inosine (Ino) and 5′-GMP complexes such as $[(NH_3)_2Pt(InoH_{-1})]^+$ and $[(NH_3)_2Pt(GMPH_{-1})]^-$; there were attributed to polynuclear complex formation.[12,13]

Furthermore, there is clear evidence that none of the species formed during the reaction is a Pt complex with two 5′-GMP molecules bound via N7 of the guanine ring to the Pt atom from both ^1H and ^{195}Pt NMR data of the *cis*-$[Pt(NH_3)_2(5'\text{-}GMP)_2]$ complex. The latter exhibits a H8 proton resonance at 3.931 ppm and a ^{195}Pt resonance of −2451.3 ppm which is considerably shifted to high field from the ^{195}Pt resonances of species IG/IIG and IIIG (see Table III). Further, the resonances for the H1′ protons in the *cis*-$[Pt(NH_3)_2(5'\text{-}GMP)_2]$ complex are at 2.143 ppm, 0.020 ppm to high field of the corresponding resonance in free 5′-GMP (2.163 ppm), while in species IG, IIG, and IIIG the H1′ signals are at ca. 2.28 ppm which is to low field of the corresponding free signal.

From the structures of species IG/IIG given in Figure 9 in which the Pt atom is bound to N7 of the guanine ring, one would expect the ^{195}Pt chemical shift of species IG/IIG to be given approximately by the mean of the ^{195}Pt chemical shifts of *cis*-$[Pt(NH_3)_2Cl_2]$ and *cis*-$[Pt(NH_3)_2(5'\text{-}GMP)_2]$; this has a value of −2306.4 ppm which is in excellent agreement with the measured value of −2302.0 ppm.

Comparison of the Kinetics of the Reactions of 5′-AMP and 5′-GMP with Excess *cis*-$[Pt(NH_3)_2Cl_2]$ in the Presence of KCl. A comparison of the kinetics of the reactions of 5′-AMP and 5′-GMP with excess *cis*-$[Pt(NH_3)_2Cl_2]$ in the presence of KCl at 80 °C leads to the following observations. Tables I and II show the relationship $k_{1G} \sim k_{1A} > k_{3A} = k_{4A} > k_{2A}$ for the second-order association rate constants, which implies that the dissociation of a Cl atom from *cis*-$[Pt(NH_3)_2Cl_2]$ is not rate limiting. Considering only the 5′-AMP reaction with *cis*-$[Pt(NH_3)_2Cl_2]$, we observe that the association rate constant for binding to N7 (k_{1A}) is larger than that for binding to N1 (k_{2A}), a finding which correlates inversely with the smaller pK of N7 compared to N1 of the adenine ring.[25] However, once a Pt atom is bound to either N1 or N7, the association rate constants (k_{3A} and k_{4A}) for binding to the remaining site are equal. This implies an electronic redistribution upon binding of a Pt atom to either N1 or N7, such that the reactivity toward *cis*-$[Pt(NH_3)_2Cl_2]$ of the remaining available site is less than that of N7 but greater than that of N1 in free 5′-AMP. Considering the schemes for the reaction of 5′-GMP with excess *cis*-$[Pt(NH_3)_2Cl_2]$, it is clear that species IG and IIG could either be formed simultaneously (as in the case of species IA and IIA in the 5′-AMP reaction) or in sequence. Given our proposed structures for species IG and IIG (Figure 9), the latter seems unlikely. Moreover, it is likely that the association rate constants for the formation of the two rotamers, IG and IIG, would be equal and given by $k_{1G}/2$. Assuming this assumption is correct, we note the relationship $k_{1A} > k_{1G}/2 > k_{2A}$ for the second-order association rate constants for the binding of the first molecule of *cis*-$[Pt(NH_3)_2Cl_2]$ to 5′-AMP and 5′-GMP which is inversely correlated with the known relationship $pK_a(N7)_{5'\text{-AMP}} < pK_a(N7)_{5'\text{-GMP}} < pK_a(N1)_{5'\text{-AMP}}$ for the protonation of ring nitrogen atoms.[25]

1,2,5-Thiadiazole 1-Oxides. 3. An Experimental and Theoretical Investigation of the Inversion Barrier

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Contribution from the Merck Sharp & Dohme Research Laboratories, Division of Merck & Company, Inc., Rahway, New Jersey 07065. *Received June 29, 1981*

Abstract: The 1,2,5-thiadiazole 1-oxide system was synthesized via cyclocondensation of diethyl oxalimidate or dimethyl thiooxalimidate with thionyl chloride. The alkoxy and alkylthio group in these products are replaced by amines, e.g., pyrrolidine, which produced 3-ethoxy-4-(1-pyrrolidinyl)-1,2,5-thiadiazole 1-oxide from the diethoxy analogue at room temperature. Examination of this product by ^{13}C NMR in the presence of a chiral shift reagent showed two isomers, indicative of a stable pyramidal sulfoxide structure. Reaction of 3,4-diethoxy-1,2,5-thiadiazole 1-oxide with optically active amines, e.g., *l*-ephedrine, produces readily separable diastereoisomeric mixtures. The diastereoisomers undergo inversion only at elevated temperature, $\Delta G^{\ddagger}_{120} = 33$ kcal mol^{-1}, compared to only ca. 14.8 kcal mol^{-1} for a thiophene 1-oxide and 36 kcal mol^{-1} for diaryl sulfoxides. X-ray analysis of 3,4-bis(methylthio)-1,2,5-thiadiazole 1-oxide demonstrates that the ring is essentially nonaromatic and confirms the pyramidal sulfoxide structure. Interaction between the sulfur lone pair and the diene is small, the C_3–C_4 bond length lying closer to that of cyclopentadiene than of thiophene or thiadiazole. Theoretical calculations indicate that aromaticity effects lower the inversion barrier nearly equally in the thiophene and thiadiazole sulfoxides by stabilizing the planar transition state and destabilizing the nonaromatic pyramidal structure. The reduction of the barrier in the thiadiazole, however, is counteracted by the effect of the electronegative nitrogen atoms, thus raising the inversion barrier back to the range of normal sulfoxides.

1,2,5-Thiadiazole (**1**) is a planar aromatic ring system with molecular parameters similar to thiophene. The aromaticity of **1** is supported by theoretical calculations, physical measurements, and chemical reactivity.[1] The 1,1-dioxides of 1,2,5-thiadiazoles **2**,[2] on the other hand, do not appear to exhibit aromatic properties and are much less stable[1] thermally and more electrophilic than the nonoxidized form. Little is known, however, about the corresponding monoxides (**3**). In fact, the literature contains very few detailed accounts of the chemistry of sulfoxides derived from thioaromatic systems. Mock[3] prepared 2,5-di-*tert*-octylthiophene 1-oxide (**4**) and showed spectroscopically that two forms of the pyramidal sulfur can be observed at −10 °C, while at room temperature the sulfoxide undergoes rapid inversion. This low inversion barrier (e.g., ca. 20 kcal mol^{-1} less than diaryl sulfoxides) was attributed by Mock to be a consequence of either a delo-

† Department of Chemistry, Wayne State University, Detroit, MI 48202.

(1) L. M. Weinstock and P. I. Pollack, "Advances in Heterocyclic Chemistry", Vol. 9, Academic Press, New York, 1968, p 107.
(2) R. Y. Wen, A. P. Komin, R. W. Street, and M. Carmack, *J. Org. Chem.*, **40**, 2743 (1975).
(3) W. L. Mock, *J. Am. Chem. Soc.*, **92**, 7610 (1970).

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Table I. ^{13}C Chemical Shift Data for 7[a,b]

shift reagent	C_3	C_4	OCH_2	$-CH_3$	$C_{2'}$	$C_{5'}$	$C_{3'}$	$C_{4'}$
none	164.0	155.1	69.1	14.1	51.1	48.6	26.5	24.0
Eu(hfc)$_3$[c] (0.25 equiv)	166.4	158.2	69.8	14.3	52.1	49.3	26.7	24.3
			69.7	14.2	51.9	48.8		24.1
Eu(fod)$_3$[d] (0.25 equiv)	166.4	158.4	70.0	14.3	52.3	49.4	26.8	24.3

[a] Concentration of [7] = 0.5 M in $CDCl_3$, chemical shifts in parts per million from internal Me_4Si (δ_C 0.0). [b] Pyrrolidinyl carbons nonequivalent due to restricted rotation. [c] Chiral shift reagent, tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III). The chemical shifts of C_3, C_4, and $C_{3'}$ were the same for the two enantiomers. [d] Achiral shift reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III).

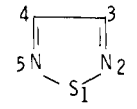
Table II. ^{13}C Chemical Shift Data for the Diastereomers of 9 and 10[a]

compd	solvent	C_5	C_6	C_8	C_9	C_6-CH_3	N-CH_3	$C_{1'}$	$C_{2'6'}$	$C_{3'5'}$	$C_{4'}$
9	$CDCl_3$	83.2	56.1	152.3	162.1	11.8	36.7	133.7	125.5	128.9	129
		80.8	59.0	153.8	160.7	11.6	36.5	133.4	125.6	129.0	129

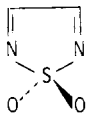
compd	solvent	C_5	C_6	C_8	C_9	$-CH_2OH$	$-C(CH_3)_3$	$-C(CH_3)_3$
10	Me_2SO-d_6	79.9	41.6	151.7	162.9	60.5	59.2	26.3
		77.9	42.6	152.4	162.2	60.3		

[a] Chemical shifts in parts per million from internal Me_4Si (δ_C 0.0).

calization energy of planar thiophene sulfoxide similar to that observed in the phosphole ring or "relief from a destabilization energy associated with the (antiaromatic) pyramidal form".



1



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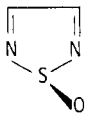

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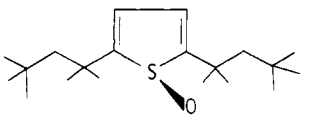


4

With this background we felt that the chemistry of 1,2,5-thiadiazole oxides was a worthwhile field of investigation. Questions to be answered include the aromaticity and relative stability of the pyramidal and planar forms of this system and its chemistry as it relates to the parent system.

In this paper we present (a) the synthesis of some 1,2,5-thiadiazole 1-oxides, (b) the geometry of the system as established by X-ray analysis, (c) preparation of stable diastereomers of optically active sulfoxides, (d) calculation of the inversion barriers from their rate of racemization, and finally (e) the interpretation of the experimental data by ab initio theoretical calculations. Further details regarding the organic chemistry of this system will be reported elsewhere.

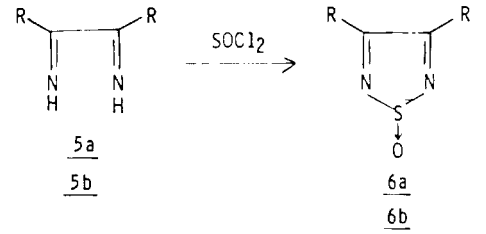
Synthesis and Measurement of the Inversion Barrier

Synthesis of the 1,2,5-thiadiazole 1-oxide system is achieved through the reaction of **5a**[4] and **5b**[5] with thionyl chloride producing **6a** and **6b**. The alkoxy or alkylthio groups of **6a** or **6b** can be readily replaced with nucleophiles. Thus, the reaction of **6a** with pyrrolidine in ethanol at room temperature gave 3-ethoxy-4-(1-pyrrolidinyl)-1,2,5-thiadiazole 1-oxide (**7**) and 3,4-bis(1-pyrrolidinyl)-1,2,5-thiadiazole 1-oxide (**8**) with excess pyrrolidine. Primary amines and other nitrogen nucleophiles reacted analogously. This behavior is similar to that of the corresponding thiadiazole dioxides[2] but is in contrast to the nonoxidized thiadiazole analogues which undergo this type of reaction only under forcing conditions.[1]

Table III. Rate of Epimerization of 9[a] at 120 °C

time, h	fraction of unepimerized 9	time, h	fraction of unepimerized 9
0	0.93	44	0.60
22	0.66	76	0.50

[a] Measured by ^1H NMR from the intensity δ 5.8 and 5.7 peaks (C_5-H). The rate constant for the reversible first-order reaction was calculated according to A. A. Frost and R. S. Pearson, "Kinetics and Mechanism", Wiley, New York, 1965.



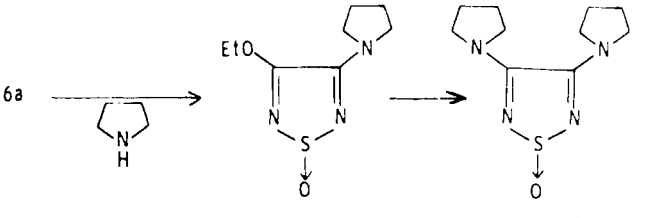
5a

5b

6a

6b

a) R = EtO-
b) R = MeS-



7

8

The sulfoxide moiety because of its pyramidal structure can give rise to asymmetry.[6] Carbon-13 NMR was used to differentiate the optical isomers of **7** employing a chiral shift reagent, tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]-europium(III). The pyrrolidine and ethyl carbons showed nonequivalence in the presence of the shift reagent, indicating that **7** can exist in two isomeric forms and that the interconversion is not rapid at room temperature. Table I presents this data for **7** and gives the results with a control shift reagent, tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)euro-

(4) J. D. Behun, U. S. Patent No. 3112334 (Nov 26, 1963); *Chem. Abstr.*, **60**, 5342 (1964).
(5) H. M. Woodburn and C. E. Sroog, *J. Org. Chem.*, **17**, 351 (1951).
(6) K. K. Andersen, *Int. J. Sulfur Chem., Part B*, **6** (Number 1), 69 (1971).

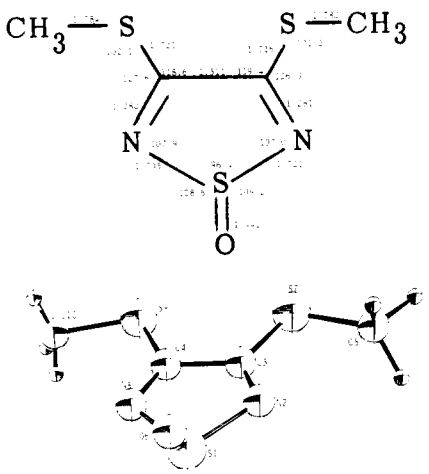
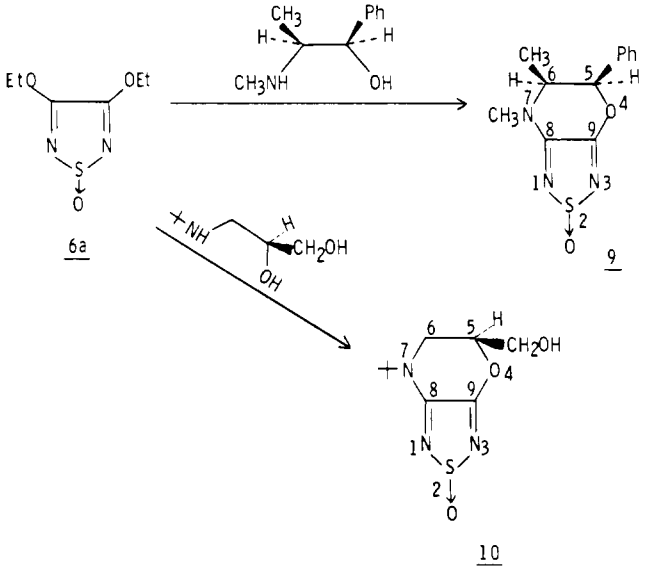


Figure 1. Bond distances (in Angstroms) and angles (in degrees) of **6b** with average standard deviations of 0.006 Å and 0.4°, respectively. Also shown is a perspective drawing of **6b**.

pium(III). Even with 0.5 equiv of this achiral shift reagent, nonequivalence was not observed.

Stable chiral sulfoxide derivatives **9** and **10** were prepared as mixtures of diastereomers by treatment of **6a** with *l*-ephedrine and (*S*)-2,3-dihydroxy-1-(*tert*-butylamino)propane.[7] Fractional



crystallization produced the pure diastereomers which were characterized by ^{13}C NMR (Table II). These diastereomers were stable at room temperature but epimerized rapidly in the presence of trace amounts of acid. The rate of epimerization of **9** in CD_3CN at 120 °C, monitored by ^1H NMR of the C_5 hydrogen (δ 5.7 and 5.8), showed a first-order rate constant of 5×10^{-6} s^{-1} (see Table III). The standard free energy of activation for the inversion derived from this was $\Delta G^*_{120} = 33$ kcal mol^{-1}. This barrier is about the same as that of diaryl sulfoxide[8] (36 kcal mol^{-1}) and significantly higher than that of the thiophene **4** (14.8 kcal mol^{-1}).[3] The aromatic stabilization of the planar form, as in the case of **4**[3], should lower the inversion barrier of thiadiazole oxides. This could be opposed by the effect of the adjacent electronegative[14] nitrogen atoms which increases the inversion barrier by stabilizing the pyramidal form. In order to assess the extent that these factors contribute to the stability of thiadiazole oxides, the ground-state geometry of the system was determined by X-ray crystallography and ab initio quantum mechanical calculations were carried out.

(7) L. M. Weinstock, D. M. Mulvey, and R. J. Tull, *J. Org. Chem.*, **41**, 3121 (1976).
(8) D. R. Rayner, A. J. Gordon, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4854 (1968).

Table IV. Comparison of the Geometry of the Nucleus of a 1,2,5-Thiadiazole Oxide (**6b**) with a 1,2,5-Thiadiazole (**11**)

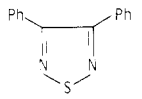
	6b	11
S-N, Å	1.712 (5)	1.632 (4)
N-C, Å	1.280 (7)	1.335 (6)
C-C, Å	1.511 (8)	1.435 (4)
N-S-N, deg	96.4 (2)	99.2 (2)

Table V. Inversion Barriers (kcal mol^{-1})

	calcd	obsd
$H_2S{=}O$	43.15	
$(CH_3)_2SO$	51.4	36-42
$(NH_2)_2SO$	66.5	
thiophene oxide (**4**)	19.6	14.8[3]
thiadiazole oxide (**9**)	31.9	33

X-ray Structure

The exact geometry of the thiadiazole oxide system was established by X-ray analysis of a single crystal of **6b**. The bond distances and angles and the perspective drawing for **6b** are shown in Figure 1. A comparison of the important structural parameters of **6b** relative to the more aromatic 1,2,5-thiadiazole nucleus of **11**[9] is given in Table IV.



11

The average S–N single bond in **6b** is 0.08 Å longer than in **11** while the average N–C double bond is 0.06 Å shorter. In addition, the C–C single bond is 0.08 Å longer in **6b**. This information serves to highlight the fact that the 1,2,5-thiadiazole nucleus in **6b** has essentially lost its aromaticity and consists of bonds which are essentially single and double.

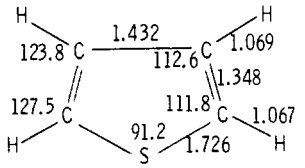
On a more subtle level the thiadiazole ring of **11** is planar to within 0.01 Å while the sulfur atom in **6b** is a small but significant 0.16 Å below the plane of the other four atoms. The oxygen atom in **6b** is 0.99 Å above this plane while the S–O bond forms an angle of 61° with the plane defined by N–S–N. The decrease in the N–S–N angle from 99.2° in **11** to 96.4° in **6b** is also consistent with a slight pucker in the ring of **6b**.

Theoretical Studies

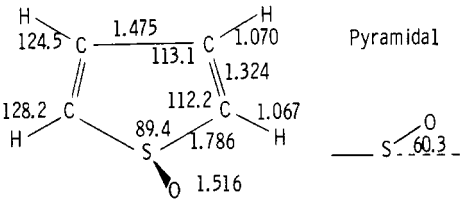
Ab initio molecular orbital calculations have been very successful in predicting equilibrium geometries and computing inversion barriers. It seemed, therefore, that they could help in understanding the inversion barrier of thiadiazole 1-oxide in comparison with thiophene 1-oxide and dimethyl sulfoxide. The calculations discussed below draw heavily from two related theoretical investigations in progress. Since three d orbitals are necessary for the correct description of sulfoxides,[10,11] d orbitals have been included for all calculations reported here.

The theoretically optimized geometries for thiadiazole and thiadiazole oxide (pyramidal and planar) are shown in Figure 3. The analogous calculated structures in the thiophene series are shown in Figure 2. The theoretical geometries agree well with the experimental structures, where the latter are available. On average, bond lengths differ by ±0.02 Å and angles by ±2.5°. Although the theoretical geometry optimizations of the sulfoxides were constrained to keep the heterocyclic ring planar, the residual forces on the ring atoms indicate a puckering in the same direction as observed in the X-ray structure and in earlier calculations.[12] The observed and calculated changes in geometry on S-oxidation are in even better agreement than the geometries themselves

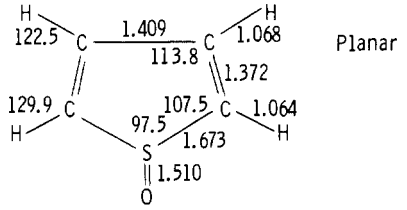
(9) M. Mellini and S. Merlino, *Acta Crystallogr., Sect. B* **B32**, 1074 (1976).
(10) H. Wallmeier and W. Kutzelnigg, *J. Am. Chem. Soc.*, **101**, 2804 (1979).
(11) E. Ball, M. A. Ratner, and J. R. Sabin, *Chim. Scr.*, **12**, 128 (1977).
(12) M. H. Palmer and R. H. Findlay, *J. Chem. Soc., Perkin Trans. 2*, 1223 (1975).



Total Energy = -550.66185 a.u.



Total Energy = -625.32659 a.u.



Total Energy = -625.29534 a.u.

Barrier to Inversion = 19.6 kcal mole^{-1}

Figure 2. Comparison of the optimized geometry and total energy for thiophene and thiophene oxide in the planar and pyramidal structures.

(±0.01 Å for bond lengths and 0.5° for angles). In all cases the comparison between theory and experiment is considerably poorer when d orbitals are not included for sulfur.

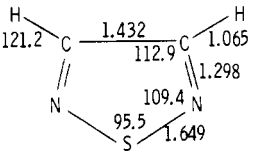
Calculated barriers to inversion are in good agreement with experiment (Table V). The thiadiazole 1-oxide barrier (31.9 kcal mol^{-1} (calcd), 33 kcal mol^{-1} (obsd)) is much higher than thiophene 1-oxide (19.6 kcal mol^{-1} (calcd), 14.8 kcal mol^{-1} (obsd)). Both compounds have barriers substantially lower than normal sulfoxides (51.4 kcal mol^{-1} (calcd) for $(CH_3)_2SO$, 36–42 kcal mol^{-1} (obsd) for aryl sulfoxides).[7] Aromaticity has been invoked to rationalize this difference.[3,13] Increasing the electronegativity of substituents is known to raise the barrier for pyramidal inversion at nitrogen, phosphorus, and sulfur.[14] This trend is also reproduced by the calculations (51.4 kcal mol^{-1} (calcd) for $(CH_3)_2SO$, 66.5 kcal mol^{-1} (calcd) for $(NH_2)_2SO$). A rationalization of the barrier in thiadiazole 1-oxide requires that the effects of both aromaticity and electronegativity be considered.

To assess the role of electronegativity, the calculated inversion barriers of $(CH_3)_2SO$ and $(NH_2)_2SO$ can be compared with those of H_2SO. The isodesmic reaction (1) probes the influence of

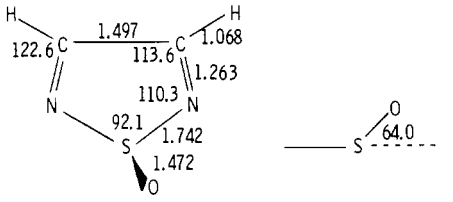
$$X_2S + H_2SO \rightarrow X_2SO + H_2S \quad (1)$$

	ΔE(pyramidal)	ΔE(planar)
X = CH_3	−19.6 kcal mol^{-1}	−11.6 kcal mol^{-1}
X = NH_2	−29.3 kcal mol^{-1}	−6.3 kcal mol^{-1}

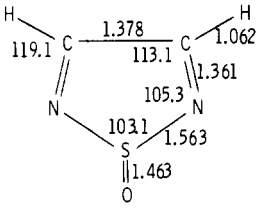
substituents (also see Figure 4). Both CH_3 and NH_2 stabilize the SO bond relative to hydrogen, affecting the pyramidal structure more than the planar and thereby increasing the barrier



Total Energy = -582.57112



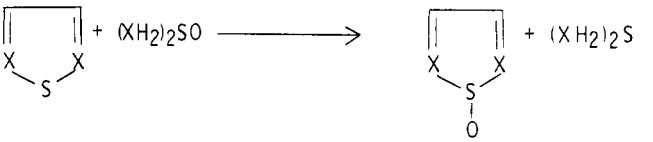
Total Energy = -657.24713



Total Energy = -657.19629

Barrier to Inversion = 31.9 kcal mole^{-1}

Figure 3. Comparison of the optimized geometry and total energy for thiadiazole and thiadiazole oxide in the planar and pyramidal structures.



	ΔE(pyramidal)	ΔE(planar)
X = CH	25.5 kcal M^{-1}	−6.6 kcal M^{-1}
X = N	28.1 kcal M^{-1}	−6.7 kcal M^{-1}

Figure 4.

compared to H_2SO (43.5 kcal mol^{-1} (calcd)). The more electronegative substituent raises the barrier by preferentially stabilizing the pyramidal structure.

Aromaticity and conjugative effects are more difficult to measure directly. As argued above for the X-ray structure, changes in the C_3–C_4 bond length of the calculated geometries can provide a clue to the relative aromaticity of the planar and pyramidal geometries of thiophene and thiadiazole oxides. Both pyramidal sulfoxides show a significant lengthening of $R(C_3$–$C_4)$, indicating destabilization due to a loss of aromaticity. In contrast, the planar forms show a decrease in $R(C_3$–$C_4)$, signaling greater aromatic stabilization of the transition structure. Both changes reduce the barrier; the effect on thiadiazole 1-oxide is similar to, or possibly slightly larger than, the effect on thiophene 1-oxide. The strain introduced by closing the five-membered ring is estimated to contribute less than 2 kcal to the inversion barrier.

The nature of the inversion barrier in thiadiazole and thiophene 1-oxides can also be examined with an isodesmic reaction. Comparison with $(CH_3)_2SO$ and $(NH_2)_2SO$ instead of H_2SO to a large extent separates the "aromaticity" influence from the electronegativity trends (Figure 4). These values confirm the qualitative arguments based on bond length. The pyramidal thiadiazole and thiophene 1-oxides are destabilized compared to the acyclic sulfoxide, while the planar structures are slightly stabilized. The changes in the two heterocyclic sulfoxides are almost the same, indicating that an argument based solely on "lack of aromaticity" cannot explain the high inversion barrier in thiadiazole 1-oxide relative to thiophene 1-oxide.

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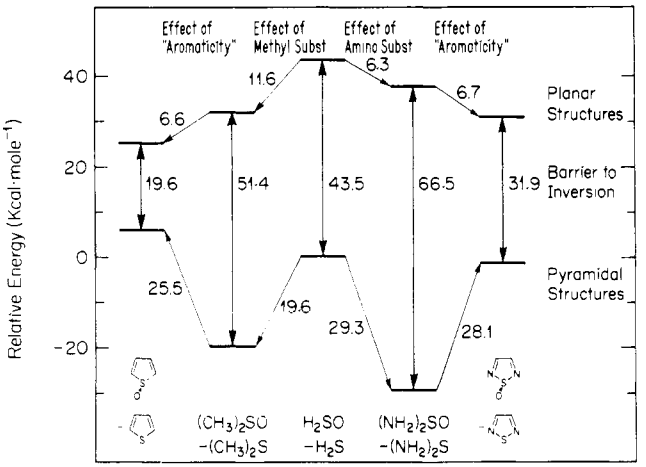

Figure 5. Factors affecting the height of the inversion barrier in sulfoxides. Both methyl and amino substituents stabilize the pyramidal and the planar sulfoxide, but the amino group lowers the energy of the pyramidal form more and the planar form less resulting in a larger barrier. Forming the "aromatic" ring destabilizes the pyramidal structure and stabilizes the planar structure, lowering the barrier by about the same amount for both the thiophene oxide and the thiadiazole oxide.

The theoretical factors influencing the barrier heights are summarized in Figure 5. Amino substituents stabilize the pyramidal sulfoxide more than methyl groups and raise the barrier. Completing the aromatic heterocycle has approximately the same effect in lowering the barrier in thiadiazole 1-oxide and thiophene 1-oxide.

Summary

The X-ray structure analysis and the ab initio theoretical calculations demonstrate that 1,2,5-thiadiazole 1-oxides are essentially nonaromatic and contain a pyramidal sulfur. Further support of these findings can be obtained from the reactivity of the 1,2,5-thiadiazole 1-oxide system; a detailed account of the chemistry will be the subject of future publications.

Chiral derivatives of the pyramidal 1,2,5-thiadiazole oxide are stable, with inversion observable only at elevated temperatures (120 °C). The barrier to inversion is similar to that of aliphatic sulfoxides and much larger than that of the analogous thiophene 1-oxide. Theoretical calculations indicate that aromaticity effects lower the barrier nearly equally in the thiophene and thiadiazole sulfoxides by stabilizing the planar transition state to inversion and destabilizing the pyramidal structure. In the thiadiazole oxide, however, this reduction in the barrier is compensated by the stabilizing effect of the electronegative nitrogens on the pyramidal sulfur, thus raising the inversion barrier back to the range of normal sulfoxides.

Experimental Section

Synthesis. Reactions, except where otherwise stated, were worked up by the following procedure: the reaction mixture was diluted with methylene chloride and extracted with equal portions of dilute HCl, saturated $NaHCO_3$, and saturated NaCl solutions. After the solution was dried over anhydrous $MgSO_4$, the solvent was removed on a rotary evaporator. NMR spectra were recorded on Perkin-Elmer R-24A and Varian CFT-20 spectrometers.

3,4-Diethoxy-1,2,5-thiadiazole 1-Oxide (6a). To a solution of 441 g (3.06 mol) of diethyl oxalimidate (**5a**)[4] in 3000 mL of methylene chloride and 780 mL (9.63 mol) of pyridine was added dropwise with cooling 195 mL (3.2 mol) of thionyl chloride at 10 ± 5 °C. The reaction mixture was stirred for 2 h at room temperature. After extractive workup, the product was crystallized from methylene chloride and hexane to yield 419 g of **6a** (72%), mp 74–78 °C. Recrystallization from cyclohexane afforded an analytical sample: mp 75–78 °C; MS, m/z 190 (M^+), 161 ($M^+ - C_2H_5$); IR (cm^{-1}, $CHCl_3$) 1625 (C=N), 1020 (SO); ^1H NMR ($CDCl_3$, 60 MHz) δ 4.5 (q, J = 7 Hz, 4 H), 1.5 (t, J = 7 Hz, 6 H).

Anal. Calcd for $C_6H_{10}N_2O_3S$: C, 37.89; H, 5.26; N, 14.74; S, 16.84. Found: C, 38.10; H, 5.36; N, 14.63; S, 17.05.

3,4-Bis(methylthio)-1,2,5-thiadiazole 1-Oxide (6b). To a solution of 353 g (2.39 mol) of dimethyl thiooxalimidate (**5b**)[5] in 1500 mL of methylene chloride and 580 mL of pyridine (7.2 mol) was added dropwise 188 mL (2.59 mol) of thionyl chloride at 0 ± 5 °C. The mixture was stirred at room temperature for 2 h. After extractive workup the product was precipitated with ether, removed by filtration, washed with ether, and dried to yield 401 g (86%) of **6b**: mp 109–112 °C; MS, m/z 194 (M^+); IR (cm^{-1}, $CHCl_3$) 1625 (C=N), 1115 (SO); ^1H NMR ($CDCl_3$, 60 MHz) δ 2.7 (s).

Anal. Calcd for $C_4H_6N_2OS_3$: C, 24.73; H, 3.11; N, 14.42; S, 49.51. Found: C, 24.89; H, 3.17; N, 14.72; S, 49.69.

3-Ethoxy-4-(1-pyrrolidinyl)-1,2,5-thiadiazole 1-Oxide (7). To a solution of **6a** (1.85 g, 10 mmol) in 10 mL of ethanol was added 0.72 g (10 mmol) of pyrrolidine, and the mixture was stirred for 30 min at room temperature, concentrated to one-fourth volume and diluted with ether. The crystals were filtered and dried in vacuo to give 1.5 g (72%) of **7**: mp 62–64 °C; MS, m/z 215 (M^+), 186 ($M^+ - C_2H_5$) 170 ($M^+ - C_2H_5O$), 145 ($M^+ - C_4H_8N$), 119 ($M^+ - C_5H_8N_2$), 70 (C_4H_8N); IR (cm^{-1}, $CHCl_3$) 1625 (C=N), 1125 (SO); ^1H NMR ($CDCl_3$, 60 MHz) δ 4.5 (q, J = 7 Hz, 2 H), 3.7 (m, 4 H), 2.0 (m, 4 H), 1.5 (t, J = 7 Hz, 3 H).

3,4-Bis(1-pyrrolidinyl)-1,2,5-thiadiazole 1-Oxide (8). The same reaction as above, carried out with 2 molar equiv of pyrrolidine produced **8**: mp 191–194 °C; MS, m/z 240 (M^+), 170 ($M^+ - C_4H_8N$), 144 ($M^+ - C_5H_8N_2$), 96 ($C_5H_8N_2$, 70 (C_4H_8N); ^1H NMR ($CHCl_3$, 60 MHz) δ 3.65 (m, 8 H), 2.0 (m, 8 H).

Synthesis of 9. Into a stirred solution of **6a** (9.5 g, 50 mmol) in 50 mL of methanol was added *l*-ephedrine (8.3 g, 50 mmol) and 1 mL of diisopropylethylamine. The solution was stirred for 3 h at room temperature and concentrated in vacuo to yield 8 g of a clear oil. Crystallization from acetonitrile produced 2.0 g of a single diastereomer of **9**: mp 194–196 °C; $[\alpha]^{MeOH}_D$ = 300° ± 0.5°; MS, m/z 263 (M^+), 172 ($M^+ - C_7H_7$), 157 ($M^+ - C_7H_6O$), 106 (C_7H_6O), 91 (C_7H_7); ^1H NMR ($CDCl_3$, 60 MHz) δ 7.7 (s, 5 H), 5.8 (d, J = 3 Hz, 1 H), 3.8 (m, 1 H), 3.13 (s, 3 H), 1.1 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96; S, 12.18. Found: C, 54.94; H, 4.94; N, 16.01; S, 12.27.

Synthesis of 10. Into a solution 8.5 g (45 mmol) of **6a** and of (*S*)-2,3-dihydroxy-1-(*tert*-butylamino)propane[7] (6 g, 45 mmol) in 50 mL of tetrahydrofuran was added 1 mL of diisopropylethylamine. The solution was refluxed for 5 h and concentrated in vacuo to an oil. After the usual extractions the product was crystallized from ethyl acetate to yield 1.3 g of a single diastereomer of **10**: mp 166–168 °C, $[\alpha]^{DMF}_D$ = 61.7° ± 0.9°; MS, m/z 245 (M^+); IR (cm^{-1}, $CHCl_3$) 3450 (OH), 1100 (SO); ^1H NMR ($CDCl_3$, 60 MHz) δ 5.15 (m, 1 H), 4.6 (m, 2 H), 3.7 (m, 2 H), 1.5 (s, 9 H).

Anal. Calcd for $C_9H_{15}N_3O_3S$: C, 44.07; H, 6.16; N, 17.13; S, 13.07. Found: C, 43.95; H, 6.39; N, 16.92; S, 13.31.

The remaining filtrate was concentrated in vacuo to yield an oil which crystallized on standing. The crystals were filtered and washed with ethyl acetate to yield 1.0 g of the other diastereomer of **10**: mp 115–120 °C; $[\alpha]^{DMF}_D$ = 18.7° ± 0.5°, MS, m/z 245 (M^+); IR (cm^{-1}, $CDCl_3$) 3450 (OH), 1100 (SO); ^1H NMR ($CDCl_3$, 60 MHz) δ 5.15 (m, 1 H), 4.6 (m, 2 H), 3.7 (m, 2 H), 1.15 (s, 9 H).

X-ray Structure Determination of 6b. Crystals of **6b** formed thick yellow needles from methylene chloride/ether solutions. The crystal symmetry was $P2_1/c$ with a = 4.174 (1) Å, b = 13.230 (4) Å, c = 14.814 (4) Å, and β = 93.41 (2)°. The calculated density was 1.58 g/cm³ for Z = 4. All unique reflections with $2\theta \leq 114°$ were measured with an automatic four-circle diffratometer using Cu K_α radiation (λ = 1.5418 Å). After correcting for background, Lorentz, and polarization effects, 1020 were considered observed ($I \geq 3\sigma(I)$). The structure was solved by using a multisolution tangent formula approach[15] and refined by using full-matrix least squares[16] by minimizing $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(F_o)^2$. The final unweighted R factor for the observed reflections is 0.068. Table VI gives the final fractional coordinates of **6b** while Figure 1 shows pertinent bond distances and angles and a computer-generated drawing.[17] Table VI is available as supplementary material.

Theoretical Calculations

Ab initio computations were carried out with the GAUSSIAN 78 series of programs.[18] Theoretical studies on a variety of normal

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and hypervalent sulfur compounds indicate that the STO-3G* basis[19] adequately models geometry and trends in barrier heights. However, an extensive series of calculations with the STO-3G* basis paralleling those reported demonstrated that it is not flexible enough to handle the subtle balance between aromaticity and electronegativity encountered in thiadiazole 1-oxide. Accordingly, the 4-31G split valence basis[20] set was used augmented by a set of six Cartesian d functions on sulfur (denoted by 4-31G+d). The GAUSSIAN exponent, $\alpha = 0.54$, was optimized for pyramidal H_2SO. This basis set overestimates the SO bond length by ca. 0.02 Å but predicts the inversion barrier approximately as well as the 4-31G* basis which contains d orbitals on first and second row atoms. Because of strongly coupled internal coordinates, cyclic structures pose a special problem for geometry optimization. To overcome these difficulties, equilibrium geometries were determined with a conjugate gradient method using analytically calculated energy derivatives. All structures were fully optimized, with the exception that the heterocyclic rings were constrained to be planar, by using the 4-31G+d basis set.

Acknowledgment. We are grateful to Drs. Arthur A. Patchett and G. B. Smith for useful discussions and Mr. Jack Smith for the mass spectra. Special thanks are due to Dr. Raymond Firestone for many helpful suggestions.

Registry No. 4, 31681-45-5; **5a**, 13534-15-1; **5b**, 79844-63-6; **6a**, 79844-64-7; **6b**, 79844-65-8; **7**, 80028-45-1; **8**, 79844-66-9; **9**, 80028-46-2; **10** isomer 1, 80028-47-3; **10** isomer 2, 80028-48-4; **11**, 4057-61-8; pyrrolidine, 123-75-1; L-ephedrine, 321-98-2; (*S*)-2,3-dihydroxy-1-(*tert*-butylamino)propane, 30315-46-9; H_2SO, 25540-60-7; $(CH_3)_2SO$, 67-68-5; $(NH_2)_2SO$, 36986-61-5.

Supplementary Material Available: The final fractional coordinates and temperature parameters for **6b** from the X-ray experiments (1 page). Ordering information is given on any current masthead page.

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A New Thermal Rearrangement in the 4-Isoxazoline System. Some Chemical and Stereochemical Properties of a Benzodiazepine Oxide–Ethyl Propiolate Adduct

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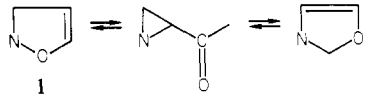
Abstract: Reaction of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide, **3**, with ethyl propiolate afforded the expected 4-isoxazoline **4** and a rearrangement product **5**. Product **5** and a further rearrangement product, **6**, could be obtained from **4** upon treatment with boiling ethanol which also yielded a dihydroquinoxalone **7**. The structures of isomers **4**, **5**, and **6** were determined by X-ray diffraction analyses. The conformational and configurational properties of these compounds were further studied by NMR. The rearrangement of **4** to **5** represents a new reaction path for 4-isoxazolines.

4-Isoxazolines, **1**, whose isolable members are relatively rare,



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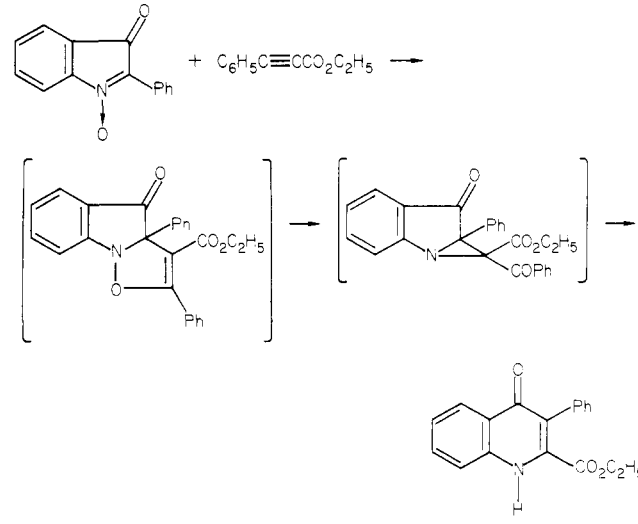
are markable heterocycles because of the number of interesting rearrangements which arise from them. Baldwin[1] has shown that in the simplest case they interconvert with ketoaziridines and 2-oxazolines. Often these primary reactions are masked by subsequent changes. For example, a 4-isoxazoline presumably is an intermediate in the conversion of 2-phenylisatogen and ethyl phenylpropiolate to quinolone **2**; in this case deacylation and ring expansion has occurred.[2] With diazacyclopentadienone *N*-oxides and oxadiazine *N*-oxides, 1,3- and 3,3-sigmatropic shifts after 4-isoxazoline formation were invoked to rationalize the formation of the ultimate products.[3] A more deep seated rearrangement was observed with a pyrrolone *N*-oxide.[4] Extensive rearrangement also was observed with the 4-isoxazolines derived from fervenulin 4-oxides.[5] In most of these cases and others the 4-isoxazolines



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were not isolable and were proposed as transient, first-formed intermediates.

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