Transannular addition of α-sulfinyl carbanions to unactivated double bonds. Intramolecularity as a reactivity factor

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Abstract. Various mechanistic and stereochemical aspects of the alkyllithium promoted transannular cyclization of meso-cyclic E homoallylic sulfoxides (ref. 5) have been examined, also in relation to the conformational features of the precursor sulfoxides. The question of timing in the addition and H^+-transfer processes has been examined with the aid of a stereochemical probe, i.e. the relative configuration of the bicyclic product at the center where the proton is being transferred. The results suggest that proton transfer may occur in concert with addition or in a separate subsequent step depending upon the nature of the substituent (Me or Ph) at that center.

The nature of the products (regio- and stereoisomers) indicate the addition is kinetically controlled. Since the double bond is not activated, the factors which determine the direction of addition must be essentially geometrical. However, the ground state geometries of the various conformers of the precursor sulfoxides (determined by force field methods) do not by themselves provide an unequivocal criterion. To explain the regiochemical preference the hypothesis is advanced of an electrostatic interaction between the developing carbanionic center and the $^+S-O^-$ dipole which is suitably placed for a very effective stabilization.

The differential reactivity of E vs Z substrates is discussed in relation to the factors contributing to intramolecular rate enhancement.

Additions of nucleophiles to isolated multiple bonds are rare. Indeed only a handful of examples are known where an alkoxide or an amino function adds under conditions which exclude prior attachment of an electrophile to the multiple bond. Pertinent examples are the addition under basic conditions of oxygen (ref. 1) and nitrogen (ref. 2) nucleophiles in alkene-alcohols and alkene-amines, and the addition of phenoxide in alkene- (ref. 3) and alkyne-phenols (ref. 4). All the known examples are characterized by a common feature, that is nucleophilic and unsaturated centers are part of the same molecule. Although necessary, intramolecularity is by no means a sufficent condition, however; some other conditions must be fulfilled related to molecular shape, as will be seen below.

The reaction we now discuss pertains to this category, its peculiarity residing in the nature of the nucleophile, a carbanion, hence in the type of bond being formed (C-C). The reaction in question is a transannular cyclization of medium-sized homoallylic sulfoxides or sulfones under the action of organo-lithium reagents, resulting in the formation of saturated bicyclics (ref. 5). This reaction was discovered accidentally when, on the way to α-methylating 9-membered homoallylic sulfoxides or sulfones, the usual metallation-alkylation sequence was found to result in sizeable loss of

unsaturation with formation of bicyclic products. Thus when E-thiacyclonon-4-
ene 1-oxide, **1**, was treated with a <u>deficit</u> of BuLi at low temperature in THF a
transannular cyclization took place (t½ ≃ 1 h) forming two saturated products,
2 and **3**, which were identified (by independent syntesis) as the cis and trans
epimers of 2-thiabicyclo[4.3.0]nonane 2-α-oxide, respectively (eq. 1). It is
clear from the products that metallation of the homoallylic sulfoxide has

(eq. 1)
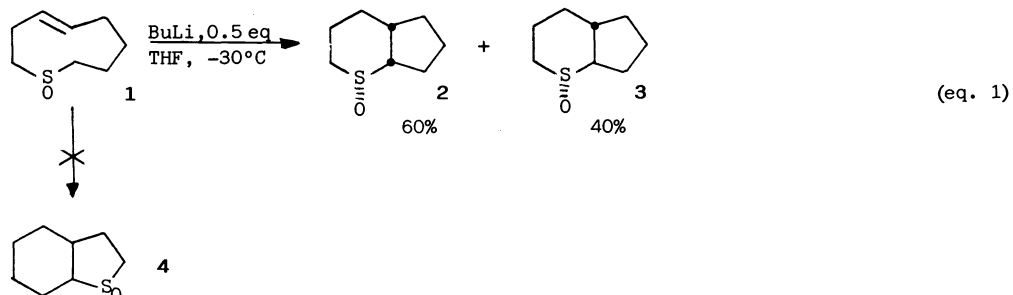
promoted the formation of a transannular bond between one of the α carbons
(that further removed from the double bond) and one of the unsaturated carbons
(C5). No trace was detected of the regioisomer (**4**) which would be formed by
attachment to the other end of the double bond, nor of the isomers that would
result from the attachment of the other α carbon (C2) to either end of the
double bond. Hence the transannular cyclization is regiospecific with respect
to both the α-carbon and the direction of double bond addition. On standing in
the presence of base the initial epimer ratio (**2:3** ≃ 1.5:1) changed until
reaching equilibrium at **2:3** ≃ 1:13. Since equilibrium must occur by reversible
proton abstraction at the α bridgehead (C1) without affecting the sulfoxide
configuration, it follows that both epimers have the same configuration at the
sulfur atom. The C-13 NMR behaviour of **2** and **3**, in comparison to that of their
epimers at sulfur which could be obtained by inversion of the sulfoxide
configuration, (ref. 6) established the relative configuration of **2** and **3** to
be α, as depicted.

In analyzing this stereochemical result it must be realized that the
unsaturated sulfoxide has two stereogenic centers, the sulfur atom and the E
double bond, hence it exists as two diastereomers. While the sulfoxide
functionality is configurationally stable, the chiral plane associated with
the E double bond is not, stereomutation simply occurring by rotation of the
π bond inside out the ring, a process which, in 9-membered rings, is
relatively fast (Note a). Indeed by low temperature dynamic C-13 NMR **1** was
found to exist as a ~6:1 equilibrium mixture of conformational diastereomers,
separated by a 17.5 kcal/mol barrier. Inspection of stereoformulas indicates
that the RR,SS and RS,SR diastereomers are precursors of α and β products,
respectively. Thus the cyclization appears to be stereoconvergent, the whole
product originating from the RR,SS form:

α   1S,4S   1S,4R   β
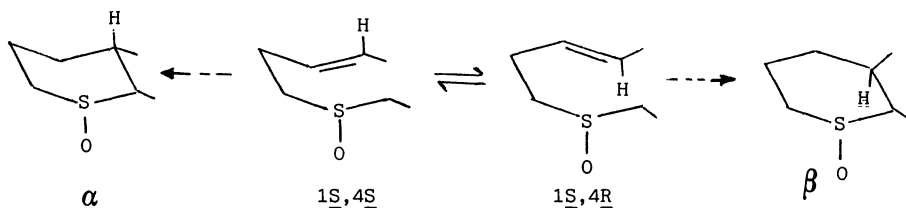
Note a: The ΔG≠ value for the racemization of E-cyclononene is ~20 kcal/mol
        (ref. 7) and that for epimerization of E-2-methylthiacyclonon-4-ene is
   17.1 kcal/mol (ref. 8).

The question arises of how general this transannular reaction may be. The 8- and 10-membered ring E homoallylic sulfoxides were similarly probed and both were found to cyclize (though somewhat less readily: 9 > 10 > 8). The reaction takes place with sulfones as well as sulfoxides, suggesting that the specific nature of the acid enhancing function is not a primary factor. However, one condition appears to be indispensable for the addition to occur, that is the E configuration of the double bond: no products of transannular addition were detected with the Z isomers, at least under conditions of time and temperature where the α-sulfinyl "carbanions" are not otherwise consumed.

For the 10-membered ring sulfoxide the results closely match those of the 9-membered homolog described above: addition takes place regiospecifically at C5 (eq 2) both epimers at the ring fusion being formed competitively (~1:1) although at equilibrium the trans epimer appears to be almost exclusively populated. In this case as well products of the α series are formed exclusively. Yet low temperature dynamic C-13 NMR experiments show that the precursor sulfoxide exists as two rapidly interconverting diastereomers separated by a 11.5 kcal/mol barrier. Therefore, for what concerns the relative configuration of the sulfur atom, the cyclization is stereoconvergent also in this case, the whole product arising from the RR,SS precursor.

(eq. 2)
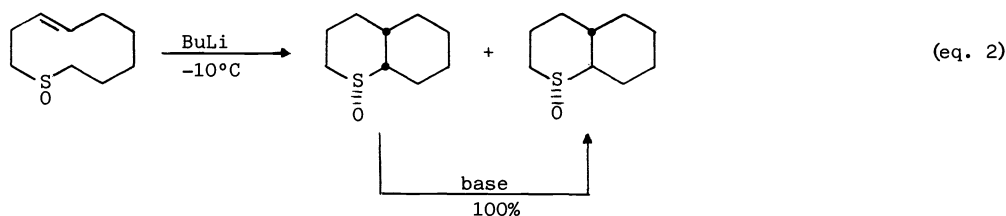
The 8-ring system offers an especially simple and revealing picture. The presence of the E double bond in the 8-membered cycle imparts conformational rigidity and this circumstance is not without consequence in the transannular reaction. From force field calculations E-thiacyclooctene is known to populate, like its carbocyclic counterpart (ref. 9), a twist conformation nearly exclusively ($E_{\text{s-chair}} - E_{\text{s-turist}} = 5.1$ kcal/mol) (ref. 10). Unlike the higher homologs, the enantiomeric forms of this sulfide are not easily interconvertible, the barrier for inversion of the chiral plane being on the order of 30 kcal/mol (ref. 11). Configurational stability and peculiar molecular shape contrive to produce spectacular stereoselectivities in the reactions of this species with external reagents (ref. 12). Thus MCPBA oxidation of the racemate yields a single sulfoxide diastereomer (Scheme 1)

Scheme 1
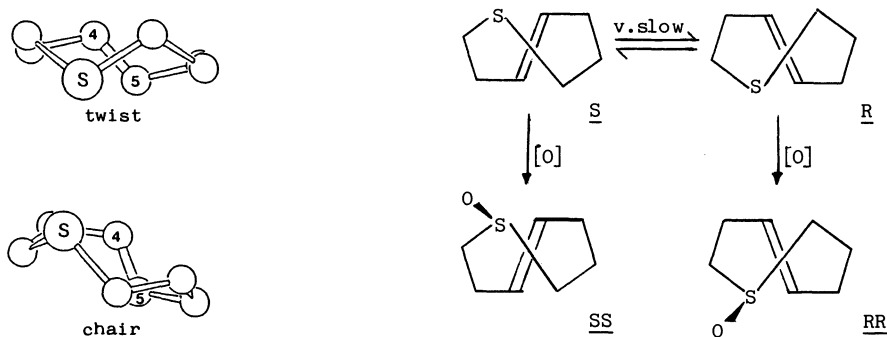
This comes about by virtue of the transannular double bond shielding one side of the S-atom against the approach of external reagents. Inspection of stereoformulas (Scheme 1) suggests the oxidation product to be the

RR,SS diastereomer. This material, **5** treated with BuLi in THF at 0° (Scheme 2) yielded a single saturated sulfoxide, **6**, which, when deoxygenated with PCl_3/CH_2Cl_2 gave cis-2-thiabicyclo[3.3.0]octane, **7**, identical with an authentic sample synthesized via an independent route. Peracid oxidation of **7** produced a ~4:1 mixture of **6** and its epimer **9**. The latter was also obtained from **6** by sulfur inversion via O-methylation followed by alkaline hydrolysis (ref. 6). On the other hand, subjected to sulfur inversion, the original monocyclic sulfoxide **5** produced its epimer **8** which, under the action of BuLi gave **9** by transannular cyclization. (Scheme 2) These transformations prove two
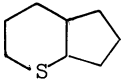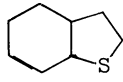
Scheme 2
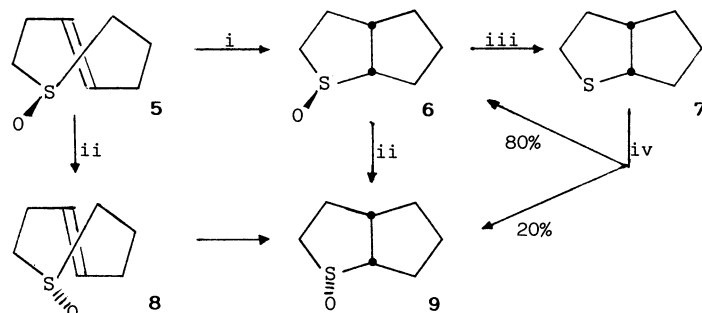
i. BuLi (0.5 eq), THF, 0°C; ii. 1. $TfOCH_3$, CH_2Cl_2; 2. NaOH;
iii. PCl_3, CH_2Cl_2; iv. m-chloroperbenzoic acid, CH_2Cl_2, -80°C.

important points: 1) wherever, as in the 8-ring system, the interconversion of diastereomeric precursors is blocked, intramolecular addition occurs stereospecifically (the RR,SS and RS,SR diastereomers giving the exo and endo bicyclic oxides, respectively). Since there is no reason why addition should not also be stereospecific in the larger rings, the stereoconvergence observed with the latter must be a consequence of rapid diastereomer interconversion, cyclization occurring from one of them highly preferentially. (The reason for such preference is obscure, however) 2. In the 8-ring system addition occurs regiospecifically at C4, i.e. the direction of addition is opposite to that of the higher homologs. That the regiochemistry may change with ring size was not too surprising since, in the absence of electronic factors, it must be geometrical factors, related to ring size, which determine which of the two ends of the double bond is the favored point of attachment. The question arising is whether the point of attachment is determined by the relative stability of the alternative bicyclics that would originate from one or the other direction of addition. There is little doubt that in cyclization of the 8- and the 10-ring the bicyclic systems actually formed are the more stable (3.3.0 vs 4.2.0 and 4.4.0 vs 5.3.0). However, for the 9-ring, a 4.3.0 bicyclic would result in either case and which of them is the more stable is not so obvious. Force field calculations (Table 1) indicate the 2-thiabicyclo[4.3.0]-nonane system, that which is actually formed, is the less stable. In fact the regioisomers where the S-atom is part of the 5-ring moiety turn out to be more stable than their counterparts, irrespective of stereochemistry of the ring junction and of the sulfoxide. (It is gratifying to see the computed strain energy differential, $[E_{s-2} - E_{s-3}] = 2.3$ kcal/mol, satisfactorily matches the experimentally determined free energy differential, $G_2 - G_3 = 1.5$ kcal/mol.) The conclusion is that the cyclization is kinetically controlled, and this is consistent with the observation that in both 9- and 10-ring cyclizations the less stable epimer (cis) is formed in a proportion larger than its equilibrium population.

Before inquiring about which factors determine the direction of addition, other questions of mechanism should be considered. Every polar addition implies

TABLE 1. Differential strain energies of 2-thia and 7-thiabicy-
clo[4.3.0]nonanes and their S-oxides (MM2)[a]

	X=S		X=SO				X=SO2	
			α		β			
	cis	trans	cis	trans	cis	trans	cis	trans
	4.9	3.8	7.0	4.7	6.5	4.9	7.5	6.4
	0.1	0.0[b]	3.6	2.3	3.1	2.1		

a. kcal/mol; b. Reference point. The computed energy strain is
11.6 kcal/mol

a nucleophilic as well as an electrophilic moiety. In the case at hand the
attachment of the carbanion at one end implies that a proton be eventually
attached at the other end of the double bond. The questions are: where does
the proton come from and at which point in time is it transferred. Relevant to
this is the circumstance, mentioned earlier in this lecture that, in order to
occur, the addition requires a deficit of metallating agent. This is
illustrated by the bell shaped curve of Fig 1 describing the change of rate
with changing metallation fraction (f). The rate is at a maximum at f = 0.5
and drops to nil at f = 0 and f ≥ 1. The likely explanation of this behaviour
is that the proton, required to complete the addition, is transferred
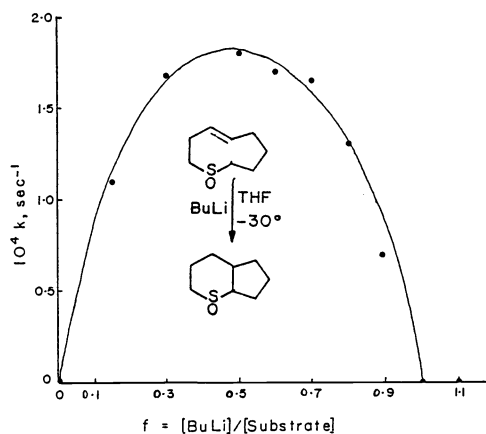intermolecularly from the unmetallated to the metallated form of the substrate

Fig. 1. Rate of transannular
cyclization of 0.1 M E-thia-
clonen-4-ene 1-oxide as a func-
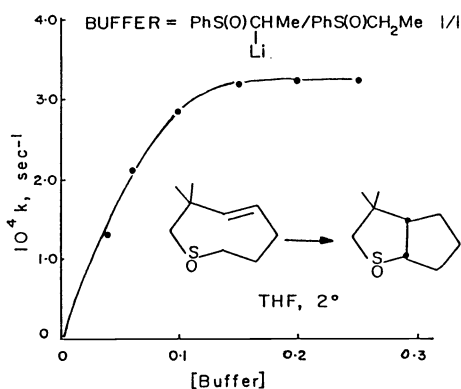tion of the metallation frac-
tion.

Fig. 2. Rate of transannular
cyclization of 0.1 M E-3,3-di-
methylthiacyclooct-4-ene 1-ox-
ide as a function of buffer
concentration.

in a slow step. The question of the timing of proton transfer may be analyzed
with the aid of a mechanistic sequence such as that depicted in Scheme 3,
where the case of the 9-ring is considered and, for the sake of simplicity,
the stereochemical options are ignored.

The first step (1) of any possible mechanism must be irreversible deproton-
ation resulting in the formation of two α-lithium regioisomers, A and B (ref.
13). Since the substrate is converted essentially quantitatively to products
arising from B, A and B must equilibrate rapidly (relative to intramolecular
cyclization) probably through the intervention of a proton transfer agent, BH.
Intermediate B may now evolve to products in one of two ways: a. addition of

Scheme 3
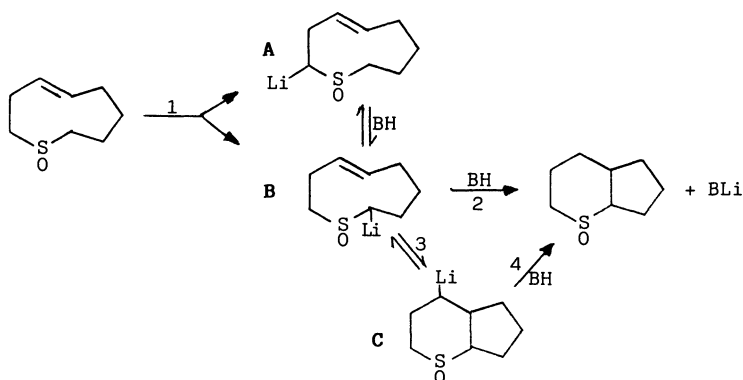
the sulfinyl carbanion to one end of the double bond occurs in concert with transfer of a proton from an acid, BH, to the other end, (step 2) or b. addition and proton transfer occur in separate steps (3 and 4) through the intermediacy of a secondary carbanionic species (**C**). A choice between the two alternatives was searched for by determining the rate as a function of concentration of a suitable buffer. The premise was that, with increasing buffer concentration, while the metallation fraction remains constant, the acid concentration increases. Thus, if proton transfer is concerted, the rate should increase linearly with buffer concentration while in the two step mechanism, the rate would eventually level off to a limiting value corresponding to the rate of (uncatalyzed) formation of intermediate **C**. The test was carried out on an 8-membered sulfoxide and the results are pictorially summarized by the curve of Fig. 2. The rate does level off with increasing buffer, suggesting the two step mechanism. After having done this test, however, it was realized that the indications it gives are ambiguous. In fact the premise ignores the circumstance that not only sulfoxides associate strongly in aprotic solvents, but also the status of their lithio derivatives is uncertain. Actually it may be shown that a curve such as that of Fig. 2 may be compatible with a concerted process if the proton donor is engaged in an association equilibrium with itself or with the metallated substrate, and the equilibrium constant is sufficently large. Thus a second test was carried out, based on the stereochemistry of proton transfer. Scheme 4 illustrates the stereochemical consequences of placing a substituent R ≠ H at the site where a

Scheme 4
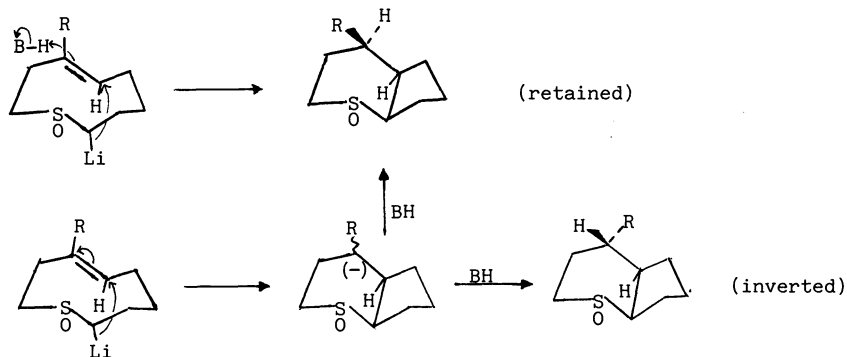
proton is transferred (C4 in the example given). The geometry of the E substrate demands that concerted H$^+$-transfer occurs with retention of configuration, i.e. the groups at C4 and C5, E in the original substrate, must turn out trans in the bicyclic product. If, however, a carbanionic intermediate of finite lifetime is formed, there is a chance for at least partial loss of configuration and the formation of products epimeric at the site of proton transfer.

For this test E-4-methylthiacyclonon-4-ene was chosen and found to cyclize much more slowly than the parent substrate exclusively yielding a product of retained configuration (trans-5-methyl-2-thiabicyclo[4.3.0]nonane 2-α-oxide) where the Me-group is axial. This result is certainly suggestive of concerted proton transfer since, had a carbanionic intermediate been formed, it would
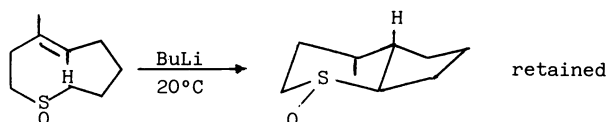

have relaxed to the equatorial epimer. It is not conclusive evidence, however, since in this experiment the intermediate, if any, would be a tertiary carbanion, a species of presumably very short lifetime, perhaps insufficent for inversion to compete with capture by a proton donor. Another experiment was then performed where the R group at C4 would stabilize an adjacent negative charge and provide a longer lifetime to a carbanionic intermediate. The obvious choice was R = Ph. For this substrate cyclization was found to take place considerably faster than for the parent compound, **1**, yielding three
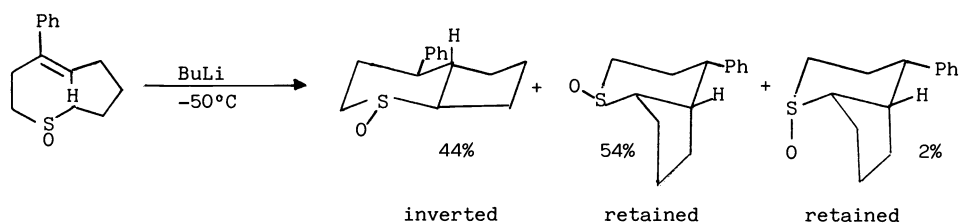
bicyclic products as shown above. Their structures indicate that cyclization occurred with overall 56% retention and 44% inversion of configuration at the site of H^{+}transfer. It is remarkable that all the products have the Ph-group equatorial in their more stable conformation as if the intermediate had been captured by the H^{+}transfer agent after equilibrium had been reached. Although this result proves addition and proton transfer occur in separate steps, there may be a question of how general this mechanism is. In the R = Ph case the intermediate is a benzylic carbanion, a species enormously more stable than the tertiary carbanion that would arise in the R = Me case. It is not unreasonable to argue that for this latter substrate acid catalysis is required to bring the system over the barrier for addition. It may well be that the concerted or the two-step mechanism prevails depending on the carbanion stabilizing ability of substituents at the site of proton transfer.

Let us now address the questions of regio- and stereoselectivity. We have seen that the direction of addition may depend on ring size, and it may be of interest to analyze which specific geometrical features determine the direction of addition. The important factors are likely to be 1) distance and 2) stereoelectronics. As to the latter, for a carbanion adding to a double bond the best trajectory would lie in a plane perpendicular to the trigonal carbon and tetrahedral with respect to the direction of the double bond as well as to the carbanionic center (ref. 14).
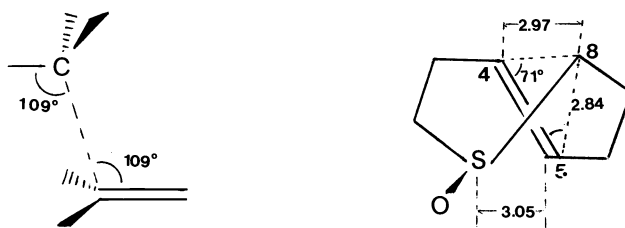
To make a sensible guess one may use the computed geometry and, assuming it is not substantially altered on removal of the   proton, determine 1) which of the two ends of the double bond is closer, and 2) which of the alternative trajectories best approximates the stereoelectronically ideal path. This approach is tantamount to assuming the regiochemistry of addition to be determined solely by the ground state geometry, an assumption which may be valid if the transition state is an early one, and/or the molecular framework is so rigid that it allows but little geometrical deformation.

Applied to the 8-membered ring the force field analysis provides the following information: in the twist conformation, the one essentially exclusively populated (ref. 10) the distances C8-C4 and C8-C5 are 2.97 and 2.84. A, respectively, while the angles C8-C4-C5 and C8-C5-C4 are 71° and 82°, respectively. Thus, based on distance and angle of approach, C5 would seem to be the favored site of addition. This is not the whole story, however; the angles which the C8-C4 and C8-C5 lines make with the C3-C4-C5 plane and, respectively, with the C4-C5-C6 plane are 71° and 48°, (note b) i.e. the former deviates much less from perpendicular relative to the trigonal plane. Moreover, the angles which the C8-C4 and C8-C5 lines make with the C7-C8-S plane are 71° and 57°, respectively; i.e. the deviation from a tetrahedral carbanion is considerably less for addition to C4, which may become the favored site in spite of its being 0.13 A farther. Since, experimentally, addition occurs at   C4 exclusively, it may be concluded that stereoelectronics ("angularity") prevails over distance in this case, contrary to other cases reported by Menger (ref. 15). This conclusion must not be regarded as conclusive, however, since the assumption of a very early transition state is unlikely to hold and, to the extent the transition state is advanced towards products, addition to C5 would be highly unfavored as it gives rise to a trans-2-thiabicyclo[4.2.0]octane 2-oxide, the strain energy of which is calculated to be some 26 kcal/mol greater than that of the cis 3.3.0 isomer actually formed.

Let us now examine the 9-ring system which provides an especially cogent case since its transannular cyclization yields the less stable regioisomer. Force fields analysis of E-thiacyclonon-4-ene (and its oxides) brings out three ring conformations, **D**,**E**, and **F**, whose energy differentials (kcal/mol) are as shown:

D 0.0   **E** 0.1   **F** 1.2
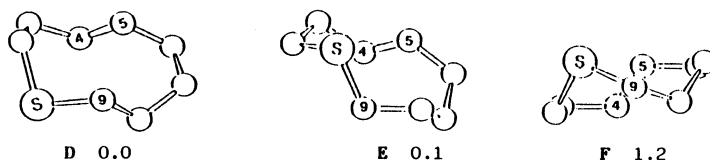
In relation to the transannular cyclization problem, conformer **F** need not be considered since both distance and relative orientation of C9 and the unsaturated carbons are too unfavorable. For the other two conformers, however, the analysis of their geometries suggests C9 would more favorably add to C5 or C4 depending on which conformer, **D** or, respectively, **E** is

G   H
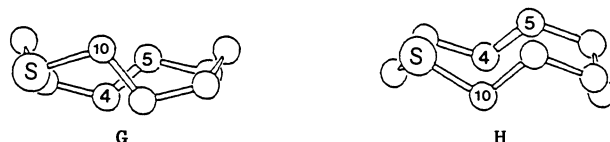
Note b: The C3-C4-C5 and C4-C5-C6 planes are not coincident due to the torsional distorsion of the double bond.

involved. (Note c) Since both ring conformers are populated but only products are formed arising from attack at C5, the approach appears to be inadequate. A similar situation was found to hold for the 10-membered ring. Here two families of ring conformations are comparably populated, typified by **G** and **H**, whose geometries suggest transannular bond formation should occur at C5 and C4, respectively, while in practice products only arise from addition to C5. It is clear that for these larger, more flexible rings the ground state geometry is not a proper criterion for predicting the preferred regiochemical path. In searching for a rationalization we may ask ourselves what other factor may induce a type **E** conformer to add at C5 rather than C4. It is not possible to invoke any degree of advancement towards product in the transition state for, in this case, this very factor would actually encourage addition to C4. There must be another effect besides stereoelectronics. An attractive hypothesis may be the interaction between the incipient carbanion at C4 and the transannular $^-O-S^+$ dipole whose distance (r C4-S = 3.05 A) and orientation are suitable for a powerful electrostatic stabilization, all the more so since at that distance no solvent molecule can get in between. No comparable effect may be forseen for attack at C4 in any conformer of the 9- or 10-membered systems since the S-C5 distance is >3.5 A in any case. Not so for the twist conformation of the 8-membered ring, however, where the S-C5 distance is 3.05 A and where in fact addition takes place at C4. Attractive as it is, however, this rationalization needs to be probed in the light of suitable experimental and theoretical tests.

A comment is in order on the very occurrence of this reaction and on the Z substrates unreactivity. Moderately stable carbanions do not normally add to unactivated double bonds. If addition does occur it must be that it is greatly favored, kinetically <u>and</u> thermodynamically, by its being intramolecular. Although, lacking an intermolecular reference point, its "effective molarity" (EM) (ref. 16) cannot be assessed, this is likely to be a case where the EM parameter would reach the highest values since, not only the entropy loss: Reactant ⟶ Product (and, a fortiori, Reactant ⟶ Transition state) must be minimal but, in addition, there is a sizeable enthalpy decrease. The enthalpy changes, in fact, estimated by force fields computation (MM2) (Table 2) appear to be large and negative in every case and this, to the extent the transition state has progressed towards the product, will further contribute to lowering the free energy of activation (ref. 17).

About the unreactivity of the Z substrates: the common notion that cis double bonds in medium rings cause less strain than trans ones might have suggested it to arise from a less favorable, or altogether unfavorable, energy change. The data of Table 2 dispose of this idea: for the 9- and, more so, for the 10-membered ring the E/Z differential enthalpy change is so slight that any differential rate enhancement related to strain release must be essentially nil. On this basis there seems to be no reason for the E/Z reactivity factor to be a large number, and probably it is not. The fact remains, however, that the Z isomers are less reactive. The answer probably lies in the confor-mational properties of the E relative to the Z cycloalkenes and their

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Note c: The relevant geometrical parameters are as follows (let α_4 and β_4 be the angles formed by the C9-C4 line with the C3-C4-C5 and C8-C9-S planes, respectively, α_5 and β_5 the corresponding angles for the C9-C5 line):

<u>Conformer **E**</u>: r C_9-C_4 = 3.11 A; $C_9C_4C_5$ = 82°; α_4 = 82°; β_4 = 68°

r C_9-C_5 = 3.21 A; $C_9C_5C_4$ = 74°; α_5 = 69°; β_5 = 60°

<u>Conformer **D**</u>: r C_9-C_4 = 3.24 A; $C_9C_4C_5$ = 70°; α_4 = 67°; β_4 = (-)54°

r C_9-C_5 = 3.05 A; $C_9C_5C_4$ = 86°; α_5 = 85°; β_5 = (-)68°

It is clear that for conformers **D** and **E** both distance and angular parameters favor attack at C4 and, respectively, at C5.

TABLE 2. Estimated enthalpy changes (kcal/mol) for: E- or Z-thiacycloalk-4-ene → 2-thiabicyclo[m.n.0]alkane.

ring size	$-\Delta H_E$	$-\Delta H_Z$	bicyclic product
8	25.9	16.3	cis, 3.3.0
9	27.2	25.0	trans, 4.3.0
10	28.6	28.1	trans, 4.4.0

consequences on 1. entropy and 2. solvation. The presence of a trans double bond in medium rings determines conformational potential surfaces with a small number of relatively deep potential wells where the molecule has little chance for internal rotational motion. For the Z cycloalkenes the potential surface has shallow minima allowing for greater freedom of rotational motion. This of course translates in to higher entropy, hence greater entropy loss and reduced rate for transannular cyclization of the Z substrates. Finally, the geometry that a trans double bond imposes upon medium rings determines, as we have seen, a sharp differentiation of the peripheral from the inner side of the ring. Specifically, as far as solvation is concerned, while the peripheral side will be solvated, the inner side will be essentially bare. Thus reaction between functional groups facing each other transannularly will not be hampered by the need of moving solvent molecules out of the trajectory of approach. In other words the extent of desolvation is less than it would be were the reactant groups uniformly solvated, as is more likely to be the case for the Z isomers.

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