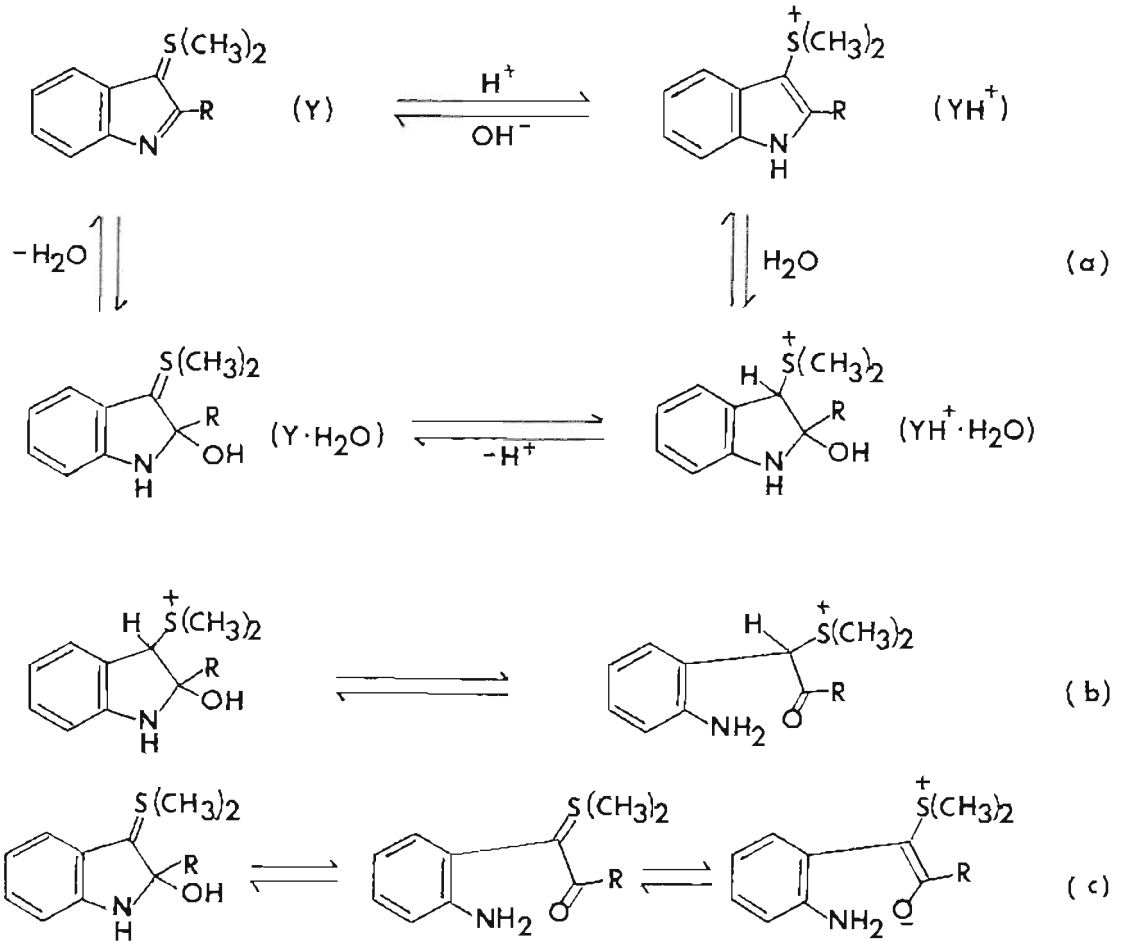
	R	R'
11a	-H	$-CH_3$
11b	$-CH_3$	$-CH_3$
11c	-Ph	$-CH_3$
11d	-H	$-C_2H_5$



Hydrates, 11b and 11d, were isolated and titrated sequentially with base and acid producing a hysteresis nearly identical with those observed using corresponding sulfonium salts. This result establishes that no important structural change has occured in generation of the new species termed a "hydrate" and is strongly indicative that it is directly related to the hysteresis phenomenon.

These studies are consistent with the proposed equilibria in solution shown in Scheme 8a. This scheme postulates equilibria among hydrated species and anhydrous species. Our ^1H nmr studies show that at pH's below neutral appreciable concentration of both the sulfonium salt (YH^+) and sulfonium salt hydrate $(YH^+ \cdot H_2O)$ coexist.

It is conceivable that once the hydrates are formed, ring



Scheme 8. Proposed Equilibria in the Solution Involving Hydration

opening-closing reactions (as in Scheme 8b and 8c) can occur. Attempts to isolate the hydrate in a pure form were unsuccessful, in each attempt extended manipulation resulted in the recovery of the original sulfonium salt. Reduction of the hydrate of 2-methylindole sulfonium salt (11b), using Zn/HOAc or sodium borohydride was also attempted with the goal of trapping a ring-opened form of the hydrate in the form of an alcohol. These attempts met with no success.

Chapter 9. Experimental

Proton magnetic resonance spectra were obtained with a Varian Associates HA-100 spectrometer and carbon-13 resonance spectra were recorded using either Varian Associates XL-100 or FT-80 spectrometers; chemical shifts are expressed as parts per million (δ) downfield from internal or external tetramethylsilane. Electron ionization mass spectra were obtained with a CEC DuPont Model 21-110B, or DuPont Model 21-491B mass spectrometer and modified Hitachi IMU6 mass spectrometer was used to obtain field desorption mass spectra. Ultraviolet spectra were obtained with a Cary 15 spectrophotometer. Melting points were determined on microscope hot stage and are uncorrected. Titrations were performed using a Radiometer pHM62 pH meter for the continuous measurement of pH.

General method of titration of sulfonium salts[53]; The sulfonium salt (0.4 mmole) was dissolved in 80 ml of methanol and manually titrated with 0.100 N standard NaOH. Back titration was then carried out with 0,100 N standard HCl.

General procedure for the study of nmr spectrum of sulfonium salts in aqueous solvents ; Sulfonium salt was dissolved in D_2O : trifluoroacetic acid (10:1), and a tetramethylsilane capillary tube was put in as an external standard. The nmr tube was warmed in a water-bath for one hour. When the sample was cooled, it separated into two layers. The top (D_2O) layer was pipetted out and the bottom layer was redissolved in CD_3OD. Nmr spectra was recorded at each step.

Isolation and titration of hydrates ; The "hydrate" of sulfonium salt was prepared and an nmr spectrum was taken as described above. The nmr sample was recovered and used for the titration in the same manner as sulfonium salts.

S-(3-indolyl)-isothiouronium iodide (3a)[28]; Indole (7.22 g, 0.055 mole) and thiourea (4.19 g, 0.055 mole) were dissolved in 500 ml of methanol and water (3:2). To this mixture, a solution of iodine-potassium iodide reagent (9.13 g, 0.055 mole : 13.96 g, 0.055 mole) dissolved in 130 ml of methanol and water (2:1) was added slowly with vigorous tirring. Rapid consumption was observed. The addition took 1/2 hour and another 1/2 hour was allowed to ensure the disappearance of iodine. Upon concentration of solvent in vacuo and cooling, pale yellow plates which formed were filtered and recrystallized from hot water yielding 16.6 g of 3a (94.5 %) with m.p. 203-206^{0}(dec.) [lit. m.p. 214-216^{0}][28].

3-Methylthioindole (4a)[16]; Thiouronium salt 3a (5 g, 0.0157 mole) was dissolved in 100 ml of water, and nitrogen was bubbled through at 80^{0}C (on the steam bath). Sodium hydroxide (1.6 g) in 100 ml of water was treated the same way. After 1/2 hour, the sodium hydroxide solution was rapidly poured into the thiouronium salt solution. With nitrogen bubbling through, the mixture was stirred for another 45 minutes on the steam-bath; during this time the solution turned clear. The solution was cooled in an ice-bath, dimethylsulfate (2.13 g, 0.0169 mole) was added, and the reaction mixture was stirred for another hour in the ice-bath. The organic layer was then extracted with dichloromethane (500 ml x 4), washed with water (50 ml x 3),

dried over sodium sulfate and the solvent was removed in vacuo. Sometimes the product was initially purified by filtration through alumina using chloroform as the elutant. Vacuum distillation at 98-100°/0.12 mmHg gave 1.2 g of 4a (48.1 %): For nmr data, see Tables 1 and 2; for uv data, see Table 5.

3-Dimethylsulfonioindole iodide (5a); Methylthioether 4a (1.4 g, 8.5 mmole) and methyl iodide (1.2 g, 8.5 mmole) were mixed, stoppered tightly and left standing at room temperature for 24 hours. The colorless crystals which formed were filtered and washed with ether yielding 2.6 g of 5a (98.8 %), m.p. 125-127°[lit. m.p. 131-133°][16]: For nmr data, see Tables 1, 2 and 9; for uv data, see Table 5; m.s. m/e 163 148.

3-Dimethylsulfonioindolide (1a); Sulfonium iodide 5a (1.9 g, 6.2 mmole) in 5 ml dimethylformamide was added to a sodium hydride suspension in ether at 0°C(in ice-bath) under a nitrogen atmosphere and the mixture was stirred for two hours. While vigorously stirring, the resulting colorless precipitate was triturated with 400 ml of chloroform. The undissolved residue was removed by filtration. The residue left after evaporating the chloroform in vacuo at or below 20°C gave colorless crystals upon addition of ether. The collected product was recrystallized from $CHCl_3$/ether to yield 0.92 g (85 %) of 1a, m.p. 125-129°[lit. 125° with final rapid melting at 147-150°][16]: For nmr data, see Tables 1 and 2; for uv data, see Table 5; m.s.(EI) m/e 177, 162, 148, 120.

S-[3-(2-methyl)-indolyl]-isothiouronium iodide (3b); To a vigorously stirred solution of 2-methylindole (3.93 g, 0.03 mole) and

thiourea (2.28 g, 0.03 mole) in 250 ml of methanol and water (2:1), a potassium iodide-iodine (4.98 g, 0.03 mole : 7.61 g, 0.03 mole) solution in 70 ml of methanol and water (2:1) was added. The mixture was stirred (1/2 hr.) until the solution turned lighter yellow in color. The solution was concentrated in vacuo to remove methanol, then extracted with ethyl acetate to remove the dark color. The aqueous layer on further concentration in vacuo gave light pink crystals which were collected and recrystallized from water to give 9.6 g (96 %) of 3b, m.p. 194-197^{o}(dec.).

3-Methylthio-2-methylindole (4b); Thiouronium salt 3b (6.0 g, 0.018 mole) dissolved in 100 ml of water and purged with nitrogen while heated on a steam-bath. A sodium hydroxide solution (100 ml), also treated the same way for 1/2 hour , was then rapidly poured into the thiouronium salt solution. With nitrogen bubbling through, the mixture was heated on the steam-bath for another 1/2 hour. The solution turned clear, and was placed in an ice-bath. To the cooled solution, dimethylsulfate (2.77 g, 0.022 mole) was added. A colorless precipitate was observed after the reaction mixture had stood for 45 minutes in the ice-bath. The organic material was extracted with 500 ml of dichloromethane, washed with water (100 ml x 2) and dried over sodium sulfate. The solvent was removed in vacuo, and the oily residue was purified by vacuum distillation to give 2.55 g (80 %) of 3-methylthio-2-methylindole, 4b, b.p. 107-110^{o}/0.01 mmHg [lit. 140-142^{o}/0.85 mmHg][24b]: For nmr data, see Tables 1 and 2; for uv data, see Table 5.

3-Dimethylsulfonio-2-methylindole iodide (5b); Methylthioether

4b (3.24 g, 0.018 mole) and methyl iodide (2.85 g, 0.02 mole) were mixed. The flask was tightly stoppered and left standing for 24 hours. The colorless needle-shaped crystals which formed were filtered and washed with ether to yield 4.99 g (85.5 %) of 5b, m.p. 134-136°: For nmr data, see Tables 1, 2 and 6.; for uv data, see Table 5; m.s. (EI) m/e 191, 192, 208, 209, 216, 217, 223, 244, 245, 256, 257, 258, 259, 339.; m.s. (FD) m/e 206. 192, 191, 177, 142.

3-Dimethylsulfonio-2-methylindolide (1b); A mixture of ion-exchange resin (5 ml, Bio-Rad AG1-X8, 100-200 mesh in OH^- form, in methanol) and sulfonium iodide 5b (1.88 g, 5.9 mmole) in methanol were stirred for 2.5 hours. The ion exchange resin was removed by filtration and washed with chloroform. The combined solvent was removed *in vacuo* at or below 20°C to yield needle-shaped pale-yellow crystals which were collected and recrystallized from chloroform/hexane to give 1.2 g of 1b (100 %), m.p. 70-75°: For nmr data, see Tables 1 and 2; for uv data, see Table 5; m.s. (EI) m/e 191, 176, 162, 159, 120, 118, 117; m.s. (EI^*) m/e 191, 192, 193, 194, 205, 219, 223, 350, 362, 364; m.s. (FD) m/e 206, 192, 191, 177.

3-Dimethylsulfonio-2-phenylindole chloride (5c); Freshly recrystallized (from benzene) 2-phenylindole (12 g, 0.062 mole) was dissolved in 75 ml of tetrahydrofuran and dimethylsulfoxide (5 ml, 0.070 mole) was added. The reaction flask was placed in an ice-bath and a slow stream of hydrogen chloride gas was passed through the reaction mixture until no further precipitation was observed. The precipitate was filtered and washed with toluene to produce 12.5 g of 5c (69.3 %) as a light-grey powder; m.p. 148-151°[lit. m.p. 158-160°][29]: For nmr data,

see Tables 1, 2 and 8; for uv data, see Table 5; m.s. (EI) m/e 239, 224, etc.

3-Methylthio-2-phenylindole (4c); Sulfonium chloride 5c (2.45 g, 8.5 mmole) was heated under nitrogen at 130-150° for one hour gave a dark purple oily substance. This crude product was chromatographed on a 50 g silica gel column using benzene for elution. Pale yellow crystals formed after evaporation of the benzene in vacuo and addition of carbon tetrachloride/hexane. The product was filtered and washed with hexane to yield 1.6 g of 4c (81.2 %); m.p. 97-100°[lit. m.p. 106-107°][29]: For nmr data, see Tables 1 and 2; for uv data, see Table 5.

3-Dimethylsulfonio-2-phenylindolide (1c): To sulfonium chloride 5c (1.07 g, 3.7 mmole) in 30 ml of methanol, was added 5 ml of ion-exchange resin (Bio-Rad, AG1-X8, 100-200 mesh in OH^- form, in methanol). The mixture was stirred at room temperature for one hour. The ion exchange resin was filtered, washed with chloroform and the combined solvent was removed in vacuo at 20°C or below. Pale yellow crystals formed upon the addition of ether. The collected product 1c was recrystallized from $CHCl_3$/ether to yield 0.82 g (87 %) of 1c, m.p. 148-151°[lit. m.p. 165-169°][29]: For nmr data, see Tables 1 and 2; for uv data, see Table 5; m.s. (EI) m/e 253, 238, 223, 205, 204.

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