Indole 3-Sulfonium Ylides and Related Sulfonium Salts. Carbon and Hydrogen Nuclear Magnetic Resonance Study

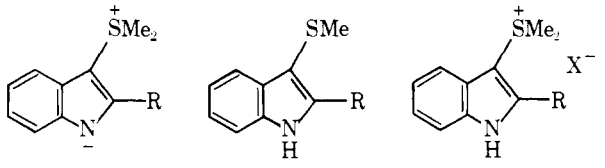
Kyong Hwi Park, George A. Gray,† and G. Doyle Daves, Jr.*

Contribution from the Department of Chemistry and Biochemical Sciences, Oregon Graduate Center, Beaverton, Oregon 97005, and Varian Associates, Palo Alto, California 94303. *Received March 15, 1978*

Abstract: ^{13}C and ^{1}H nuclear magnetic resonance data for 3-dimethylsulfonioindolide, its 2-methyl and 2-phenyl analogues, and related 3-methylthio-1*H*-indoles and dimethyl-1*H*-indol-3-ylsulfonium salts are reported. These data are analyzed in terms of the electronic changes associated with the sequential change at sulfur: thioether ⇄ sulfonium salt ⇄ sulfonium ylide. Relatively small changes observed for *S*-methyl resonances suggests limited involvement of sulfur in delocalizing ylide anionic charge. In contrast, the significant ^{13}C chemical shift changes observed for each of the four carbons of the indole pyrrole ring are consistent with ylide electron delocalization throughout this system.

Introduction

Recently, we reported the preparation and some properties of 3-dimethylsulfonioindolide (**1a**),[1] a stable, crystalline, unusually basic (pK_a = 11) sulfonium ylide. We now report a ^{1}H and ^{13}C nuclear magnetic resonance study of **1a**, its 2-methyl (**1b**) and 2-phenyl[2] (**1c**) analogues, and precursor 3-methylthio-1*H*-indoles[3,4] (**2**) and dimethyl-1*H*-indol-3-ylsulfonium salts[4] (**3**). The current work is part of a broader investigation



1 2 3

a, R = H
b, R = Me
c, R = Ph

of the chemical and physical properties of this interesting sulfonium ylide system.[5]

A number of nuclear magnetic resonance (NMR) studies of phosphorus ylides[6-13] and corresponding phosphonium salts[7,9-11] have been undertaken with the goal of improving the description of bonding and electron distribution of these systems.[6-16] Similar, although less extensive, studies have been made of arsonium ylide systems.[8,14,17] Surprisingly, few NMR data (^{1}H[16,18-20] or ^{13}C[16,21]) for sulfonium ylides are available. The present experiments, while undertaken to improve our understanding of the indole sulfonium ylides,[1,2,5] 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 descriptions of ylides.[6-21]

Experimental Section

The compounds used in this study were prepared as described.[5] ^{1}H NMR spectra were obtained with a Varian Associates HA-100 spectrometer using solutions (10–20 mg/mL) as indicated in Table I. ^{13}C NMR spectra were recorded using either of Varian Associates XL-100 or FT-80 spectrometers and solutions (≥100 mg/mL) in the solvents noted in Table II.

Results

Tables I and II contain the ^{1}H and ^{13}C chemical shifts, respectively, for ylides (**1**), thioethers (**2**), and sulfonium salts (**3**). The methyl carbon shift in 2-methylindole (Table II) is sufficiently shielded to clearly separate 2-methyl and *S*-methyl derivatives, and allow methyl assignment by inspection. Line width, intensity, and off-resonance data identified the nonprotonated carbons. Carbon 7a in **2a** was assigned in view of its similarity to C-7a in 3-methylindole (Table II) 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 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 **2a**.[22] 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 couplings 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) **2b** and **2c** have similar shifts to **2a**. In the *coupled* spectrum of **2b** C-2 shows a quartet of doublets while C-3a and C-7a are featureless, broad multiplets. C-5 and C-6 in **2b** were identified from their coupling patterns and ordered similarly to their order in 2-methylindole, 3-methylindole, and indole. Methylation of **2a** results in the salt **3a**. C-2 was again confirmed in the coupled spectrum of **3a** through a $^{1}J_{CH}$ = 191.4 Hz. C-7a in **3a** was assigned based on intensity and expected line position relative to **2a**. 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 **3a** were assigned based on the pattern characteristics in the coupled spectrum. Compounds **3b** and **3c** were assigned similarly. Phenyl resonances in **2c** and **3c** were assigned based on intensity and expected proximity of the meta resonance to 128.5 ppm.

The ylides exhibited large enough changes that assignment of C-4, C-5, and C-6 is tenuous. C-3 stands out in all three ylides 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 quaternary 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.[23,24] Currently, methods (theoretical and empirical) for rationalizing and/or predicting chemical shifts of such compounds are of only

† Varian Associates.

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Table I. ^{1}H Nuclear Magnetic Resonance Chemical Shifts for 3-Dimethylsulfonioindolides (**1**), 3-Methylthio-1*H*-indoles (**2**), and Dimethyl 1*H*-Indol-3-ylsulfonium Salts (**3**)

	resonance, δ[a]			
compd	H-2	2-Me	S-Me	aromatic
1a	8.02		3.07	7.08–7.20, 7.57, 7.80
2a	6.82		2.24	7.03–7.10, 7.62
3a	8.45		3.47	7.27–7.44, 7.66, 8.01
1b		2.53	2.92	6.98–7.10, 7.41, 7.65
2b		2.04	2.15	6.89–7.01, 7.51, 7.82
3b		2.65	3.40	7.20–7.32, 7.53, 8.06
1c			3.02	7.08–7.20, 7.32–7.68, 7.80
2c			2.20	7.07–7.14, 7.30–7.46, 7.68–7.80, 7.98
3c			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.

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.[24,25] As a result, systematic studies involving chemical shift assignments within series of closely related compounds are important.

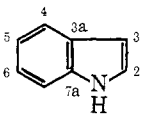
S-Methyl Resonances. The reasonable assumption that the electron demand of the sulfur nucleus and the resulting electron donation by the *S*-methyl substituents increases in the order thioether (**2**), sulfonium ylide (**1**), sulfonium salt (**3**) is supported by the chemical shifts of the *S*-methyl hydrogens, which exhibit stepwise increases in nuclear shielding according to this ordering (Table I). The relatively small chemical shift differences (0.4–0.5 ppm) between *S*-methyl hydrogen resonances of ylides **1a–c** and corresponding sulfonium salts **3a–c** suggest an ylide structure in which negative charge distribution involves the dimethylsulfonium center minimally.

The ^{13}C chemical shifts (Table II) for the various *S*-methyl substituents do not correlate directly with corresponding hydrogen shifts (Table I). The *S*-methyl ^{13}C resonances for thioethers **2a–c** appear at higher field than the corresponding resonances for the ylides (**1a–c**) 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 ylide (**1**) *S*-methyls occur downfield of sulfonium salt (**3**) *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, 2a, 3a**) and for C-2 Me (compounds **1b, 2b,** and **3b**) exhibit the same order of shielding, **2 < 1 < 3**, 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., **2b < 3b < 1b**, in which the ylide substituent is most shielded. The C-1′ carbon of the C-2 phenyl substituent shows still a different order of nuclear shielding (**3c < 2c < 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 iodole is relatively electron deficient whereas C-3 is the site of highest carbon electron density.[26] As shown by the reference data in Table II, the chemical shifts for these carbons reflect this 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

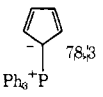
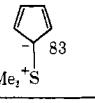
Table II. ^{13}C Nuclear Magnetic Resonance Chemical Shifts for 3-Dimethylsulfonium Indolides (**1**), 3-Methylthio-1*H*-indoles (**2**), Dimethyl 1*H*-Indol-3-ylsulfonium Salts (**3**), and Related Indoles



	resonance, δ[a]										
compd	C-2	C-3	C-3a	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		
2a	127.7	108.0	128.70	119.18	122.7	120.30	111.57	136.3	20.1		
3a	133.74	92.62	124.06	118.35	123.58	121.72	113.34	136.51	29.29		
1b	119.96	108.94	150.64	(119.40)	(120.15)	(118.96)	114.92	156.70	30.50	15.75	
2b	139.10	103.95	129.96	118.51	121.72	120.17	110.74	135.12	19.63	11.78	
3b	145.89	87.31	124.03	117.73	123.29	121.98	113.04	136.68	29.06	12.74	
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
2c	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
3c	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] Parts per million downfield from Me_4Si; solvents used were $CDCl_3$ for **1** and $CDCl_3$–$(D_3C)_2SO$ for **2** and **3**. 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", Wiley, New York, N.Y., 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 Trans. 1*, 8 (1975).

Table III. ^{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 8, 11, 12
B	$Ph_3\overset{+}{P}\overset{-}{C}H_2$ −4.1	$Ph_3\overset{+}{P}CH_3$ 11.4	ref 9
C	$Me_2\overset{+}{S}\overset{-}{C}H_2$ (O) 32.8	$Me_2\overset{+}{S}CH_3$ (O) 5.9	ref 16, 27
D	$Ph_3\overset{+}{P}\overset{-}{C}H-C(=O)-C_6H_5$ 50.5 184.8	$Ph_3\overset{+}{P}CH_2-C(=O)-C_6H_5$ 38.7 196.5	ref 7, 13
E	 78.3		ref 7, 12
F	 83		ref 21

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 **3a–c** causes the ^{13}C resonance of C-2 to move downfield an additional 4–7 ppm and C-3 to experience an 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 Figure 1.

Effects of Ylide 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 ylide. Figure 1 shows these changes diagrammatically for the 2-methylindole pair **1b** and **3b**. In this pair, C-2 of ylide **1b** is deshielded 26 ppm with respect to C-2 of sulfonium salt **3b**. 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 ylide carbons experience more shielding than the corresponding sulfonium salt carbons. The pyrrole ring carbon resonances of the C-2H ylide–sulfonium salt pair (**1a** and **3a**) exhibit similar behavior, although the magnitudes of the chemical shift differences are smaller than in the C-2 methyl compounds. The C-2 phenyl pair (**1c** and **3c**) show a significantly different behavior in that C-3 as well as C-2 is deshielded in ylide **1c**; C-3a and C-7a are shielded in comparison with corresponding carbons of sulfonium salt **3c** as was observed in the other series.

While the other carbons of the carbocyclic ring (C-4, C-5, C-6, and C-7) are only slightly shifted as a result of ylide 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 ⇄ sulfonium ylide 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 Ylide Systems. There is a dearth of ^{13}C chemical shift data for other sulfonium salt–sulfonium ylide pairs;[16,21] as a result it is useful to use data for selected phosphonium salts and phosphonium ylides as models in considering the present results. In Table III are representative data from phosphorus ylide studies and, in addition, ^{13}C chemical shift data for two sulfur ylides, dimethyloxosulonium methylide[16] and dimethylsulfonium cyclopentadienide,[21] previously studied.

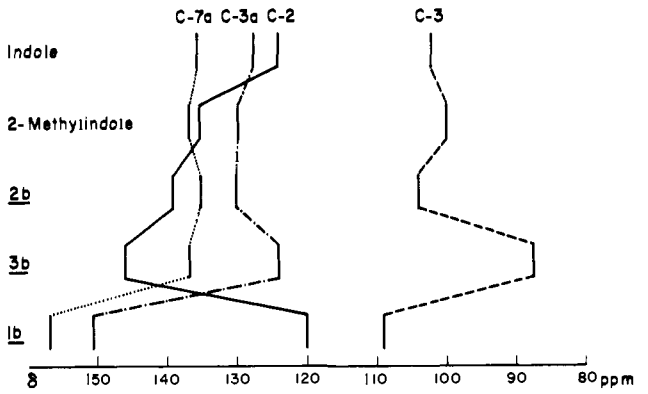


Figure 1. Comparison of ^{13}C chemical shifts for pyrrole ring carbons of indole and 2-methylindoles. For carbon numbering system see Table II; data for 2-methylindole are taken from footnote *b* of Table II.

Entries A and B in Table III, trimethyl- and triphenylphosphonium methylides and corresponding phosphonium salts, show the expected deshielding of the carbanionic carbons as compared with the protonated forms.[8,9,11,12] However, in sharp contrast, the carbanionic carbons of the "stabilized" triphenylphosphonium phenacylide[7,13] (entry D) appears 12 ppm downfield of the corresponding carbon of the phosphonium salt. In this phosphonium ylide–phosphonium salt pair, it is the carbonyl carbon which is deshielded as a result of converting the phosphonium salt to ylide. Thus, the changes in carbon shielding associated with the transformation from phosphonium salt to ylide (or vice versa) parallel those observed in the present study for the 3-dimethylsulfonium indole salt–ylide system (**1**), 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 cyclopentadienide ylides (Table III, 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 suggest limited involvement of sulfur in delocalizing the ylide 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.[23,24]

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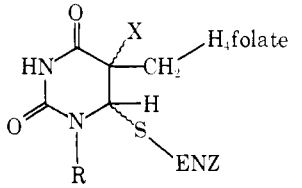
Elucidation of the Detailed Structures of the Native and Denatured Ternary Complexes of Thymidylate Synthetase via ^{19}F NMR

R. Andrew Byrd,[1a] William H. Dawson, Paul D. Ellis,*[1b] and R. Bruce Dunlap*[1c]

Contribution from the Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208. *Received April 19, 1978*

Abstract: It is known that the inhibition of thymidylate synthetase by the substrate analogue FdUMP results from the formation of a tightly bound ternary complex in which both FdUMP and the cofactor (5,10-CH_2H_4folate) are simultaneously bound to the enzyme. It is believed that the ternary complex results because FdUMP is able to function in a manner identical with dUMP during the initial stages of catalysis, but gets "stuck" partway through. The stage at which no further reaction occurs is postulated to be a proton abstraction which, in the case of FdUMP, would require an unfavorable C–F bond cleavage. In this work we investigated the structure of the ternary complex by ^{19}F NMR to determine the structure of the proposed intermediates and to explore the possible mechanistic implications. The binding of FdUMP to form a ternary complex is accompanied by an 12.4-ppm shift toward increased shielding. With the aid of model compounds it is possible to interpret this shift to be the result of an attack at the pyrimidinyl 6 position by a nucleophile (presumably a cysteinyl SH) followed by attachment at the 5 position to the CH_2 of the cofactor. Verification of the latter point was obtained indirectly by loss of H–F coupling (unresolved) and directly by observing a ^{13}C–^{19}F coupling constant when ternary complex was formed from cofactor prepared with CD_2O and $^{13}CD_2O$ (90% ^{13}C enriched), respectively. Denaturation of the ternary complex causes an 10.5-ppm shift of the ^{19}F resonance toward decreased shielding. The ternary complex remains intact as evidenced by the retention of the ^{19}F–^{13}C coupling to the cofactor. By analogy to α-fluorocyclohexanone, this shift reveals that the C–F bond has moved relative to the plane of anisotropy of the adjacent carbonyl group, i.e., upon denaturation the pyrimidine ring undergoes a conformational change. A sharpening of the ^{19}F resonance upon denaturation concurs with the greater mobility of the denatured complex. Indirect measurement of the ^{1}H–^{19}F coupling constants to both the CH_2 of cofactor and H_6 of the pyrimidine ring (using deuterium differencing) and application of the Karplus-type relationship enable a detailed representation of the relative spatial orientations of the groups on the pyrimidine 5,6 bond to be derived. In native ternary complex one proton of the methylene group of 5,10-methylenetetrahydrofolate is trans to the fluorine while the other is gauche. The proton at C-6 of the nucleotide and the fluorine are in a pseudo-trans-diequatorial relationship (i.e., the cysteine and the methylene group must be trans diaxial). Denaturation alters this arrangement such that the fluorine and the C-6 proton are trans diaxial.

Thymidylate synthetase catalyzes the reductive methylation of 2′-deoxyuridylate via the coenzyme 5,10-methylenetetrahydrofolate (5,10-CH_2H_4folate)[2] to form thymidylate and 7,8-dihydrofolate. The proposed involvement of de novo synthesis of thymidylate as a rate-determining factor in DNA synthesis and cell division has resulted in many attempts to elucidate the mechanism of action of thymidylate synthetase. Model studies suggested that the catalytic mechanism is initiated by attack of an active site nucleophile on carbon 6 of the pyrimidine ring to generate a carbanion which subsequently attacks 5,10-CH_2H_4folate to yield a transient ternary complex (**1a**). Methylation is completed by the transfer of the proton from carbon 6 of tetrahydrofolate[4] to the methylene group and abstraction of the hydrogen from carbon 5 of the pyrimidine ring. Chemical modifications of the enzyme by various sulfhydryl reagents[5] have indicated the presence of cysteine in the active site, and it has been suggested that cysteine acts as the catalytic nucleophile.[3a-d,5a-d,g,h,6] Addition of the inhibitor



1a, X = H
b, X = F
R = 5′-phospho-2′-deoxyribose

FdUMP to a mixture of the enzyme and 5,10-CH_2H_4folate results in the formation of stable ternary complexes.[7] Formation of the ternary complexes was postulated to involve the same enzyme-bound nucleophile that participates in the catalytic mechanism; hence, the mechanism describing inhibition by FdUMP terminates with the formation of a stable covalent ternary complex whose proposed structure is **1b**. The utility

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