

accompanying collapse of the high-field (H_x) resonance. This observation verifies a 1,2 shift as the rearrangement mechanism.

The tentative conclusion put forward above is supported overwhelmingly by examination of the temperature dependence of proton-decoupled ^{13}C NMR spectra for I-III. Observed frequencies at the slow limit of rearrangement are listed in Table I. In the olefinic region the *n*-butyl compound II shows two resonances, which we assign to $\text{C}^{2,5}$ diastereotopically shifted from one another by 3.8 ppm, flanking an unsplit $\text{C}^{3,4}$ resonance at 132.6 ppm. For I and III both pairs of carbon atoms are anisochronous: the $\text{C}^{2,5}$ resonances remain ~ 3 ppm apart, but a separation which is much smaller (0.7, I; 0.4 ppm, III) is also found between C^3 and C^4 . The temperature dependence of these spectra is typified by that shown in Figure 2 for the trimethylsilylmethyl compound III. With increasing temperature and in spite of the substantially larger chemical-shift difference between them, the outer pair of lines (attributed to $\text{C}^{2,5}$) begin to broaden and lose intensity more rapidly than the central signals. Exactly similar changes occur in the spectra of I and II: for the latter the resonance due to the carbon atoms showing no resolvable diastereotopic effect ($\text{C}^{3,4}$) collapses more slowly than those for the anisochronous pair.

By providing a new approach to the assignment of resonances due to the cyclopentadienyl ring nuclei these observations constitute a more convincing substantiation of the 1,2 (equivalent to 1,5) migration pathway than those put forward hitherto.

Acknowledgment. We thank the National Research Council (Canada) and the University of Victoria for financial support.

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Hemiothiothiolate Ester Anions— $\text{RC}(\text{OR}')_2\text{S}^- + \text{Na}$. A Novel Class of Thermally Stable Tetrahedral Intermediates¹

Sir:

Tetrahedral intermediates play a pivotal role in a whole host of enzymatic and nonenzymatic carbonyl reactions.² Our

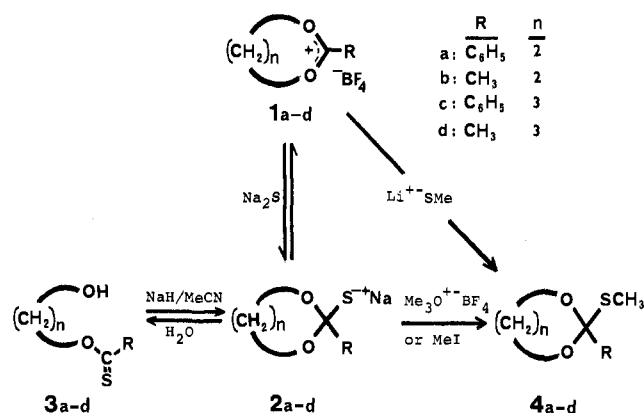


Figure 1. Synthesis and trapping of tetrahedral intermediates 2a-d.

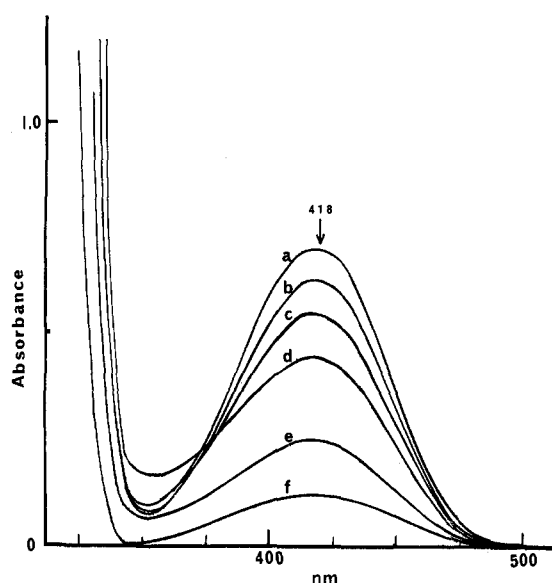


Figure 2. Visible spectra of the $3a \rightarrow 2a$ transformation: a, 6.09×10^{-3} M solution of $3a$ (hexane); b-f, after addition of 1.0, 1.5, 2.5, 4.0, and 6.0 mg of NaH to 3.0 mL of a.

knowledge of the chemistry of three-heteroatom tetrahedral intermediates³ is derived from numerous kinetic,⁴ spectroscopic,⁵ and theoretical studies.⁶ Deslongchamps' elegant investigations⁷ have furthered our understanding of stereoelectronic effects in the generation and breakdown of short-lived tetrahedral species of the type $\text{RC}(\text{OR})(\text{OH})_2$, $\text{RC}(\text{OR})_2(\text{OH})$, and $\text{RC}(\text{OR})(\text{NR}_2)(\text{OH})$; stereoelectronic effects have also been noted in the breakdown of hemiothioamide intermediates— $\text{RC}(\text{OR})(\text{NR}_2)(\text{SH})$.⁸ While a variety of neutral intermediates (T^0) have been isolated,⁹ only three stable anionic three-heteroatom intermediates (T^-) are known.¹⁰ We report on the isolation and characterization of a novel class of thermally stable anionic tetrahedral intermediates— $\text{RC}(\text{OR}')_2\text{S}^- + \text{Na}$ —formed during the intramolecular transesterification of thionobenzoate and thionoacetate esters.

We recently reported that the sulphydrolysis of various acyclic and cyclic dialkoxycarbonium ions may be carried out through a two-step addition-protonation sequence to give good yields of thionobenzoates and monothionoesters of 1,2- and 1,3-diols.¹¹ In the course of these experiments, it was observed that the reaction of 2-phenyl-1,3-dioxolan-2-ylum fluoroborate (**1a**) with an equivalent amount of anhydrous sodium sulfide in acetonitrile gave a crude white solid which, after thorough washing with dry acetonitrile under nitrogen, could be hydrolyzed to give a yellow oil, **3a**, in 27% yield. Treatment of the crude solid above with 1.5 equiv of $\text{Me}_3\text{O}^+ - \text{BF}_4^-$

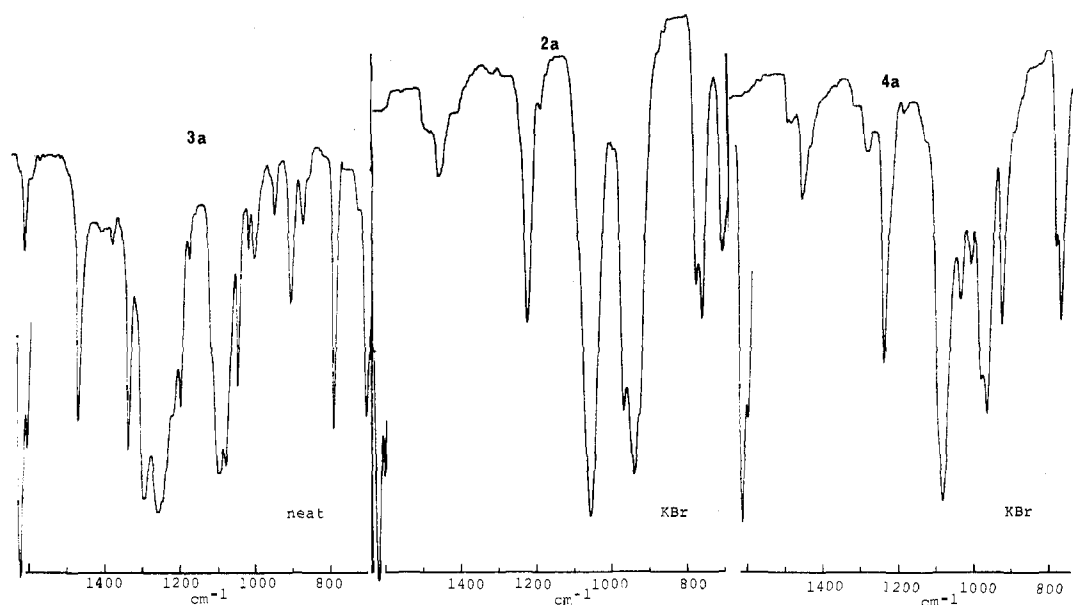


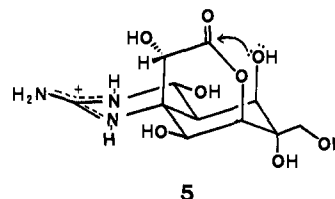
Figure 3. Infrared spectra of **3a** (neat), **2a** (KBr pellet), and **4a** (KBr pellet).

CH_2Cl_2 (0°) led to orthothioester **4a**¹² (Figure 1, 59% yield) which proved to be identical (IR, NMR) with the product obtained from the reaction of **1a** with $\text{Li}^+ \text{SCH}_3^-$ (CH_2Cl_2 , 0°C). Parallel observations were made on solids derived from sodium sulfide and each of **1b-d**.

The results described above suggested that the white solids derived from Na_2S and each of **1a-d** consisted, *in part*,¹⁴ of hemiothioester anions **2a-d** (Figure 1). To verify these structural assignments, an independent route to these intermediates was sought. To that end, pure **3a** was treated with an equivalent amount of NaH in CH_3CN (0°C , 30 min; -4°C , 24 h) and the resulting white moisture-sensitive solid (**2a**) was filtered under nitrogen (77.6% yield, mp 115°C dec). Anal. Calcd for $\text{C}_9\text{H}_9\text{O}_2\text{SNa}$: C, 52.93; H, 4.44. Found: C, 52.60; H, 4.61. Unfortunately, the solid proved to be insoluble in a wide variety of inert solvents; hence, it could not be crystallized, nor could its ^{13}C NMR, ^1H NMR, UV, and solution IR spectra be recorded.¹⁵ However, treatment of **2a** with water (27°C) gave **3a** quantitatively. Also, alkylation of **2a** with $\text{Me}_3\text{O}^+ \text{BF}_4^-/\text{CH}_2\text{Cl}_2$, $\text{Me}_3\text{O}^+ \text{BF}_4^-/\text{CH}_3\text{CN}$, and $\text{CH}_3\text{I}/\text{CH}_3\text{CN}$ gave **4a** in 94, 88, and 100% yields, respectively.¹⁶ Spectroscopically, one could follow the progress of the **3a** \rightarrow **2a** transformation by monitoring the disappearance of the $n \rightarrow \pi^*$ (418 nm) of **3a** in acetonitrile and in hexane, as one added increasing amounts of NaH (Figure 2). Furthermore, the fingerprint regions of the infrared spectra of **2a** and **4a** (KBr) are strikingly similar, suggesting that these compounds have a common skeletal structure; also, both spectra lacked the strong band centered around 1230 cm^{-1} attributable to $\text{C}=\text{S}$ vibration of **3a** (Figure 3).¹⁷ On the basis of the spectral and chemical evidence presented above, we assign to **2a**, in the solid state, the structure shown in Figure 1.¹⁸ Analogous reactions of **3b-d** with NaH/ CH_3CN yielded **2b-d** (42.2, 66.8, and 47.3% yield, respectively), all of which were hydrolyzed to the hydroxythioesters **3b-d**¹⁹ and cleanly methylated ($\text{Me}_3\text{O}^+ \text{BF}_4^-/\text{CH}_2\text{Cl}_2$) to produce orthothioesters **4b-d**. The latter compounds were identical with the respective products of the reactions of LiSMe with each of **1b-d**; the structures are depicted in Figure 1.

According to the stereoelectronic theory,⁷ species **2a-d** are subject to not only primary stereoelectronic effects (responsible for the lengthening^{6d,e} and hence weakening of the $\text{C}-\text{O}$ bonds) but secondary ones (tantamount to resonance stabilization of the incipient $\text{C}=\text{S}$ π bond) as well,^{7d} that is, these

T^- -type intermediates ought to have a very short lifetime.^{7d} In that regard, the thermal stability of intermediates **2a-d**, in the solid state and in aprotic solvents CH_2Cl_2 and CH_3CN is surprising, remarkable, and significant. Whereas the stabilities of $\text{CF}_3\text{C}(\text{O}^-)(\text{OEt})_2$ and $\text{EtO}_2\text{CC}(\text{O}^-)(\text{OEt})_2$ are attributable to the strong electron-withdrawing effects of the trifluoromethyl and carboxy groups, such inductive effects in **2a**, **2c**, and **2b** or **2d**, in particular, are absent. In the synthesis of tetrodotoxin, on the other hand, the intramolecular formation of the hemilactal salt moiety was facilitated by the very close proximity of the alcohol and lactone groups as dictated by the unique architecture of precursor **5**.²⁰ In **2a-d**, in contrast, such



geometrical constraints are nonexistent. Admittedly, the reactions leading to **2a-d** do take advantage of an appreciable intramolecular entropy factor.²¹ The principal driving force for the cyclization is provided by (i) the localization of the negative charge on the softer sulfur atom (instead of the oxygen of $-\text{O}(\text{CH}_2)_n\text{O}(\text{C}=\text{S})\text{R}$),²² (ii) the formation of a strong $\text{C}-\text{O}$ σ bond at the expense of the weaker $\text{C}-\text{S}$ π bond,²³ and (iii) the insoluble nature of **2a-d** in aprotic acetonitrile.

Intermediates **2a-d** should lend themselves to further chemical studies. We are currently exploring their hydrolytic behavior.

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- (15) Attempts at making the lithium salt using LiH were unsuccessful; also, in view of anticipated overlap of ^1H NMR signals, crown ethers could not be used.
- (16) One observes no acyclic O-alkylated product (viz., $\text{MeOCH}_2\text{CH}_2\text{OC}(\text{S})-\text{C}_6\text{H}_5$) in these methylation reactions of solid **2a**; this was confirmed by comparison of TLC, IR, and NMR data of authentic material prepared by the reaction of 2-methoxyethanol and methyl thionobenzoate in the presence of NaH /dimethoxyethane. However, when, instead of solid **2a**, the entire heterogeneous reaction mixture (i.e., **3a** + NaH \rightarrow **2a**) was trapped (after 15-min reaction time) with 1 equiv of $\text{Me}_3\text{O}^+ \text{BF}_4^-$, one did observe (TLC, NMR) a small amount (<3%) of 2-methoxyethyl thionobenzoate.
- (17) In the IR spectra of thiono compounds, one generally finds strong bands in the region 1200–1000 cm^{-1} attributable to $\text{C}=\text{S}$ vibration; unfortunately, certain single-bond vibrations also appear in this region (cf. Janssen, M. J. in "The Chemistry of Carboxylic Acids and Esters", Patai, S., Ed.; Interscience: New York, 1969; p 715). Nevertheless, in our hands, the spectra of methyl thionobenzoate and ethyl thionobenzoate reveal characteristic strong $\text{C}=\text{S}$ bands at 1235 and 1245 cm^{-1} , respectively; these bands are absent in the spectra of methyl and ethyl benzoate. In the spectrum of **2a**, the sharp medium-intensity band at 1210 cm^{-1} has a counterpart in the spectrum of **4a** at 1225 cm^{-1} ; these bands are in all likelihood due to $\text{C}-\text{O}$ vibrations and not to $\text{C}=\text{S}$ vibration.
- (18) To the extent that **2a** has to dissolve in CH_2Cl_2 or in MeCN in order to be alkylated (with $\text{Me}_3\text{O}^+ \text{BF}_4^-$ or MeI), it is quite likely that this structural assignment also holds for the dominant solution structure of **2a**.¹⁶ To rule out a kinetic preference of S- over O-methylation, a mixture of $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{O}^- \text{Na}^+$ and $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{S}^- \text{Na}^+$ (0.77:1.00 molar ratio) was treated with 0.5 equiv of $\text{Me}_3\text{O}^+ \text{BF}_4^-$ in CH_2Cl_2 ; the ^1H NMR spectrum of the resulting solution revealed a MeO/MeS ^1H NMR signal ratio of 1.6:1.0, thereby proving that there is no overwhelming preference for S- over O-methylation.
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- (22) Interestingly, the reaction of NaH and $\text{HSCH}_2\text{CH}_2\text{OC}(\text{S})\text{C}_6\text{H}_5$ in MeCN, followed by treatment with MeI, gave only $\text{MeSCH}_2\text{CH}_2\text{OC}(\text{S})\text{C}_6\text{H}_5$ and no 2-methoxy-2-phenyl-1,3-oxathiolane.
- (23) The reaction of NaH and $\text{HOCH}_2\text{CH}_2\text{OC}(\text{S})\text{C}_6\text{H}_5$ in MeCN, followed by treatment with $\text{Me}_3\text{O}^+ \text{BF}_4^-/\text{CH}_2\text{Cl}_2$, did not lead to any 2-methoxy-2-phenyl-1,3-dioxolane; instead, the predominant products appeared to be dimethoxyethane and 1,2-dibenzoyloxyethane.

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A Pair-Specific Osmium Reagent for Polynucleotides

Sir:

Osmium(VIII) reagents show kinetic specificity for thymine residues among the common bases in polynucleotides.¹ An osmium(VI) ester is formed by addition to the 5,6 double bond. Ligands alter the nature of the reaction of osmium(VIII) species with olefins profoundly. The structures,^{2a} the kinetics of formation,^{2b} and the hydrolytic stability^{2b} of the products are all changed. We have used the effects exerted by ligands to design a pair-specific osmium reagent. Scheme I outlines our strategy. The ligand, instead of being free in solution, is specifically attached to a cytosine residue. This specifically localized ligand then affects the kinetics of formation and stability of an osmate ester formed at thymine residues in its vicinity. Thymine residues not in the vicinity of the ligand would be attacked by osmium(VII) reagents very slowly and, if formed, would be hydrolyzed rapidly.^{2b}

Table I reports kinetic data for the formation of the osmate ester of a modified thymine-cytosine dinucleoside monophosphate³ together with some relevant comparative data.

The rate law for the reaction of osmium tetroxide with olefins contains two terms, one for the reaction without and one for the reaction with ligand:⁷ rate = $(k_0 + k)[L][\text{OsO}_4][S]$ where L is ligand and S is the olefin. When the ligand is attached to the substrate (SL), the rate law contains only one term: rate = $k_0'[\text{OsO}_4][\text{SL}]$. The k_0 and k_0' terms can be compared directly by their rate constants. Our results show that k_0' is ~ 1600 times larger than k_0 . This shows that, in the absence of added external ligand, a polynucleotide so modified could probably be labeled with an osmium atom with excellent selectivity at those thymine residues adjacent to modified cytosine residues.

Scheme I

