

maintain a definite stereochemical relationship between the side chains of the interacting monomers. The tyrocidines constitute an excellent example in which the line broadening in the nmr spectra is clearly shown to result from self-aggregation. In proteins which have both tertiary and quaternary structure this distinction cannot be made as clearly.

A more rigorous analysis of the effect of aggregation on line widths and other nmr spectral parameters is now being carried out. Hopefully these may shed further light on the actual mechanism of aggregation and on the role played by the various side chains.

Acknowledgment. A. S. was supported by post-doctoral fellowship G.M. 29,426 from the National Institutes of Health. We wish to thank Miss Josephine Chang for the dialysis experiments.

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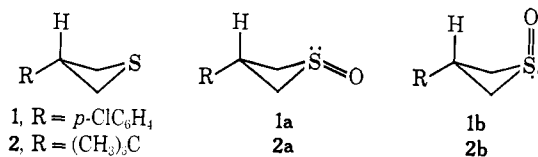
Received March 8, 1969

Equilibration of 3-Substituted Thietane 1-Oxides^{1,2}

Sir:

The significant stereochemical consequences of lone electron pairs on heteroatoms have come under scrutiny only in recent times. The sulfoxide group, which retains its stereochemical integrity at room temperature, provides an intriguing example for studies of the com-

in benzene solution were found to be 3.22 ± 0.09 and 2.80 ± 0.03 D, compared with calculated values of 2.99 and 2.47 D, respectively. The theoretical moments were obtained from values of 1.95 D for the



p-chlorophenyl^{7b} and 4.19 D for the sulfinyl⁸ moieties and a 37° angle of ring puckering.⁹

The stereochemical assignment was extended to the 3-*t*-butylthietane 1-oxide system by observing the deshielding effect of the S=O bond on the β-hydrogen when they are *cis* (i.e., *trans* sulfoxide). First observed for cyclic sulfites,¹⁰ the deshielding effect of the S=O bond has been utilized for the assignment of stereochemistry to five- and six-membered ring sulfoxides.¹¹⁻¹³ The pronounced deshielding of a β-hydrogen which is *syn* and axial to the S=O bond, as in certain six-membered ring systems, has been attributed to a proximity effect^{12a,14} and/or acetylenic type anisotropy of the S=O bond.¹² The observed chemical shift difference of the β-hydrogen between *cis*- and *trans*-3-*p*-chlorophenylthietane 1-oxide, **1a** and **1b**, was 65 Hz and the analogous difference for the *t*-butyl system, **2a** and **2b**, was 68 Hz. In the *trans* isomers of these puckered^{9,15} thietane oxides, **1b** and **2b**, the

Table I. Equilibration of 3-Substituted Thietane 1-Oxides

Compounds	Method (°C)	<i>cis/trans</i> composition		Method of analysis
		Starting material	Equilibrium	
2a + 2b	HCl-dioxane (25)	15/25	85/15	Vpc
2a + 2b	HCl-benzene (25)	55/45	86/14	Vpc
1a + 1b	HCl-dioxane (25)	Predominantly <i>trans</i>	Predominantly <i>cis</i>	Nmr
1a -d ₄ + 1b -d ₄	HCl-dioxane (25)	46/54	87/13	Nmr
2a + 2b	Decalin (170-175)	63/37	82/18	Vpc
2a + 2b	Decalin (170-175)	35/65	85/15	Vpc
2	N ₂ O ₄ (0)	Sulfide	82/18	Vpc

petitive conformational requirements of an oxygen *vs.* an electron pair. The axial preference exhibited by sulfinyl oxygen in six-membered rings is now well established.³⁻⁵ We report here our observation that sulfinyl oxygen in a four-membered ring exerts a pseudoequatorial preference.

Stereochemistry was assigned to *cis*- and *trans*-3-*p*-chlorophenylthietane 1-oxide,⁶ **1a** and **1b**, from their dipole moments.^{7a} The dipole moments of **1a** and **1b**

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S=O bond and β-hydrogen may approach a *syn*-axial relationship.

The isomeric sulfoxides were separated by elution chromatography over silica gel; *cis* isomers eluted prior

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to *trans*. For the 3-*t*-butylthietane 1-oxides, **2a** and **2b**, isomer purity could be quantitatively determined from vapor phase chromatography.¹⁶ For the 3-*p*-chlorophenylthietane 1-oxides, **1a** and **1b**, a qualitative analysis of isomer purity was allowed from the nmr spectra, but quantitative determinations could only be made by integration of the nmr signal for the β -hydrogens in the α -tetradeuterated sulfoxides.

Stereomutation of sulfoxides¹⁷ may be effected either by heat or light, or by the action of reagents such as hydrogen chloride or dinitrogen tetroxide. Both chemical and thermal equilibration of the 3-substituted thietane 1-oxides yielded mixtures of similar isomer ratios (Table I).

Thermally induced racemization of mixtures of differing isomer ratios of **2a** and **2b** in purified decalin under nitrogen at 170–175° led to establishment of equilibrium in less than 15 min; despite the difference in temperature, the position of equilibrium was nearly the same as in the catalyzed equilibrations (Table I).

The sulfone **1c** on treatment with sodium deuterioxide in a deuterium oxide–dioxane solution was converted to the tetradeuterated sulfone.¹⁸ Reduction of the sulfone with lithium aluminum hydride in ether yielded the tetradeuterated sulfide **1-d₄** and oxidation of the sulfide with sodium metaperiodate yielded a mixture of the two α -deuterated sulfoxides, **1a-d₄** and **1b-d₄**. Equilibration of this mixture with hydrochloric acid in dioxane yielded an isomer ratio in fair agreement with ratios obtained from the *t*-butyl system (Table I).

Recent calculations¹⁹ have substantiated the earlier suggestion³ that the axial preference exhibited by sulfinyl oxygen in thiane 1-oxides may result from an attractive van der Waals interaction between the oxygen and carbons 3 and 5 or their attached axial hydrogens. No repulsive interactions were calculated between the oxygen and carbons 3, 4, or 5 or any of their attached hydrogens.

Usually the preferred geometry for 1,3 disubstitution on a nonplanar cyclobutane ring is *cis* diequatorial, attributed to the tendency to minimize 1,3 (cross-ring) nonbonded repulsions.^{20,21} In the puckered thietane ring where a bulky substituent at C₃ exerts an equatorial preference, the oxygen is forced to assume a pseudoaxial or pseudoequatorial position. The experimental observation that 3-substituted thietane 1-oxides prefer the *cis* (diequatorial) geometry would appear to be the result of a repulsive interaction between oxygen and carbon 3 and/or its attached axial hydrogen in the *trans* isomer; depending on the degree of puckering the nonbonded distances of concern may be significantly shorter than in the thiane 1-oxide case.

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Received January 27, 1969

The Effects of Structure on the Rates of Neutralization and the Ionization Constants of Nitrocycloalkanes

Sir:

Previous studies of the effects of structure on the rates of neutralization and the ionization constants of nitro compounds reveal that nitroalkanes which neutralize relatively rapidly may be much weaker than more slowly neutralized but yet stronger homologs. The reactivities for neutralization of the indicated nitroalkanes by aqueous hydroxide ion (k_2 , $M^{-1} \text{ min}^{-1}$, 0°) are: nitromethane (238) > nitroethane (39.1) > 2-nitropropane (2.08); that for dissociation ($K_{\text{ion}} \times 10^{11}$, 25°), however, is 2-nitropropane (1980) > nitroethane (252) > nitromethane (5.75).¹ The nucleophilicities for reversal in these systems are thus $\text{CH}_2\text{NO}_2^- > \text{CH}_3\text{CHNO}_2^- > (\text{CH}_3)_2\text{CNO}_2^-$. The striking behavior of these ions has been attributed to dielectric^{1b} and electronic and steric effects² and to reduction of the nucleophilicities of electron-rich nitronates resulting from hydrogen-bonded solvation at nitronate oxygens.²

A study has now been made of the effects of ring size on the rates of neutralization and the ionization constants of homologous nitrocycloalkanes. The objectives of this investigation are to evaluate structural influences on the kinetics and thermodynamics of formation of cycloalkanenitronates.

Neutralizations of nitrocycloalkanes were studied as second- and as first-order processes using rapid conductometric methods in which consumption of the bases was essentially complete, oxidants were excluded, and the nitro compounds could be regenerated almost quantitatively. The kinetic data were satisfactorily accurate and the results are summarized in Table I.

The conductometric reactivities for neutralization of nitrocycloalkanes are: 4 > 5 > 7 > 8 > 6 >> 3. The results of interest are: (1) nitrocyclobutane neutralizes faster than any of its higher homologs, (2) nitrocyclopropane does not undergo conductivity change, (3) the reactivity order of the C₄–C₈ nitrocycloalkanes is not altered by bases of different strengths,³ and (4) except for nitrocyclopropane, nitrocycloalkanes neutralize more rapidly than their acyclic analogs.

Rapid neutralization of nitrocyclobutane is not predicted by I strain.⁴ The kinetic results for neutralization of 1-deuterionitrocyclobutane, 1-deuterionitrocyclopentane, and 1-deuterionitrocyclohexane by hydroxide (Table I) do not reveal any difference in reaction mechanism of these homologs. The near-maximum isotope effects observed, $k_{\text{H}}/k_{\text{D}} \cong 8.3\text{--}8.9$ at 0°, indicate that in neutralization of nitrocycloalkanes the reacting carbon–hydrogen bond is highly broken and that between hydroxide and the removable proton is weakly developed (I). The remarkable behavior of nitrocyclobutane may be due, in combination, to the s character of the electrons of the removable hydrogen and to the favorable geometry for attack on hydrogen which will allow (partial) delocalization involving the

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