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THE LACHRYMATORY FACTOR OF THE ONION: AN NMR STUDY[1]

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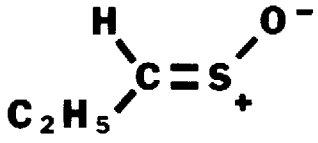
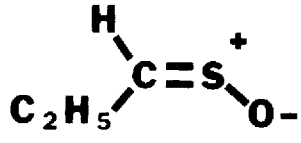
The lachrymatory factor of the onion is shown by NMR analysis to be a 19 to 1 mixture of (Z)- and (E)-propanethial S-oxide.

The unique ability of the onion (*Allium cepa* L.) to bring tears to the eyes of those that would open it must surely have been noticed at the dawn of civilization with the cultivation of this venerable plant. The first suggestion that sulfur compounds might be responsible for the odor of the onion appears to have been made in 1892.[2] In the intervening years the application of increasingly sophisticated methods of analysis led ultimately to the characterization in 1971 of the so-called lachrymatory factor (L.F.) as the sulfine, propanethial S-oxide, 1, shown to be identical with the compound produced by dehydrochlorination of propanesulfinyl chloride.[3] This sulfine can exist as (E)- and (Z)-diastereomers, *e.g.* 1-E and 1-Z, respectively. The 1971 study arbitrarily indicates (E)-stereochemistry[3] while other papers either follow suit or depict the



1-E



1-Z

L.F. with a linear CSO grouping devoid of any stereochemistry.[4,5] We now report the determination of the stereochemistry of 1 from natural as well as synthetic sources by Fourier-transform NMR techniques, thereby completing the characterization of the L.F.

Approximately 1 kg of fresh white globe onions were peeled, quartered and frozen in Dry Ice and then crushed with a hammer and while still cold, converted into a white powder in a "Waring" blender. The powder was then vigorously mixed in the blender with 1 L of CCl_3F (Freon 11) at *ca.* 0° and the CCl_3F layer separated, dried ($MgSO_4$) and concentrated at -78°C/0.05mm. Trap-to-trap distillation at -20°C and 0.05mm afforded the L.F. in essentially pure form as judged by NMR analysis. Thus, in $CDCl_3$ the L.F. showed δ 1.156 (t, J=7.32 Hz, 3H, CH_3), 2.798(q, J=7.81 Hz, 2H, CH_2) and 8.211 (t, J=7.81 Hz, 1H, CH) in good agreement with the spectrum of 1 from propanesulfinyl chloride (δ 1.156 (t, J=7.5 Hz), 2.794(q, J=7.82 Hz) and 8.191(t, J=7.81 Hz)) and with the published spectrum of the previously isolated L.F. and synthetic counterpart.[3] However, careful examination of the 100 MHz ^1H FT-NMR spectrum of the natural L.F. in $CDCl_3$ revealed the presence of a second low field triplet at δ 8.882 (J=8.79Hz), integrating to about 5% of the area of the δ 8.211 triplet. This minor triplet, which is not reported in earlier

NMR studies of the onion L.F., was shown to be neither a spinning side band nor a satellite band nor was it due to propionaldehyde (a known decomposition product of the L.F. showing a triplet at δ 9.789, J=1.46 Hz), and was found to be present at somewhat lower intensity in the NMR spectrum of synthetic 1 (δ 8.873, t, J=8.79 Hz in $CDCl_3$). After 4.5h at 30°C the L.F. NMR signal at δ 8.211 was reduced to *ca.* half of its original intensity, the δ 8.882 signal was now about 10% of the area of the δ 8.211 triplet and the propionaldehyde signal at δ 9.789 had increased to *ca.* the same intensity as the δ 8.211 signal. In C_6D_6 synthetic 1 showed δ 0.750 (t, J=7.44 Hz), 2.421(q, J=7.82 Hz), 7.605(t, J=7.82 Hz) and a minor triplet at δ 8.373(J=8.89 Hz).

To summarize, the NMR spectrum of natural or synthetic 1 reveals a minor triplet 0.67-0.68 ppm downfield from the major triplet in $CDCl_3$ and 0.77 ppm downfield from the major triplet in C_6D_6. In synthetic 1 the major triplet underwent a 0.59 ppm shift to higher field on going from $CDCl_3$ to C_6D_6 as solvent while the minor triplet underwent a 0.50 ppm shift to higher field upon this same solvent change. On the basis of a comparison of this NMR data with data from extensive NMR studies of related structures of the type RCH=N-X (X=OH, OMe, N(Me)Ph, NHMe, NHPh, etc.)[6] we suspected that our samples of 1 were composed of a mixture of 1-E and 1-Z *with the latter as the major component.* This assignment is fully consistent with the observations in the nitrogen systems that 1) protons resonate at lower fields when *syn* than when *anti* to X in RCH=N-X, 2) *anti* protons are shifted further upfield than *syn* protons on changing the solvent from CCl_4 to C_6D_6, and 3) the coupling constant $J_{H_1H_\alpha}$ (*e.g.* $J_{H_1H_2}$ in 1) is slightly larger in the *anti* compound than the *syn* compound.[6] In analogy with the mechanism proposed for the aromatic solvent induced shifts in the nitrogen systems[6] we suggest that dipole forces favor the benzene orientation shown in 2 in which the *anti*-proton (R_1=H) in the (Z)-isomer should experience greater shielding than the *syn*-protons (R_2=H) in the (E)-isomer.

To augment our NMR analysis we have synthesized (according to eq 1 or 2) and determined the NMR spectra of three closely related sulfines, ethanethial S-oxide, 3, 2-methylpropanethial S-oxide, 4, and 2,2-dimethylpropanethial S-oxide, 5. The NMR data for 3-5 presented in the Table is completely consistent with our above analysis and with NMR data on related RCH=N-X systems. In all cases the *syn* or (Z)-isomer is the major component. We have also established by microwave spectroscopy that in the case of 1 from the onion and 1 and 3 from synthetic sources (including both low temperature dehydrochlorination of sulfinyl chlorides and flash vacuum pyrolysis of diverse precursors) the (Z)-isomer predominates.[1c,7]

To the extent that the "syn-effect" is thermodynamically determined, we suggest that steric repulsion in the *syn* or (Z)-form is counterbalanced by bonding between the alkyl group and the oxygen. Our microwave study of 1-Z reveals that the preferred conformation is "syn,staggered"[8] as shown in 6, a conformation which in analogy to studies on alkylperoxymethylenes (carbonyl oxides) should possess some stability (σ-stabilization[8]) relative to the various *anti* or (E)-conformations.[8,9] Sulfine stereochemistry may be influenced by kinetic factors when the sulfines are formed by dehydrochlorination of alkanesulfinyl chlorides at -20° in that transition state 7 may be favored over 8.[10]

Another interesting feature noted for the series of alkanethial S-oxides in the Table is that as the "R" group in RCH=SO becomes more bulky, the lachrymatory effect diminishes to the

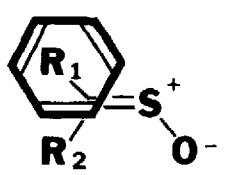
Table 1. ^1H NMR data (in ppm) for the low field proton in alkanethial S-oxides and an oxime

Compound (rel. abundance)	$CDCl_3$ $\delta(J_{H_1H_\alpha}, Hz)$	$CDCl_3$ $\delta_E-\delta_Z$	C_6D_6 $\delta(J_{H_1H_\alpha}, Hz)$	C_6D_6 $\delta_E-\delta_Z$	$\Delta\delta$[a]
(Z)-MeCH=SO (97%)[e]	8.31(7.33)		7.43		0.88
3		0.57		0.69	
(E)-MeCH=SO (3%)[e]	8.88(8.79)		8.12		0.76
(Z)-EtCH=SO (95%[d], 98%[e,f])	8.19(7.81)		7.60(7.82)		0.59
1		0.68		0.77	
(E)-EtCH=SO (5%[d], 2%[e,f])	8.87(8.79)		8.37(8.89)		0.50
(Z)-*i*-PrCH=SO (92%)[e]	8.10		7.45(9.28)		0.65
4		0.68		0.92	
(E)-*i*-PrCH=SO (8%)[e]	8.78		8.37(9.76)		0.40
(Z)-*t*-BuCH=SO (75%)[e]	7.62		6.86		0.76
5		1.38		1.64	
(E)-*t*-BuCH=SO (25%)[e]	9.00		8.50		0.50
(Z)-EtCH=NOH[b] (44%)[g]	6.75(5.47)[c]		6.52		0.23
		0.72		0.87	
(E)-EtCH=NOH[b] (56%)[g]	7.47(6.10)[c]		7.39		0.08

a $\delta_{CDCl_3}-\delta_{C_6D_6}$. b Reference 6. c Neat. d Natural L.F. e From RS(O)Cl. f From FVP of *t*-BuS(O)CH=CHR'. g Equilibrium composition.

$$RCH{=}CHS(\mathbf{O})t\text{-}Bu \xrightarrow{250^\circ C} RCH_2CH{=}SO \quad (R=H \text{ or } Me) \qquad (1)$$

$$R'CH_2S(\mathbf{O})Cl \xrightarrow[CCl_3F,\,-20^\circ C]{Et_3N} \underset{1,3\text{-}5}{\overset{1,3}{R'CH{=}SO}} \quad (R'=Me,Et,i\text{-}Pr,t\text{-}Bu) \qquad (2)$$



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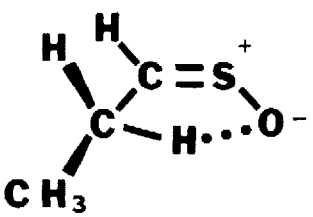

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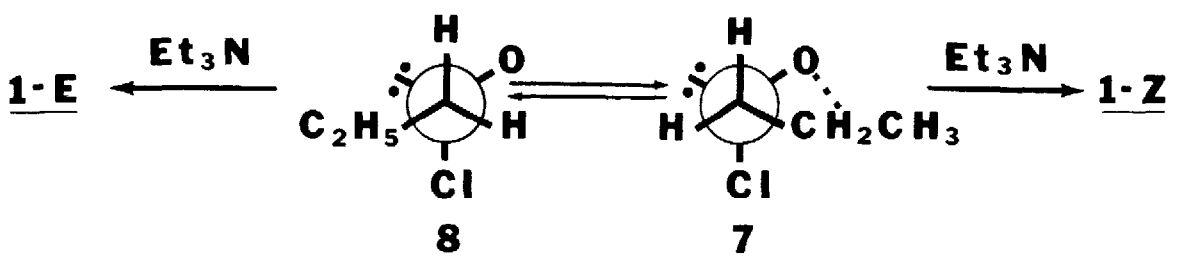

8 7

point where 5 (R=t-Bu) is devoid of lachrymatory activity. This observation leads us to suggest that the *physiological (enzymatic ?) process associated with lachrymation from the onion L.F. is subject to steric inhibition.*[11]

The dependency of the "syn-effect" in alkanethial S-oxides on structure and conditions of generation as well as the variation of the lachrymatory "potency" of these compounds with structure is being actively investigated.

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