to be 21 M^{-1}. Very weak fluorescence of **1** precluded fluorescence quenching studies.
(18) This interpretation is rather oversimplified and does not exclude the intermediacy of charge-transfer complexes or exciplexes.
(19) A solution of **7** in acetone containing toluenesulfonic acid (0.1 equiv) was stood overnight at room temperature. The transformation was quantitative as measured by ^{1}H NMR.
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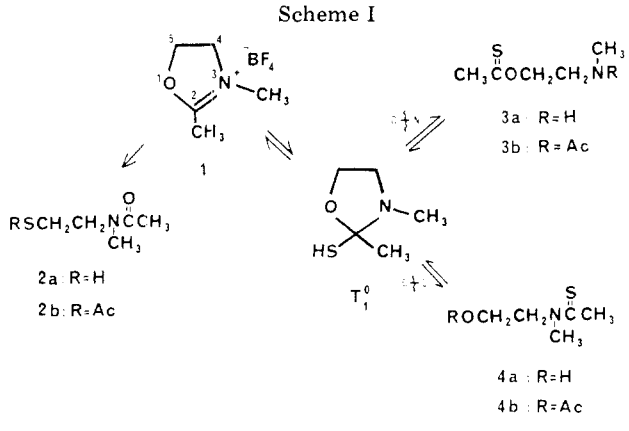
Breakdown of Hemiorthothioamide Tetrahedral Intermediates[1]

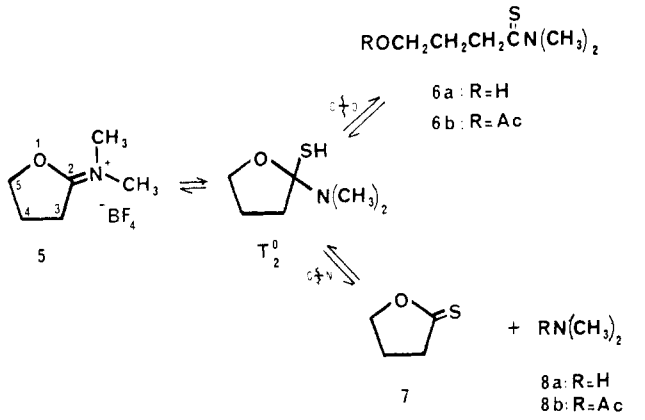
Summary: The sulfhydrolyses of 2,*N*-dimethyl-1,3-oxazolinium fluoroborate (**1**) and *N,N*-dimethyliminobutyrolactonium fluoroborate with anhydrous sodium hydrosulfide in solvent acetone at −78 °C were found to involve the preferential cleavage of the C–N bond rather than the C–O bond.

Sir: Tetrahedral intermediates play a central role in a wide variety of enzymatic and nonenzymatic reactions.[2] The involvement of such intermediates in enzymatic reactions, e.g. those involving α-chymotrypsin, carboxypeptidase, and lysozyme,[3] has been deduced by analogy with nonenzymatic intermolecular as well as intramolecular model reactions involving similar tetrahedral intermediates. Since the pioneering work of Bender,[4] transient tetrahedral intermediates have been invoked in the lytic reactions of carboxylic esters,[5] lactones,[6] amides,[7] thiolo[8] and thiono esters,[9] thioamides,[10] and amidines.[11] Tetrahedral intermediates have been detected spectroscopically,[12] trapped,[13] or isolated.[14] We report on the kinetic breakdown of hemiorthothioamide tetrahedral intermediates of the type $RC(SH)(OR)(NR_2)$ and on the first intramolecular O → N thionacyl transfer. These intermediates, which, in principle, may form during the alcoholysis of thioamides and aminolysis of thiono esters, were generated directly in an aprotic solvent (acetone) from anhydrous sodium hydrosulfide and two model imino ether salts (**1** and **5**).[15]

Scheme I



Scheme II



TLC analysis (at room temperature) of the reaction mixture obtained from equimolar amounts of 2,*N*-dimethyl-1,3-oxazolinium fluoroborate[16] (**1**) and anhydrous sodium hydrosulfide[17] in acetone at −78 °C revealed **4a** (Scheme I) as the only organic product ($2R_f$ 0.48, $CHCl_3$–MeCN (1:1 v/v)): IR($CHCl_3$) 3500–3200, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.69–2.75 (3 H, 2 s, $CH_3C{=}S$), 3.38, 3.53 (3 H, 2 s, CH_3N), 3.92 (1 H, s, **OH**), 4.05, 4.35 (4 H, m, OCH_2CH_2N). However, TLC analysis of the latter reaction mixture *after* low-temperature trapping (AcCl/pyridine, −78 °C) showed **3b** as the major product along with **4b** (**3b/4b** ~9:1). **3b:** R_f 0.32, $CHCl_3$–MeCN (3:1 v/v); IR ($CHCl_3$) 1660, 1280 cm^{-1}; NMR ($CDCl_3$) δ 2.20, 2.25 (3 H, 2 s, CH_3CO), 2.72 (3 H, s, $CH_3C{=}S$), 3.13, 3.23 (3 H, 2 s, CH_3N), 3.83–4.05 (2 H, m, CH_2N), 4.76–4.95 (2 H, m, CH_2O). **4b:** R_f 0.61, $CHCl_3$–MeCN (3:1 v/v); IR ($CHCl_3$) 1760, 1540, 1300 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (3 H, s, CH_3CO), 2.71, 2.78 (3 H, 2 s, $CH_3C{=}S$), 3.40, 3.54 (3 H, 2 s, CH_3N), 4.36–4.54 (4 H, m, OCH_2CH_2N). At room temperature, the reaction of **1** and NaSH led to **4a,** along with **2a** (**4a/2a** ratio ~3:2). **2a:** R_f 0.35, $CHCl_3$–MeCN (1:1 v/v); IR ($CHCl_3$) 3450, 2520, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (1 H, t, J = 8.0 Hz, **SH**), 2.08, 2.13 (3 H, 2 s, CH_3CO), 2.67–2.91 (2 H, m, CH_2N), 2.91, 3.05 (3 H, 2 s, CH_3N), 3.40–3.66 (2 H, m, CH_2S).[18]

TLC analysis of the reaction mixture from equimolar amounts of anhydrous NaSH and *N,N*-dimethyliminobutyrolactonium fluoroborate[16] (**5**) in acetone at room temperature revealed **6a** (Scheme II) as the exclusive sulfur-containing component:[20] R_f 0.46, $CHCl_3$–MeCN (1:1 v/v); IR ($CDCl_3$) 3400, 1525, 1395, 1280, 1050 cm^{-1}; NMR ($CDCl_3$) δ 1.72–2.24 (m, 2 H, CCH_2C), 2.96 (m, 2 H, $CH_2C{=}S$), 3.38 (s, 3 H, NMe), 3.53 (s, 3 H, NMe), 3.74 (t, J = 6.5 Hz, 2 H, CH_2O). However, when the reaction was run at −78 °C and the mixture acetylated at −78 °C (AcCl/pyridine), compounds **7** and **8b** were the major detectable products. **7:** R_f 0.36, $CHCl_3$–MeCN (99.5:0.5 v/v); IR (neat) 1460, 1380, 1270, 1180, 920, 740 cm^{-1}; NMR ($CDCl_3$) δ 2.36 (2 H, q, J = 6.5 Hz, CCH_2C), 3.10 (2 H, t, J = 6.5 Hz, $CH_2C{=}S$), 4.70 (2 H, t, J = 6.5 Hz, CH_2O).

As shown in Scheme I, the nucleophilic attack on **1** at −78 °C is exclusively at C-2, and the resulting transient tetrahedral intermediate T_1^0,[21] under kinetic control, breaks down by cleavage of the C_2–N bond to yield **3a.** The latter, at −78 °C, is efficiently trapped as the acetamide **3b;** in the absence of an acetylating agent, as the temperature is increased from −78 °C to room temperature, **3a** undergoes an unprecedented intramolecular O → N thionacyl transfer, most probably through the intermediate T_1^0, to yield the more stable isomer **4a.**[22]

Similarly, the initially formed intermediate T_2^0 [21] undergoes kinetic breakdown by cleavage of the C_2–N bond (in preference to C_2–O) to yield **7** and **8a** (Scheme II); after acetylation (−78 °C) the products are **7** and **8b.** In the absence of acetylating agent at room temperature the more stable

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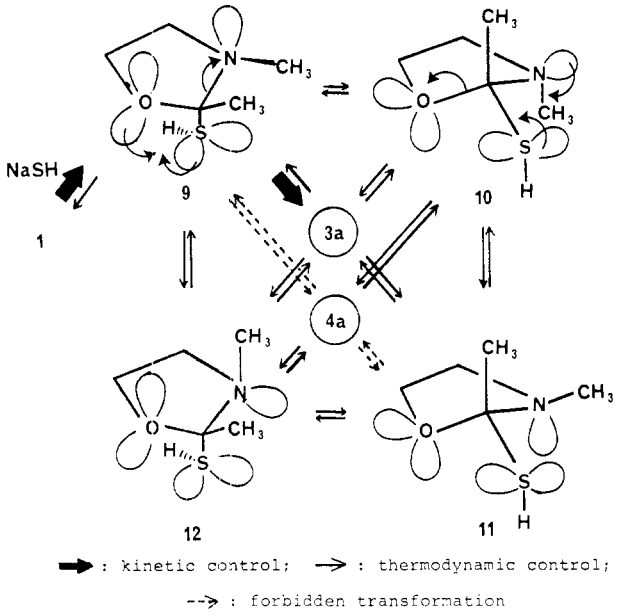
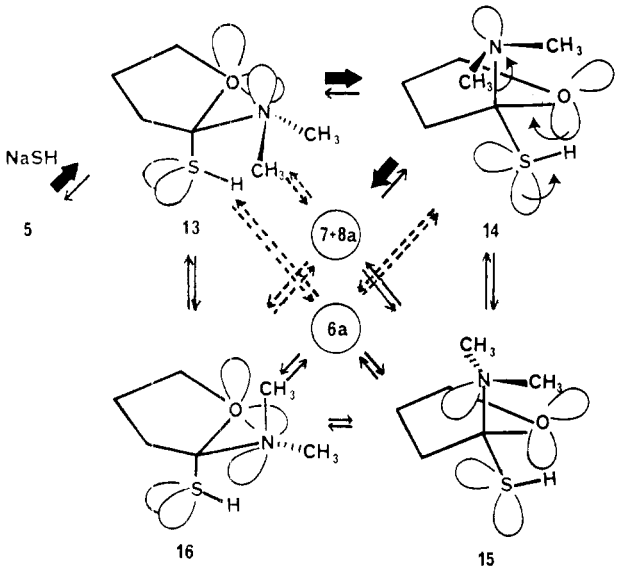
Scheme III



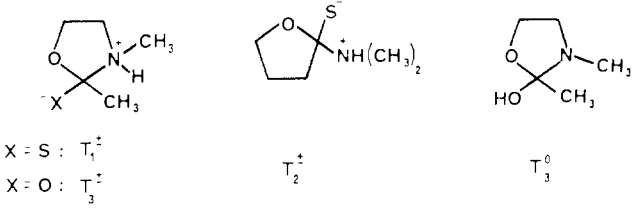
Scheme IV



product **6a** is formed, perhaps also through T_2^0.

The breakdown of both tetrahedral intermediates T_1^0 and T_2^0 may be rationalized on the basis of Deslongchamps' stereoelectronic theory for the breakdown of hemiorthoamide and hemiorthoester tetrahedral intermediates.[23] The breakdown of T_1^0 may be envisioned through the initially formed pseudoaxial conformation **9** (Scheme III), in which the cleavage of the C–N is facilitated by one primary (i.e., the interaction of the orbitals of two antiperiplanar lone pairs (one from sulfur and one from oxygen) with the orbital of the C–N bond) and two secondary stereoelectronic effects.[24] The scission of the C–O bond, on the other hand, is subject to no primary (there is only one (sulfur) lone pair antiperiplanar to C–O) but two secondary stereoelectronic effects.[25] However, with increasing temperature the higher barrier to C–O cleavage is overcome through changes in ring conformations and/or inversion at N (**9** → **10** → **11** → **12**; Scheme III), and the thermodynamically more stable product **4a** is formed through conformations **10** and **12**. T_2^0, on the other hand, is initially formed in the pseudoaxial conformation **13** (Scheme IV) in which the cleavage of neither C–O nor C–N is assisted stereoelectronically (primary effect), even though each cleavage is subject to two secondary stereoelectronic effects.[26] Conformation **13** may transform into **14** in which primary stereoelectronic assistance helps sever the C–N bond; the alternative conformations **15** and **16** which would allow scission of C–O appear to be energetically unfavorable, presumably due to repulsive nonbonded interactions.

While our findings are consistent with Deslongchamps' theory, it is conceivable that the breakdown of T_1^0, and of T_2^0, may proceed partially or exclusively through the corresponding zwitterionic forms $T_1^{\pm}$ and $T_2^{\pm}$, which would arise through an intra- or intermolecular transfer of the thiolic hydrogen to nitrogen.[27] A definitive choice between the two



modes of breakdown must await detailed measurements of the kinetics of intramolecular and intermolecular S → N proton transfer in aprotic solvents,[28] such as acetone, and the determination and/or calculation[29] of the lifetime of transient tetrahedral intermediates. We are currently exploring other experimental approaches for elucidating the mechanism of the sulfhydrolysis.

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(20) Visualization on E. Merck silica gel 60 F-254 TLC sheets is best carried out using 0.5% $PdCl_2$ spray.
(21) T_1^0 and T_2^0 represent the neutral tetrahedral intermediates derived from **1** and **5**, respectively; $T_1^{\pm}$ and $T_2^{\pm}$ designate the zwitterionic intermediates derived from T_1^0 and T_2^0, respectively, after S→N proton transfer.
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(25) The primary and secondary stereoelectronic effects refer to the actual positioning in space of lone pairs on heteroatoms X, Y, and Z and the corresponding C–X, C–Y, and C–Z bonds; they make no reference to the actual identity of the heteroatoms.
(26) Inasmuch as a secondary stereoelectronic effect represents resonance stabilization of an incipient π bond,[24] these effects for C–N vs. C–O cleavages do not cancel out, since the resonance energies for the thiono ester and thioamide groups are different [17.4 kcal/mol (cf. Janssen, M. J.; Sandström, J., *Tetrahedron,* **1964,** *20,* 2339) and 25.1 kcal/mol (cf. Walter, W.; Maerten, G.; Rose, H. *Justus Liebigs Ann. Chem.,* **1966,** *691,* 25) respectively]. Hence, in principle, the fractional contributions to the respective transition states are not equal.
(27) A calculation of the approximate pK_as of protonic hydrogens using the base pK_a values of 10.61 (CH_3CH_2SH; cf. Irving, R. J.; Nelander, L.; Wadso, I. *Acta Chem. Scand.,* **1964,** *18,* 769), 9.76 (Me_3NH^+/ cf. Hansen, J. *Svensk. Kem. Tidskr.,* **1955,** *67,* 256), 15.9 (CH_3CH_2OH; cf. Riddick, J. A.; Bunger, W. B. "Organic Solvents"; Wiley-Interscience: New York, 1970; p 147, and references cited therein), $\rho_I = -8.4$ (for RCH_2OH),[7e] $\rho_I = -8.0$ (for $XCH_2NH^+R_1R_2$),[7e] $\rho_I = 6.23 \times (-1.47) = -9.2$ (for RCH_2SH; cf. Barlin, G. B.; Perrin, D. D. *Q. Rev., Chem. Soc.,* **1966,** *20,* 75), and $\sigma_I = 0.25$ (OMe), 0.10 (NMe_2), 0.25 (SH), −0.05 (Me) (cf. Taft, R. W., Jr., Deno, N. C.; Skell, P. S. *Ann. Rev. Phys. Chem.,* **1958,** *9,* 287; Taft, R. W., Jr.; Lewis, I. C., *J. Am. Chem. Soc.,* **1959,** *81,* 5343), and by correcting for the electrostatic effect (12.3/2.8; cf. Branch, G. E. K.; Calvin, M. "The Theory of Organic Chemistry"; Prentice-Hall: New York, 1941; pp 203–205) gives the following results: T_1^0, 7.4; $T_1^{\pm}$, 10.6; T_3^0, 13.0; $T_3^{\pm}$, 10.6. There appears to be, at least in aqueous solutions, a thermodynamic driving force for the S→N proton transfer, $\Delta pK_a = 10.6 - 7.4 = 3.2$. This situation is in marked contrast to that for analogous hemiorthoamide intermediates where the corresponding $\Delta pK_a = 10.6 - 13.0 = -2.4$, i.e. the relative acidities are reversed. For the oxygenated intermediates, in basic proton-donating media, the dominant species would be T_3^0 and T_3^-, since $T_3^{\pm}$ in such media would give way to T_3^- by abstraction of the more acidic proton on N. In contrast, for the sulfur analogues, the dominant species in basic proton-donating solvent would be T_1^- and $T_1^{\pm}$ (rather than T_1^0). These considerations imply that because of the reversal in relative acidities, the use of basic and proton-donor solvents would not enable a distinction between the two mechanisms. The principle of microscopic reversibility (to allow kinetic product to revert to thermodynamic product, e.g., **3a** → **4a**) would suggest that T_1^0 and T_2^0 are more plausible intermediates, in solvent acetone, than $T_1^{\pm}$ and $T_2^{\pm}$. This argument, however, does not rule out simultaneous proton transfer to N and cleavage of the C–N bond.
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