Theoretical investigations were carried out using ab initio gradient techniques[24] and the 3-21G basis set.[25] The computed structures of the reactants, an organolithium–ethylene complex, **8**, and the transition structure **9** are shown in Figure 2. Energies of the various species are given in Table I. The $LiCH_2F$ carbenoid and ethylene form a complex, **8**, which has only slight distortions from reactant geometries and Li–C (ethylene) distances (2.49 and 2.52 Å) only slightly different from those of the LiH complex.[23] Although such a complex is expected to be stable in the gas phase, it is not expected to be present in solution, where the carbenoid is undoubtedly aggregated and solvated.[7,15] Similarly, the products, LiF and cyclopropane, form a complex that is 14.1 kcal/mol more stable than the separated entities. This also would not be expected to be present in solution.

The transition structure **9**, is related to the "butterfly" **3** but the CH_2 group is in a plane nearly parallel to the ethylene plane, like the arrangement proposed by Closs. The methylene fragment is aligned so that the LUMO can interact in an electrophilic sense with the ethylene HOMO on one side and simultaneously with a fluorine lone-pair on the other side. Li^+ is loosely associated with the lone-pair HOMO on the methylene and bonded more strongly to the departing fluoride. The CF bond is stretched by 0.58 Å (35%), while the CLi bond is stretched by 0.12 Å (6%) and the LiF length is shortened by 0.14 Å (8%). The LiF moiety is substantially "decomplexed", freeing the carbene character of CH_2. Transition structure **9** also resembles the transition structure for isomerization of the carbenoid to the nearly linear isomer, H_2CLiF,[3,6] which would have very strong electrophilic properties. Other carbenoids, such as Cl_3CLi, undergo isomerization to higher energy isomers (Cl_2CLiCl) with great ease.[5] The transition structures for carbenoid cycloadditions involving more nucleofugic halogens are expected to have lower activation energies but involve less advanced C–X bond breaking and earlier transition structures.

The CH_2 group does not invert (in the sense implied by **3**) during the reaction. Indeed, the carbenoid transition structure **9**, is quite similar to the transition structures for free halocarbene cycloadditions,[17,18] except that the carbene fragment of **6** is less strongly bound to ethylene in the transition structure.

Although carbenoids are expected to be aggregated[7] and solvated in solution,[15] the essential features of the methylene-transfer cycloaddition revealed by **9**, namely a carbene-like transition structure with advanced C–X bond breaking and loose coordination of Li^+ to electron-rich centers, are expected to be maintained in solution reactions.

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Registry No. 6, 59189-61-6; **7**, 74-85-1; **8**, 87555-38-2; LiF, 7789-24-4; cyclopropane, 75-19-4.

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Regiochemistry in Thiocarbonyl Diels–Alder Additions: Reversal of Selectivity by Substituent Effects in Thioaldehydes

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Thiocarbonyl dienophiles, ZC(R)=S where Z = acyl, CN, carboethoxy, etc., react with donor-substituted unsymmetrical dienes to give [4 + 2] cycloadducts with path b selectivity (Scheme I).[1,2] In contrast, carbonyl dienophiles react with high path a selectivity.[1]

It has been reported that certain thioketones,[3a] simple dithioesters,[3b] and thermally generated PhCH=S[3c] show little preference for either path a or b. To probe the relationship between regiochemistry and the effect of thiocarbonyl substituents, we have examined a series of thioaldehydes, ZCH=S, which retain high dienophilic reactivity for Z = alkyl, aryl, H, acyl, etc. As summarized in Table I, the regiochemistry of cycloaddition with electron-rich dienes is reversed for Z = alkyl compared to Z = acyl, CN, etc. Computations for representative thioaldehydes provide an explanation for the variable regiochemistry observed in these [4 + 2] cycloadditions.

Systematic comparisons have been made by using 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene as the trapping agent for thioaldehydes generated by the photochemical method[2e] (Table I). In borderline cases where yields are low due to thioaldehyde self-condensation, the more reactive Danishefsky diene has been employed. To verify that thioaldehydes are generated with similar

Table I. Thioaldehyde Trapping from $PhCOCH_2SCH_2Z$, $h\nu$, and Diene in Situ

	yields, %				
ZCH=S, Z	1	2	3	4	6
CN[a]	4	70			
COC_6H_5[a]	5	59	c	90[d,f]	
C_6H_5[g]	10	5	74[b]	c	
$CH=CH_2$	trace	c	7[b]	c	92[d]
$SiMe_3$	30	3			
H	68	6			73
$C(CH_3)_3$[e]	4.5	c	25[b]	c	93
$CH_2CH_2C_6H_5$	23	c	84[b]	c	91[d]

[a] From ref 1e. [b] Yield after acid treatment to give a 2,3-dihydrothiopyran-4-one. [c] Isomeric adducts not detected. [d] Mixture of stereoisomers. [e] 2,2-Dimethylpropanethial has been shown to survive in solution at 20 °C (ref 5). [f] Yield of adducts estimated by NMR vs. internal standard; chromatography or acid treatment causes elimination to a mixture of unstable 2,4- and 2,6-dihydrothiopyran-3-ones. [g] See ref 3c for similar results.

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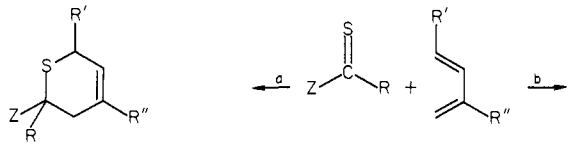
Table II. Orbital Energies, π_{CS} and π^*_{CS} Coefficients,[a] and Total Charges[b] for Thioaldehydes

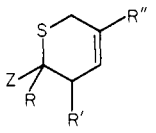
ZCHS, Z	orbital energies: $\epsilon(\pi^*_{CS}$, LUMO)	$\epsilon(n_S$, HOMO)	$\epsilon(\pi_{CS}$, SHOMO)	coefficients: π^*_{CS} C	π^*_{CS} S	π_{CS} C	π_{CS} S	charges[b] C	charges[b] S
CN	−0.34	−10.72	−11.56	0.51	−0.54	0.32	0.34	−0.52	+0.32
CHO	−0.21	−10.34	−11.52	0.52	−0.52	0.34	0.36	−0.67	+0.26
Ph	0.78	−9.00	−8.98	0.51	−0.46	0.15	0.32	−0.54	+0.16
$CH{=}CH_2$	0.92	−9.34	−9.60	0.53	−0.48	0.21	0.37	−0.56	+0.15
SiH_3	0.88	−9.35	−11.20	0.60	−0.56	0.34	0.37	−0.96	+0.18
H	1.26	−9.66	−11.29	0.68	−0.57	0.35	0.38	−0.70	+0.17
Me	1.67	−9.33	−10.72	0.70	−0.55	0.34	0.40	−0.65	+0.15

[a] Only the coefficients of the outer portion of the C2p and S3p orbitals are listed. The inner coefficients have the same relative magnitudes as the outer coefficients listed here. [b] Mulliken population analysis.

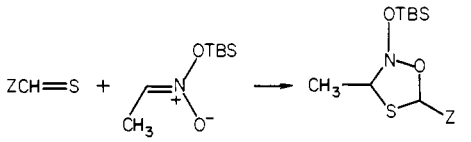
Scheme I



1, R = R′ = H; R″ = $OSiMe_2t$-Bu
3, R = H; R′ = OCH_3;
R″ = $OSiMe_2t$-Bu



2, R = R′ = H; R″ = $OSiMe_2t$-Bu
4, R = H; R′ = OCH_3; R″ = $OSiMe_2t$-Bu



5 **6**

efficiency in all examples, several trapping experiments have also been performed in the presence of the highly reactive nitronate ester **5**.[4] In the latter case, 1,3-dipolar cycloadducts of structure **6** are obtained, usually in >90% yield based on thioaldehyde precursor ($PhCOCH_2SCH_2Z$).

According to Table I, path b is preferred only in those examples where Z in ZCH=S is strongly electron withdrawing (CN and COPh). Since the diene is the nucleophilic partner in these reactions, the results suggest that the carbon of thioformaldehyde is somewhat more electrophilic than sulfur and that C-alkyl substituents reinforce this trend. Conjugating substituents (COPh, CN) at carbon reverse the trend and make sulfur more electrophilic than carbon.

Molecular orbital calculations on various model systems confirm this conclusion. Ab initio molecular orbital calculations with the split-valence 3-21G basis set[6] were performed. Thioformaldehyde was fully optimized,[7] and the geometries of the substituted derivatives were constructed by replacement of one of the hydrogens of thioformaldehyde with the substituent in a standard geometry.[8]

The energies, coefficients, and charges of the frontier π orbitals of thioformaldehyde and substituted derivatives are shown in Table II. The vacant π^*_{CS} orbital energy calculated for thioformaldehyde is 2.8 eV lower than that calculated for the π^*_{CO} vacant orbital energy of formaldehyde. The sulfur lone-pair orbital is the HOMO and is calculated to be 2.1 eV higher in energy than the n_O lone-pair on oxygen in formaldehyde. The π_{CS} orbital is calculated to be 3 eV higher in energy than the π_{CO} orbital of formaldehyde. These trends are in qualitative accord with experimental comparisons, where available.[9] Thiocarbonyl compounds are both more electrophilic (lower LUMO) and nucleophilic (higher HOMO) than carbonyl compounds.

The substituent effects on these orbital energies are in general accord with the substituent effects on alkenes and carbonyls.[10] Thus, the electron-donating methyl group raises the energy of the π_{CS} orbital the most and the π^*_{CS} orbital to a lesser extent. Electron-withdrawing groups (CHO, CN) lower the energies of all orbitals in the order $\pi^*_{CS} > n_S > \pi_{CS}$. Conjugating substituents (Ph, vinyl) lower the π^*_{CS} orbital energy and dramatically raise the π_{CS} orbital energy. The SiH_3 group is unique, lowering the π^*_{CS} orbital energy to a moderate extent but having little effect on the π_{CS} orbital.

The relative magnitude of the coefficients of the π^*_{CS} molecular orbitals of these molecules vary according to the substituents. For thioformaldehyde, the π and π^* orbitals are polarized in the same direction but to a smaller extent than for formaldehyde. The charges are decidedly in the opposite direction. The electron-donating methyl group accentuates the LUMO polarization, electron withdrawers such as CN tend to reverse the polarization, and conjugating groups and H_3Si reduce it.

The orientation of cycloadditions of unsymmetrical electron-rich dienes is related to the LUMO coefficients in the thiocarbonyl, which is invariably the electrophilic partner in such reactions. The stabilization of the two regioisomeric transition states arising from this HOMO–LUMO interaction depends upon interaction terms $C_aC_b\gamma_{ab}S_{ab}$, where C_a and C_b are coefficients of frontier orbitals at centers a and b, S_{ab} is the overlap integral for atomic orbitals at the centers, and γ_{ab} is the proportionality between overlap and stabilization for a given atom pair.[11] Since details of transition-state geometry are not known, we cannot evaluate γ_{ab}. However, a comparison of the trends in Tables I and II shows that regioselectivity reverses from path a to path b when the ZCH=S LUMO coefficient at sulfur equals or exceeds that at carbon (Z = CHO; CN).[12]

With this *caveat*, the π^*_{CS} coefficients shown in Table II rationalize the trends shown in Table I. Strong electron-withdrawing groups make the S terminus more electrophilic by enlarging the S LUMO coefficient. Milder electron-withdrawing groups lower the difference between S and C electrophilicity, while conjugating

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(7) The 3-21G geometry of thioformaldehyde (r_{CS} = 1.638 Å, r_{CH} = 1.073 Å, ∠HCH = 116.5°) is in reasonable agreement with that determined by microwave spectroscopy: Johnson, D. R.; Powell, F. X.; Kirchhoff, W. H. *J. Mol. Spectrosc.* **1971**, *39*, 136 (r_{CS} = 1.611 Å, r_{CH} = 1.093 Å, ∠HCH = 116.9°).
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(12) This imples that $\gamma_{CS}S_{CS}$ is larger than $\gamma_{CC}S_{CC}$ but may reflect instead our neglect here of electrostatic and closed-shell repulsion influences on regioselectivity.

groups make C somewhat more electrophilic than S. Electron donors enhance the greater electrophilicity of C that is already present in thioformaldehyde. Furthermore, the selectivity of the more reactive Danishefsky diene is greater than for 2-alkoxybutadiene, in accord with greater frontier orbital control for the diene which has the higher energy HOMO.[10]

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Hematin-Catalyzed Rearrangement of Hydroperoxylinoleic Acid to Epoxy Alcohols via an Oxygen Rebound

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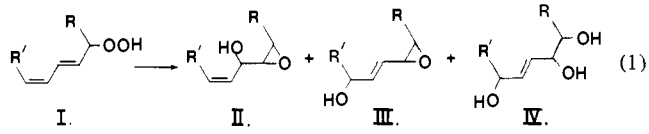
Fatty acid hydroperoxides arise in mammalian tissue by lipid peroxidation and by the action of lipoxygenases on unsaturated fatty acids.[1] Cleavage of the hydroperoxide group concomitant with cyclization to an adjacent double bond generates several different epoxide-derived products including leukotrienes, epoxy alcohols, and trihydroxy fatty acids.[2] The pathways of leukotriene biosynthesis are well understood because of the importance of leukotrienes as mediators of inflammatory and hypersensitivity reactions.[3] Less information is available on the synthesis of epoxy alcohols (eq 1). Pace-Asciak et al. have recently demonstrated

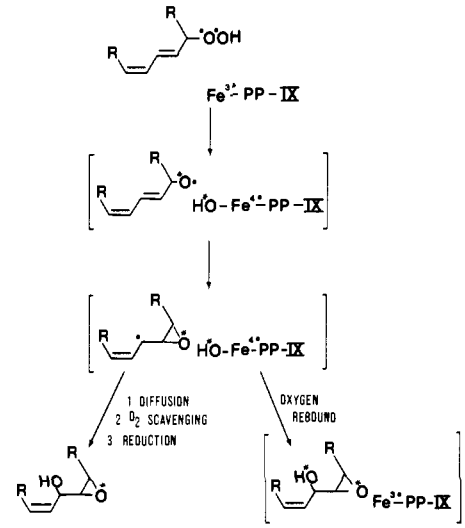


(1)

$R = C_5H_{11}$, $R' = (CH_2)_7COOH$

that both hydroperoxide oxygens are retained in the conversion of 12-hydroperoxy-5,8,10,14-eicosatetraenoic acid to epoxy alcohols and triols by subcellular fractions of rat lung.[4] This observation raises the intriguing question of how the terminal peroxide oxygen is transferred to carbons four and six atoms removed from the peroxide group. We have been studying the reaction of fatty acid hydroperoxides with hematin [hydroxo(porphyrinato)iron(III)], the prosthetic group of several hydroperoxide-metabolizing enzymes.[5] We wish to report that hematin catalyzes the rearrangement of I to isomeric 9- and 11-hydroxy-12,13-epoxyoctadecenoic acids in which both the hydroxyl and epoxide oxygens derive from the hydroperoxide group. The most likely mechanism for this transformation is a unique example of an oxygen rebound in which the metal complex reduces the hydroperoxide group to an alkoxyl radical and transfers the hydroperoxy oxygen to intermediate carbon-centered radicals generated by alkoxyl radical cyclization.

Scheme I. Proposed Mechanism for the Hematin-Catalyzed Conversion of Hydroperoxy Fatty Acids to Epoxy Alcohols[a]



[a] For simplicity, hydroxylation is only considered at the allylic terminus proximal to the epoxide.

Hematin (5×10^{-7} M) and I[6] (5×10^{-5} M) were stirred at 25 °C in 0.1 M sodium phosphate (pH 7.8) containing 2×10^{-4} M Tween 20. After 10 min, the solution was acidified to pH 3.5 and products extracted into ethyl acetate. Solvent was removed in vacuo, the residue was methylated with diazomethane, and the products were isolated and purified by a combination of reversed- and normal-phase HPLC. The purified product zones were silylated and analyzed by gas chromatography–mass spectrometry (GC-MS).[7] Five products were identified; the two major ones were 11-hydroxy-12,13-epoxy-9-octadecenoic acid (II) and 9,12,13-trihydroxy-10-octadecenoic acid (IV). Together, they account for 66% of the identified products.[8] Triol IV is presumed to arise via hydrolysis of the unstable allylic epoxy alcohol III and, in fact, a trace of III is detected.

Experiments were performed in which [$^{18}O_2$]-I[6] was reacted with hematin under an $^{16}O_2$ atmosphere. The 11-hydroxyl of II retained 93% ^{18}O and the 9-hydroxyl of IV retained 66%. When [$^{16}O_2$]-I was reacted with hematin under an $^{18}O_2$ atmosphere, the 11-hydroxyl of II contained 18% ^{18}O, and the 9-hydroxyl of IV contained 32% ^{18}O. The results of these experiments indicate that the 11-hydroxyl oxygen of II and the 9-hydroxyl oxygen of IV are derived predominantly from the hydroperoxide.[9] A percentage of the hydroxyl oxygens in II and IV is derived from O_2. The incorporation of hydroperoxide oxygen is higher at carbon 11 than at carbon 9 in both II and III.

The possibility of an intermolecular hydroperoxide oxygen transfer was evaluated by reacting hematin with an equal mixture of [$^{18}O_2$]-I and [$^{16}O_2$]-I followed by determination of the isotopic composition of epoxyol II. Intermolecular transfer would yield II containing one atom of ^{18}O and one atom of ^{16}O whereas intramolecular transfer would produce II with two atoms of either isotope but not one of each. The relative intensities of the mo-

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(7) The details of product identification will be the subject of a separate publication. Epoxy alcohol II was identical chromatographically and spectroscopically with an authentic standard provided by Dr. H. W. Gardner.

(8) The other products were 13-keto-9,11-octadecadienoic acid and 13-hydroxy-9,11-octadecadienoic acid. In addition, 18% of hydroperoxide I was recovered.

(9) The epoxide oxygen of II and the 13-hydroxyl oxygen of IV are derived quantitatively from the hydroperoxide, as expected.

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