Acid-catalyzed transannular cyclization of medium ring unsaturated sulfides. The effect of ring size and double bond geometry on rate

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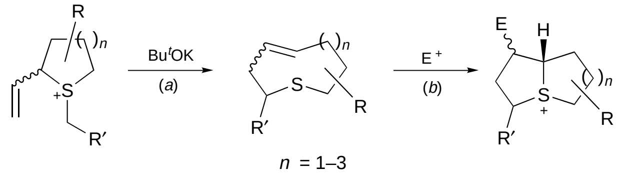
The acid-catalyzed transannular cyclization of 8–10-membered γ,δ-unsaturated cyclic sulfides yields *cis* fused bicyclic sulfonium salts independently of the geometry of the double bond. The rate varies linearly with the acidity function $-(H_0)_I$ with a slope of 1. The rate variations span about six powers of ten range, the maximum rate difference being observed for the *E*/*Z* thiacyclooct-4-ene pair. The data are consistent with the classical interpretation of the intramolecular reactivity in terms of internal strain of the substrate and/or of the transition state.

Introduction

Several years ago we reported on the syntheses of variously alkyl substituted medium size (8–10-membered) *E* and *Z* thiacycloalk-4-enes by ring expansion of cyclic sulfonium ylides occurring *via* 2,3-sigmatropic rearrangement [Scheme 1, step (*a*)].[1] Due to the presence of a reactive heteroatom and an *E* or *Z* double bond, these systems exhibit interesting chemical behavior. Thus in the years following their synthesis, for the *E* and *Z* olefins with 8- and 9-membered rings, we have been engrossed in the study of a number of their features, including their conformational behavior (NMR and force field),[2,3] and their ability to undergo electrophile-promoted transannular addition of sulfide sulfur to bicyclic bridgehead sulfonium cations [Scheme 1, step (*b*)].



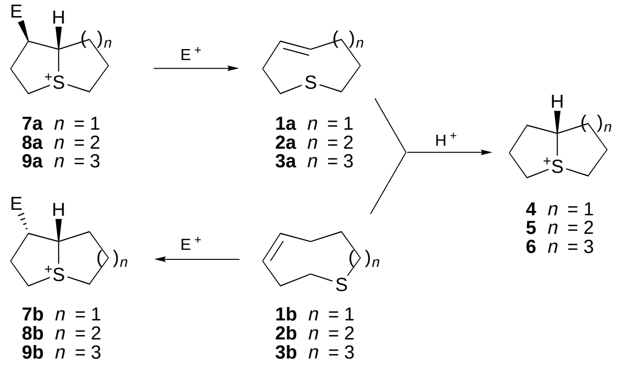
Scheme 1

We have proved, with a thorough study, that the junction of these bicyclic compounds is *cis*.[3,4] In this paper we show that even the transannular acid-catalyzed reaction of *E* and *Z* 10-membered olefins gives only one product [Scheme 1, step (*b*)] which can be confidently identified as a *cis* bicyclic sulfonium salt.[5]

Although in the course of such studies on the cyclization of these cyclic olefins ample rate variations had been often observed, no quantitative study was ever carried out. That large rate differences may be found in reactions where a medium size ring is transformed into a bicyclic system is not surprising in view of the large strain characterizing medium sized rings,[6] and the notion that such strain may be, at least in part, relieved in the transition state for transannular cyclization. We have therefore carried out, and herein report the results of, a kinetic study of the acid-catalyzed cyclization of 8-, 9- and 10-membered *E* and *Z* thiacycloalk-4-enes. The rate data are discussed in relation to the energy strain differences as determined by force field calculations.

Results and discussion

The choice of a proton as the electrophilic reagent was suggested by the notion that the product's stereochemistry would be independent of the double bond configuration of the starting olefin (**1a**–**3a** and **1b**–**3b**), unlike other electrophiles which due to the stereospecificity of the addition (*anti*), would end up producing diastereomers **7a**, **8a**, **9a** or **7b**, **8b**, **9b** (Scheme 2).



Scheme 2

The circumstance that the same product (**4** *n* = 1, **5** *n* = 2, **6** *n* = 3) issues from either *E* or *Z* olefinic starting material suggests that any effect which may be due to final product energy differences is unimportant. Thus any *E*–*Z* cyclization rate difference could be more reliably related to initial state strain differences, quantities which are accessible to estimation by molecular mechanics methods.

The kinetic of transannular cyclizations of medium size thiacycloalk-4-enes was studied with an acidic system constituted by $HClO_4$–AcOH–H_2O. The choice of this mixture represents the best compromise for a complete solubilization of the substrates and, moreover, varying the concentration of perchloric acid allows the determination of the rates of cyclization for all the substrates, except two, in reasonable times.

Values of the acidity $(H_0)_I$ of solutions containing varying amounts of perchloric acid in aqueous 90% acetic acid were taken and/or evaluated from data reported in the literature.[7] As shown in Fig. 1 (see also data in kinetic procedure), the plot of log k_{obs} for *trans*-thiacyclonon-4-ene varies linearly with the acidity function $-(H_0)_I$ and the slope of the line is 1.0 ± 0.1, unlike other alkene protonations which generally give values different from 1 and do not obey the same acidity function.[8] This fact is mainly due to the different solvation requirements of cations and the protonated base used as reference.[8] The unitary slope, in our case, indicates that the transannular cyclization parallels the acidity function as measured by $-(H_0)_I$,

Table 1 Rate of transannular cyclization and strain energy of (*E*)- and (*Z*)-thiacycloalk-4-enes

Ring configuration and size	$k_{obs}/s^{-1\,a}$			Relative rate[b]	Strain energy/kcal mol$^{-1\,c}$
	14% $HClO_4$	0.5% $HClO_4$	0.35% $HClO_4$		
(*Z*)-10	1.3×10^{-5}	—	—	1	10.4
(*Z*)-9	5×10^{-4}	—	—	38	12.0
(*Z*)-8	3.8×10^{-4}	—	—	29	12.3
(*E*)-10	1.3×10^{-3}	—	—	100	11.2
(*E*)-9	0.6[d]	6.4×10^{-4}	5.0×10^{-4}	46 000	14.9
(*E*)-8	7.2[e]	7.7×10^{-3}	6.0×10^{-3}	554 000	20.6

[a] Determined at 23.0 ± 0.1 °C in 90% AcOH–H_2O. [b] (*Z*)-10 was taken as reference. [c] Calculated using force field methods. [d] Calculated *via* $\log k_{obs} = -(H_0)_I - 2.44$ with $(H_0)_I = -2.21$ (ref. 7). [e] Since the reactivity ratio between (*E*)-8 and (*E*)-9 does not seem to depend on $HClO_4$ concentration, the rate constant is calculated from the ratio $k_{obs}/0.6 = (7.7 \times 10^{-3})/(6.4 \times 10^{-4})$.

Table 2 Rate ratios, differences in activation free energy of transannular cyclization and differences in strain energy of (*E*)- and (*Z*)-thiacycloalk-4-enes

Configuration	*n*–*n*′	$k_n/k_{n'}$[a]	$\Delta\Delta G^*_{n-n'}$/kcal mol$^{-1\,b}$	ΔE_s/kcal mol$^{-1\,b}$
E	8–9	12	−1.5	5.7
E	9–10	460	−3.6	3.7
Z	8–9	0.8	0.2	0.3
Z	9–10	38	−2.1	1.6

[a] From data in Table 1. [b] Calculated from $\Delta G^{\ddagger} = RT \ln(kT/hk)$.

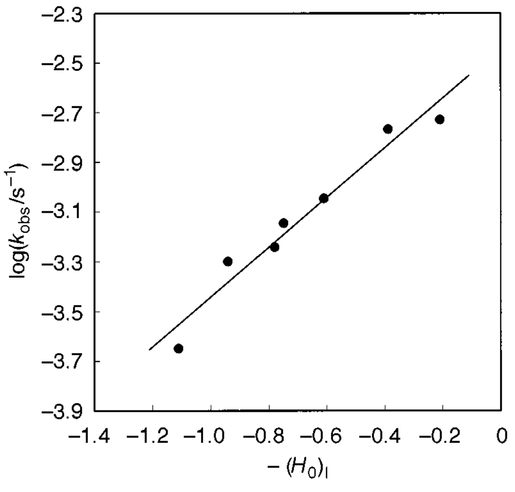


Fig. 1 Plot of $\log k_{obs}$ *vs.* $-(H_0)_I$ for transannular cyclization of *trans*-thiacyclonon-4-ene (*E*)-9 in 14% $HClO_4$ in 90% AcOH–H_2O at 23 °C

supporting a unimolecular mechanism of cyclization of the coniugate acid of olefin.

Having preliminarily determined the dependence of rate on acidity, significant comparison could be made between the rates in relation to ring size and stereochemistry of the starting alkene.

For each substrate the relative reactivity has been related to the strain energy determined by molecular mechanics and the results are reported in Table 1 and Fig. 2. As shown in both the *E* and *Z* olefins, although there is not a strict correlation, the strain energy of the ring decreases, from 8- to 9- and 10-membered olefins, keeping approximate pace with the decrease of the cyclization rate.

This circumstance suggests that an important factor determining the cyclization rate is the major or minor release of strain during the cyclization.

An interesting illustration of the internal strain effect on the reaction rate could be obtained by relating the rate ratios ($k_n/k_{n'}$) or the differences of activation free energy $\Delta\Delta G^*_{(n-n')}$ to the strain energy differences (ΔSE) between pairs of substrates having different ring sizes (*n* and *n*′) but the same configuration at the double bond (*E* or *Z*), as shown in Table 2.

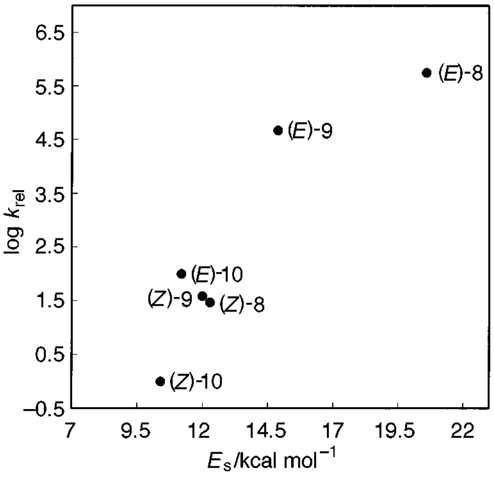


Fig. 2 Dependence of $\log k_{rel}$ *vs.* strain energy (E_s) for the acid-catalyzed transannular cyclization of thiacycloalk-4-enes (data in Table 1)

It can be observed that there is no simple proportionality between cyclization rate ratios $k_n/k_{n'}$ ($\Delta\Delta G^*_{n-n'}$) and strain energy differences ΔE_s. In particular, for the *E* olefins it can be noted that the ratio 12 obtained between olefins with 8- and 9-membered rings, corresponds to a strain energy difference of 5.7 kcal mol^{-1}, while the rate ratio of 460, between olefins with 9- and 10-membered rings, corresponds to a small value, 3.7 kcal mol^{-1}, of strain energy difference. Therefore the ring closure rate is not dependant exclusively on the strain energy of relaxation.

The relatively low reactivity of 10-membered olefins could be related to the high strain of the cyclization product, which is partly transferred to the corresponding transition states. In fact, calculation of the internal strain of the cyclization products (see Table 3) supports the hypothesis and shows that the cyclization product deriving from 10-membered olefins has a significantly higher strain energy.

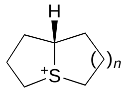
In conclusion the data shown in this study are consistent with the classical interpretation of the intramolecular reactivity in terms of the internal strain of the substrate and products or transition states.[13] Other factors, for instance an entropic one, can contribute to the principle lower reactivity of the *Z* isomers which suffer, in the cyclization, from greater entropy release.

Experimental

The energies of molecules to which reference is made throughout this paper were obtained from molecular mechanics calculations performed using the MMX force field,[9] which is an extension of Allinger's MM2.[10] Geometry optimization was obtained incrementally, varying ring dihedral angles so as to obtain a complete scan of the potential energy surface.

GLC analyses were performed on a Varian 3700 instrument using a 25 m column WB OV 17, film thickness 1.0 µm. Irradi-

Table 3 Strain energy of bicyclic compounds



n	E_s/kcal mol$^{-1\,a}$	Δn	E_s/kcal mol^{-1}
1	11.8	(2–1)	0.5
2	11.3	(2–2)	0
3	14.8	(3–2)	3.5

^{a} Calculated using force field method.

ations were performed using a 125 W high pressure quartz mercury vapor lamp. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively, on a Varian Gemini at 200 MHz. Chemical shifts were measured in δ and referenced to $CDCl_3$ (7.25 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR).

Cyclic homoallylic sulfides: 1a, 1b, 2a and 3a

The title compounds were all synthesized by ring expansion of the appropriate 2-vinyl cyclic sulfide methylides *via* [2,3]-sigmatropic rearrangement.[1]

(*E*)- and (*Z*)-Thiacyclooct-4-ene (1a and 1b) separation

The title compounds, obtained as a mixture of *Z* and *E* isomers (85 : 15),[1] were separated by exploiting a rate differential for formation of the $HgCl_2$ adducts with the *Z* and *E* homoallylic sulfides. To a stirred solution of crude sulfide in pentane solution was slowly added 6% aqueous $HgCl_2$. GLC monitoring showed the gradual decrease of minor product **1a**, which was converted to a white solid by addition of $HgCl_2$. The addition was stopped when the isomer which reacts preferentially had reached 90% conversion. The adduct was filtered, then treated with 50% aqueous KI and extracted with pentane to regenerate the sulfide **1a** which was obtained 98% pure. A small amount of $HgCl_2$ solution was then added to the mother liquor to remove the last traces of the *E* isomer while monitoring the organic layer by GLC. After filtration of solid, evaporation of pentane gave the *Z* isomer 98% pure.

(*Z*)-Thiacyclonon-4-ene (2b)

Compound **2b** obtained 98% pure from **2a** by irradiation under N_2 for 5 h at room temp. in hexane solution with a 125 W high-pressure quartz mercury vapor lamp.[11]

(*Z*)-Thiacyclodec-4-ene (3b)

A 1 : 1 mixture of *Z* and *E* isomers[11] was obtained *via* irradiation of **3a** for 10 h. The isomers were separated analogously to (*E*)- and (*Z*)-thiacyclooct-4-ene **1a** and **1b**.

cis-1-Thionia[3.5.0]decane trifluoromethanesulfonate (6)

This compound can be quickly obtained as described for the [3.3.0] analog[3] from (*E*)- and/or (*Z*)-thiacyclodec-4-enes (1 mmol) in 2 ml of CH_2Cl_2 and trifluoromethanesulfonic acid (1.03 mmol). The mixture was stirred for 4 h at room temperature and the solvent removed *in vacuo* to give 2.80 g of the title compound (95%); δ_H[$(CD_3)_2CO$] 4.58 (m, 1H), 3.50–3.75 (m, 4H), 2.25–1.32 (m, 12H); δ_C[$(CD_3)_2CO$] 62.11 (CH), 46.13, 38.53, 36.83, 31.68, 29.74, 29.08, 27.12, 26.92 ($8CH_2$) (Found: C, 34.05; H, 6.08. $C_8F_3H_{17}O_3S_2$ requires C, 34.03; H, 6.07%).

Thiacyclodecane[12]

The title compound was obtained from **3a** *via* the following procedure. To a solution of 0.56 g (3.6 mmol) of **3a** in 25 ml of EtOH, cooled to 18 °C, 8.5 ml (18 mmol) of hydrazine monohydrate (98%) and 0.90 ml of $CuSO_4$ (0.2 M, 0.18 mmol) were added. Then O_2 was bubbled (200 ml min^{-1}) through the mixture for 3 h and 50 ml of water were added to the mixture which, after neutralization with HCl (1 : 1), was extracted with light petroleum. Evaporation of the solvent gave a crude product which was purified by recrystallization from absolute ethanol to yield thiacyclodecane (0.37 g, 66%): $\delta_H(CDCl_3)$ 2.62 (m, 4H), 1.55 (m, 14H); $\delta_C(CDCl_3)$ 31.75 ($2CH_2$), 27.24 ($2CH_2$), 25.80 (CH_2), 24.57 ($2CH_2$), 23.74 ($2CH_2$) (Found: C, 68.33; H, 11.46. $C_9H_{18}S$ requires C, 68.31; H, 11.47%).

Kinetic procedure

The kinetics were followed by gas chromatography by measuring the disappearance of thiacycloalk-4-enes over time at 23.0 ± 0.1 °C. A typical procedure is as follows: 2.5 mmol of thiacycloalk-4-ene were added to a prethermostatted vessel containing a solution (30–50 ml) of $HClO_4$ at various concentrations in 90% AcOH–H_2O prepared as described by Rocek,[7] and containing 15 mmol of thiacyclodecane, added as internal standard. At set times, 3 ml of solution were removed, neutralized, then extracted with *n*-pentane and submitted to GLC analysis to determine the percentage of unreacted olefin. The confidence of the chromatographic technique was preliminarily confirmed by comparing the results obtained with those derived from ^{1}H and ^{13}C NMR spectra. The rates were followed at least to 80% and were performed in duplicate runs. The first order rate constants were calculated from the equation $C = C_0\ e^{-kt}$ using a least-square routine. Values of $HClO_4$ (%) and the rate constants (k_{obs}/s^{-1}), found for thiacyclonon-4-ene are reported in the order: k_{obs}/s^{-1} (%$HClO_4$): 2.23×10^{-4} (0.25), 5.01×10^{-4} (0.35), 5.72×10^{-4} (0.5), 7.13×10^{-4} (0.6), 8.96×10^{-4} (0.7), 1.70×10^{-3} (1.0), 1.86×10^{-3} (1.5).

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