

Carbenes in Sulfur and Nitrogen Heterocycles: A  $\pi$ -Electron-SCF-MO Study (1)

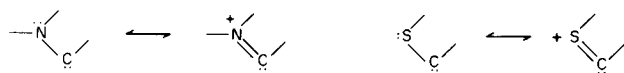
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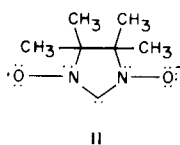
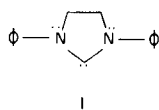
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The properties of a lone pair carbon orbital have been assessed in the context of self consistent field molecular orbital theory. An improved parameter for sulfur is presented as well as a derivation of "carbene" type parameters. The relative effects of adjacent nitrogen and/or sulfur on a carbene have been predicted and compared to experiment. Special reference has been made to the biological systems of thiamine and anhydroleucovorin.

A variety of aromatic systems lend themselves to stabilization of singlet carbenes (3). One type of system that has received considerable attention is that in which a carbene is found adjacent to a nitrogen or sulfur atom. Such systems give rise to nucleophilic carbenes by virtue of the following types of resonance:

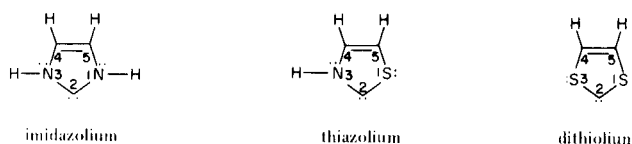


Specific examples of these types of systems are numerous; including imidazolium, dithiolium (4), and thiazolium carbenes. Two systems closely related to the imidazolium carbene are the imidazolinium carbene (I) (5-7) and the nitronyl nitroxide radical anion (II) (9).



Compound II is of experimental interest because of its great relative stability (*ca.* 30 minutes in strongly basic solution at room temperature). Compound I is a near analog of  $N^5,N^{10}$ -methenyltetrahydrofolate, a biological methyl transfer agent. In addition, the key role of the thiazolium moiety in Vitamin B<sub>1</sub> (thiamine) catalysis makes an understanding of the electronic behavior of the species important.

In order to evaluate the relative effects of nitrogen and sulfur on the general type of carbene outlined above, we have computed the properties of the following series of compounds as predicted by molecular orbital theory:

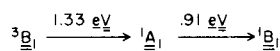


The results of these calculations have been interpolated to explain some of the physical chemical properties of biological substances.

## Method and Parameters.

The method of calculation used is basically that of Pople (10,11) which uses empirical integrals and the zero differential overlap (10) (ZDO) approximation. The integrals treated as empirical parameters include environment dependent ionization potentials,  $W\mu$ , bond resonance integrals,  $\beta\mu\nu$ , as well as various electron repulsion integrals,  $\gamma\mu\mu$ ,  $\gamma\mu\nu$ ,  $\gamma\sigma\pi$ ,  $K\sigma\pi$ , the last two of which are necessary only for lone pairs of electrons. We have adopted the parameters for carbon from Roos and Skancke (12) and those for nitrogen from Fischer-Hjalmars and Sundbom (13). In order to treat the molecules under consideration, parameters for a lone pair orbital on carbon (the "carbene" orbital) and for a sulfur orbital are also necessary. The carbene requires five parameters,  $W\sigma$ ,  $\gamma\sigma\sigma$ ,  $\gamma\sigma\pi$ , and  $K\sigma\pi$  where both sigma and  $\pi$ -orbitals are centered on the same atom and the parameter,  $\gamma\sigma\sigma$ , where the repulsion is between the carbene sigma orbital and the  $\pi$ -orbital on the adjacent carbon atom. All the parameters between the  $\pi$ -orbital on the carbene and other atoms were taken equal to that for a normal carbon  $\pi$ -orbital and the corresponding atom. Because of the paucity of data, it is not possible to empirically evaluate these parameters by comparing many calculations to a large amount of experimental information. The lack of empirical data for carbenes may be somewhat offset by a detailed knowledge of its electronic states obtained by an *ab*

*initio* molecular orbital study of singlet carbene. The results of such a study have recently been published by Harrison and Allen (14). According to their data, a carbene in an aromatic system (bond angle near  $120^\circ$ ) should have electronic states in the following order:



These data allow independent determination of only two parameters, necessitating some assumptions. We assumed that the one center integrals for the carbene lone pair bear the same proportion to the corresponding integrals for a lone pair on a pyridine type nitrogen, *i.e.*,  $\gamma_{\text{carbene}} = f X \gamma_{\text{pyridine}}$  where  $\gamma$  is any one center repulsion integral. After obtaining the two center repulsion integral between the sigma orbital on the carbene and the

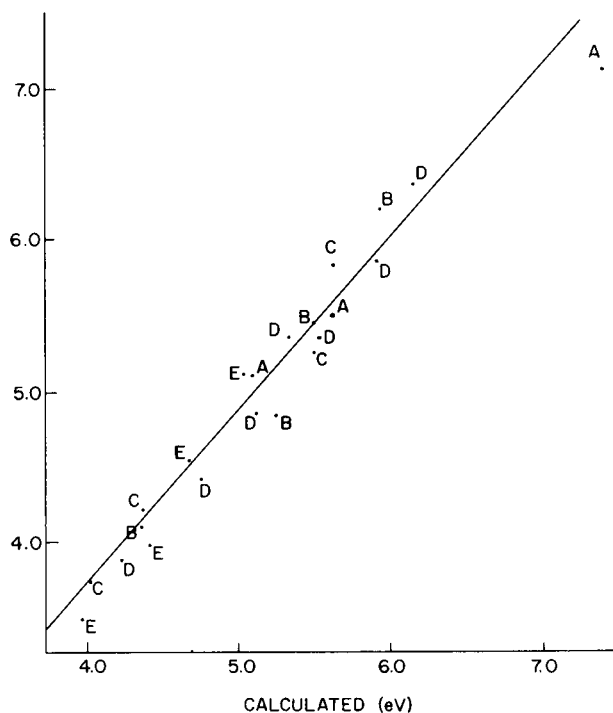


Figure I. Spectral correlation for sulfur compounds. The experimental transitions (14,41) in electron-volts for a series of compounds have been plotted against the calculated values for these compounds. The letter refers to the compounds as follows: thiophene (A),  $\alpha$ -thianaphthene (B),  $\beta$ -thianaphthene (C), dibenzothiophene (D), benzonaphothiophene (E). No transitions have been omitted for each compound so that the third B is the third transition of thianaphthene.

$\pi$ -orbital on the adjacent atom by a charged sphere approximation (13), the parameters  $f$  and  $W_\sigma$  were fitted to the *ab initio* data (14) by trial and error. The best parameters obtained for a carbene orbital located 0.323 Å from the nucleus are given in Table III.

Since previous work (15) has shown that *d*-orbital contributions from sulfur have minimal effects on the results of this type of calculation, we have used a *p* model exclusively. Presumably, the semiempirical values for the *p*-orbitals include the effects of *d*-orbitals. Sulfur parameters have been surveyed by several authors with varying degrees of success (15-23). A summary of some of the previously used parameters for sulfur orbitals in aromatic heterocycles is given in Table I. The electron repulsion integrals have usually been evaluated by some theoretical approximation (24-26) whereas the ionization potential,  $W_s$ , and resonance integral,  $\beta_{cs}$ , have been retained as empirical parameters.

Our experience with several of these parameter sets yielded predictive results of only minor value. Attempts to improve computed ionization and spectral correlation by making slight variations in the sulfur parameters demonstrated a remarkable insensitivity of these properties to the parameters. Thus, variation of  $\beta_{cs}$  by up to 1 eV and

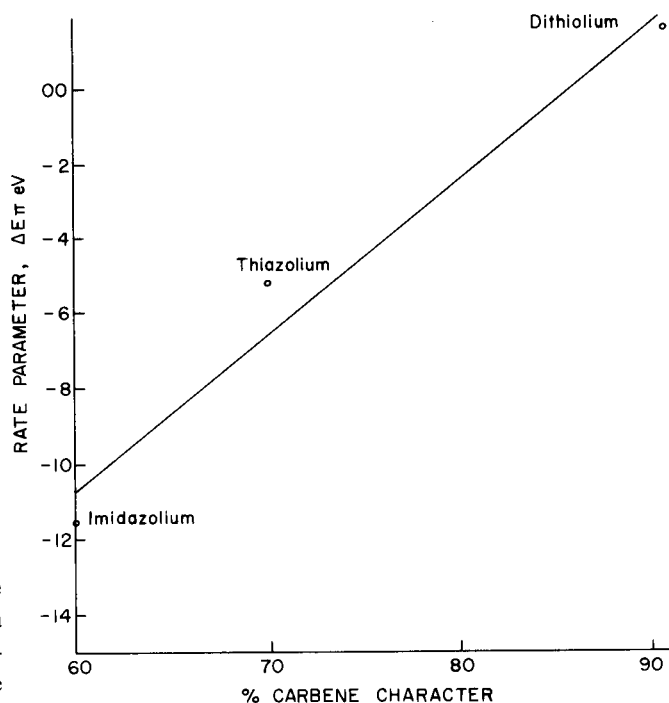


Figure II. Relation between  $\Delta E\pi$  and Carbene Character (35) where the value  $\Delta E\pi$  is the difference between the  $\pi$ -electron energy calculated for the ion and that for the carbene (ion-carbene).

TABLE I  
Parameters Previously Used for  
Sulfur Heterocycles (in eV)

$W_s$	$\beta_{cs}$	$\gamma_{ss}$	Reference
-22.88	-1.00 eV	12.14	(15)
-20	-1.623	10.84	(16)
-24.35	-1.43	10.405	(17)
-22.20	-1.50(-1.00)	13.05	(18)
-20.00	-1.36(-1.00)	9.79	(19)
-12.50		9.80	(20)
-22.20			(21)
-20.20	-1.37	9.58	(22)

TABLE II  
Ionization Potentials (eV)

Compound	$C_s^2$	Calc.	Expt.	Reference
Dimethyl Sulfide	.98	8.90	8.73	(28)
Thiophene	.00	8.98	8.95	(29)
$\alpha$ -Thianaphthene	.20	8.35	7.96	(23)
$\beta$ -Thianaphthene	.00	7.39		
Dibenzothiophene	.43	8.56	7.82	(23)
Benzonaphthothiophene	.11	7.63		
Phenothiazine	.09	7.01	6.70	(30)

TABLE III

Parameters Used in This Study (eV)

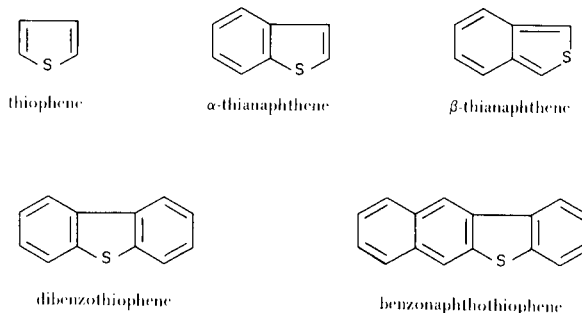
Parameter (a)	Carbon	Carbene	Methyl	Nitrogen	Sulfur
$W_x$	-9.84	-11.62	-12.02	-8.52	-8.95
$\beta_{cx}$	-2.42	--	-1.38	-2.25	-1.37
$\gamma_{xx}$	11.97	12.49	10.01	15.44	9.58
$\gamma_{cx}$	6.91	8.00	5.70	6.34	7.28
$\gamma_{\sigma\pi}$		9.94			
$K_{\sigma\pi}$		1.13			
$R_{cx}^0$ (Å)	1.397	1.60	--	1.338	1.714

(a) The designation cx refers to orbital x and a  $\pi$ -orbital on an adjacent carbon whereas  $\sigma\pi$  refers to the carbene sigma orbital and  $\pi$ -orbital on the same carbon atom.

of  $W_s$  by up to 10 eV did not effect drastic changes in the computed properties. Examination of the computed molecular orbitals revealed that the highest orbitals contained little or no contribution from sulfur. The sensitivity of the ionization potential of a molecule (Koopman's Theorem [27]) to the sulfur ionization potential ( $W_s$ ) may be quantitated by the square of the coefficient of the

sulfur atomic orbital in the highest molecular orbital ( $C_s^2$ ) because the dependence of the ionization of the molecule on the sulfur ionization parameter is directly dependent on the electron density on sulfur of the highest molecular orbital. Similarly, spectral sensitivity to  $\beta_{cs}$  can be expressed by the change in C-S bond order during a transition ( $\Sigma\Delta P_{cs}$ ) because if there is no change in carbon-sulfur bond order between the ground and excited states then  $\beta_{cs}$  will have no effect on energy of the transition.

For example, the properties of  $\alpha$ -thianaphthene were calculated using Skancke's parameters (22). The sensitivity parameters ( $C_s^2$  and  $\Sigma\Delta P_{cs}$ ) were both found to be zero. This result shows that any computed spectral or ionization data is a functional primarily of the pure hydrocarbon fragment and therefore only of carbon parameters. This observation is typical of our primary test sample including thiophene,  $\alpha$ -thianaphthene,  $\beta$ -thianaphthene, dibenzothiophene, and benzonaphthothiophene:



There is no *a priori* reason for insisting that the properties of these molecules should be sensitive to the parameters used for sulfur but in view of the only moderate success of previous calculations it seemed likely that this insensitivity might be a causative factor. Others, for partially theoretical reasons, have used very high absolute values of  $W_s$  centering around -20 eV. We chose to treat  $W_s$  strictly as an empirical parameter. It was necessary to lower the absolute value of  $W_s$  considerably to obtain any sulfur dependency but the results were gratifying. Figure 1 records the spectral correlation between a large number of experimental transitions in sulfur compounds and the corresponding calculated values obtained when  $W_s = 8.95$  eV,  $\beta_{cs} = 1.37$ . The spectral correlation coefficient for this experimental set is 0.98 which compares very favorably with values near .89 obtained for other parameter sets. Paralleling the increased correlation is the increase in sensitivity where the average absolute sensitivity ( $\Sigma\Delta P_{cs}$ ) went from essentially nil to 0.17.

Table II gives the calculated and experimental ionization potentials with the corresponding sensitivities. Dimethyl sulfide and phenothiazine have been included for

comparison. Correlation here is .96 - also a substantial improvement. We believe these results justify the use of a low value for  $W_s$ . A summary of the parameters used in this study is given in Table III. With the exception of  $W_s$  the sulfur parameters are from Skancke (22). Perhaps the strongest argument for the low value of  $W_s$  is the experimental value for dimethyl sulfide. In many sulfur heterocyclic compounds it is not clear whether the first ionization potential involves sulfur electrons or only carbon  $\pi$ -electrons.

In each calculation the variable electronegativity method of Brown and Heffernan was used to obtain maximum consistency of the charge distribution (31). The correlations applied to the ionization potential and one center repulsion integrals were as follows:

$$W = W^{\circ} + A Q + B Q^2$$

$$\gamma = \gamma^{\circ} (1 - CQ)$$

where  $Q$  = charge. The constants  $A$ ,  $B$ , and  $C$  are given below. Sulfur was treated the same as carbon.

	A	B	C
Carbon	5.377	0.429	0.108
Nitrogen	7.270	0.418	0.090

#### Results and Discussion.

The computed charges based on orbital densities for a series of ions and carbenes are given in Table IV. These data are valuable for assessing the relative contributions of sulfur and nitrogen to heterocyclic chemistry and to their respective ylids (32).

The difference in computed energy for an ion and its corresponding ylid (carbene) should be a measure of the rate of ionization of the  $C_2$ -H bond. These differences predict rates in the order dithiolium > thiazolium > imidazolium. It is known that thiazolium ions exchange

deuterium at carbon 2 about 3000 times faster than do imidazolium ions (33). Although precise rate data is not available for dithiolium, a recent report states, "1,3-dithiolium perchlorate undergoes rapid deuterium exchange at C-2 and reacts with triethylamine to give a high yield of  $\Delta^2,2'$ -bi-1,3-dithiole" (34). It seems that adjacent sulfur is more effective in weakening a carbon hydrogen bond than is nitrogen.

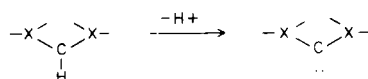
This effect is related to the degree of carbene character (*i.e.*, neutrality) in the dissociated species (35). Figure II shows the relationship between the computed parameter  $\Delta E\pi$  and the corresponding percent carbene character where  $\Delta E\pi$  is the difference between the calculated  $\pi$ -electron energy for the ion and that for the carbene (ylide-carbene). Evidently, ionization is favored by a high degree of carbene character in the dissociated species. Sulfur is then expected to affect the reactions of dithiolium and thiazolium by facilitating ionization of the  $C_2$ -H bond and by increasing the electrophilicity of the resultant carbon lone pair. The correctness of this prediction is confirmed by the rate data cited above and by the ease with which dithiolium carbene dimerizes (34). It is interesting that thiazolium ions may also react *via* carbene mechanisms (36). By way of contrast, no reactions of imidazolium species are known to proceed *via* carbene mechanisms.

Comparison of imidazolium to dithiolium shows that in the ions sulfur supports a larger positive charge than nitrogen but that in the ylids nitrogen tends to retain its high charge while sulfur accommodates an adjacent carbene by resonance. The greater tendency of nitrogen to bear a positive charge is reflected by the greater nucleophilic character of the adjacent carbene.

The nucleophilicity of a carbene adjacent to a nitrogen is seen, for example, in the catalysis of acyloin condensations by thiazolium ions (37). In view of the slow rate

TABLE IV

Computed Charge Densities and Energies



Atom	Dithiolium		Thiazolium		Imidazolium		Thiamine (a)		Diphenylimidazolium (b)	
	ion	carbene	ion	carbene	ion	carbene	ion	carbene	ion	carbene
1	+0.44	+0.06	+0.38	+0.04	+0.41	+0.30	+0.35	-0.04	+0.33	+0.23
2	+0.09	-0.09	+0.13	-0.30	+0.15	-0.40	+0.07	-0.33	+0.22	-0.34
3	+0.44	+0.06	+0.45	+0.36	+0.41	+0.30	+0.46	+0.38	+0.33	+0.23
4	+0.02	-0.01	+0.09	+0.02	+0.02	-0.10	+0.07	+0.00		
5	+0.02	-0.01	-0.05	-0.13	+0.02	-0.10	-0.05	-0.13		

(a) Thiazolium moiety only. (b) Analog of  $N^5, N^{10}$ -methenyltetrahydrofolic acid.

TABLE V  
Nuclear Magnetic Resonance Data

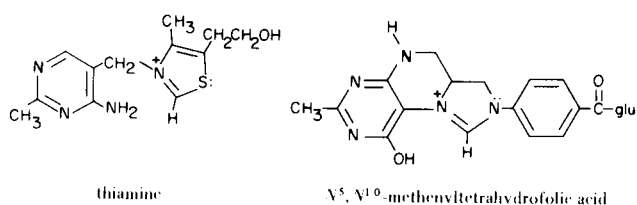
proton	$\delta$ calc. (a)	$\delta$ exp. (b)
2	8.75	10.0
4	8.35	8.45
5	6.95	8.25

(a)  $\delta$  calc. =  $10 Q + \delta C_6H_6$  (39). (b) See ref. 38.

of exchange of imidazolium ions it is not surprising that they are unreactive; although presumably any reaction would be *via* a nucleophilic mechanism.

We summarize the preceding statements by noting that sulfur tends to remain neutral, increases lability of an adjacent  $sp^2$  C-H bond, and favors electrophilicity of an adjacent carbene. Nitrogen tends to assume a positive charge, has a weak ionizing effect on an adjacent  $sp^2$  C-H bond, and favors nucleophilicity of an adjacent carbene. The correctness of these relative predictions is also confirmed by the observed relative order of nuclear magnetic resonance shifts in thiazolium ions (38). These are given in Table V.

These properties of nitrogen and sulfur are important in interpreting chemical and biological phenomena. It has already been noted that thiazolium ions catalyze benzoin type condensations *via* the classic Lapworth mechanism. The function of the thiazolium moiety in thiamine is to stabilize an acyl carbanion in a manner analogous to cyanide ion stabilization of the benzoyl carbanion. The



relative effects of sulfur and nitrogen on thiamine catalysis have been the subject of some conjecture (8,33,37). The results of our calculations show that the sulfur atom increases the concentration of the catalytic species by virtue of its weakening effect on the  $C_2$ -H bond and carbene stabilization whereas the nitrogen serves primarily to give the necessary nucleophilic character to the resultant carbene. In this conjunction, it is noteworthy that thiamine was found to yield a more nucleophilic carbene than the parent thiazolium ion. The effect of three alkyl groups no doubt accounts for this increased nucleophilicity.

Since  $N^5, N^{10}$ -methylnitro-tetrahydrofolic acid is known to exchange at about the same rate as thiamine and since its near analog 1,3-diphenylimidazolium ion is here found to have a nucleophilicity comparable to thiamine, the

question arises of whether it might not also catalyze acyloin condensations (8,40). The analog does not catalyze such reactions and it seems that the lack of aromaticity in the heterocyclic ring favors formation of an adduct rather than service as a catalyst (6). This fact emphasizes the necessity of considering other factors (such as the aromaticity) in the overall function of these heterocycles. Bond lability-carbene character (sulfur) and nucleophilicity (nitrogen) can be controlling influences.

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(32) We have adhered to the following nomenclature:

undissociated species, *e.g.*



thiazolium ion

dissociated species, *e.g.*



thiazolium carbene



thiazolium ylid

(33) P. Haake, L. P. Bausher, and W. B. Miller, *J. Am. Chem. Soc.*, **91**, 1113 (1969).

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(35) The dissociated species may be properly referred to as either a *carbene* or a *ylid*. In discussing resonance we refer to the carbene canonical form when  $Q_{c_2} = 0$  and the ylid canonical form when  $Q_{c_2} = 1$ . Percent carbene character is then expressed as:

$$\% \text{ carbene character} = (1 + Q_{c_2}) \times 100$$

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