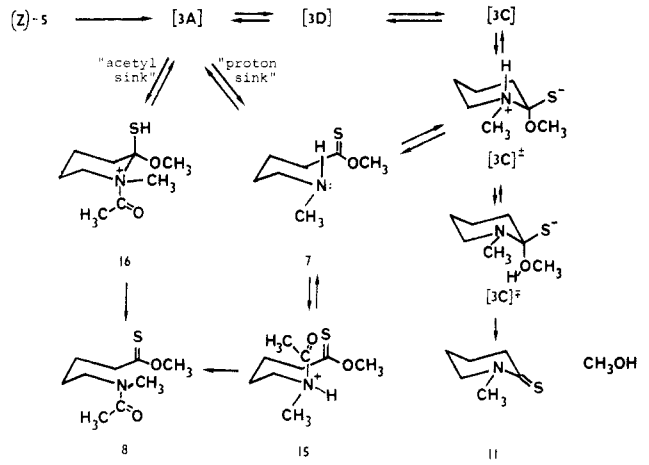
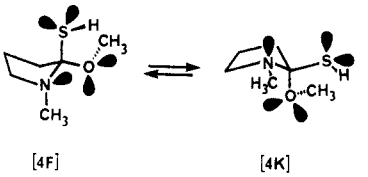
Scheme III



whereas the C–O cleavage products (**11** + **12**, or **11** + **14**) may arise from conformers [3C] (upper floor) or [3K] (lower floor). It appears that over the −78–27 °C range, the kinetically preferred course of the sulfhydrolysis reaction of **5**, in acetone, is through the upper pathway (*Z*)-**5** → [**3A**] → **7**. Owing to the highly reactive nature of **7** (C≠N), little or none of **7** is trapped (as **8**) (Table I, entries 1, 2), since it rapidly rearranges through the irreversible[10] **7** (C≠N) → [3C] → **11** + **12** (C≠O) pathway.[11] In the presence of acetylating agent,[12] **7** is efficiently trapped (87–92%; Table I, entries 4, 5), possibly through the **7** → **15** → **8** route (Scheme III). In solvent chloroform, the rearrangement of **7** to **11** through the **7** → [**3C**]$^{\pm}$ → [3C]$^{\mp}$ → **11** + **12** route[13] appears to be sluggish even at 61 °C. It is not surprising that in the less polar solvent chloroform (as contrasted to acetone), both the formation of [**3C**]$^{\pm}$ from **7** (Scheme III), as well as the [**3C**]$^{\pm}$ → [3C]$^{\mp}$ transformation through an already-unfavorable N→O proton transfer, are both adversely affected.[13] Thus, in effect, the lifetime of **7** is prolonged, and at 61 °C, 80% of it can be trapped as the acetyl derivative **8** (Table I, entry 3).[14] In the presence of *preadded* acetic anhydride,[12] one isolates only **8** (100% C–N cleavage); the formation of **8** may well proceed through the interception of [**3A**] by way of the [**3A**] → **16** → **8** pathway (Scheme III).

For the sulfhydrolysis of **5**, under conditions of kinetic control, it is the upper (i.e., (*Z*)-**5** → [**3A**] → ...) pathway that consumes **5** through its less stable but more reactive (*Z* conformer (Scheme II).[15] This kinetic pathway involves exclusive C–N cleavage of [**3A**] and is favored in the presence of an "acetyl sink", even at the *highest* temperature studied. Under similar conditions, the sulfhydrolysis of **6** involves the dominant (rather than exclusive) cleavage of the C–N bond (**10**:**13** = 95:5; Table I, entry 11). Here, the analogous (*E*)-**6** → [**4G**] → [**4F**] → [**4K**] → **13** + **14** pathway may gain in importance, since the six-ring inversion ([**3F**] → [**3K**]) is replaced by a facile five-ring pseudorotatory motion [**4F**] → [**4K**].[16]



These results underscore the role of stereoelectronic effects in the breakdown of hemiorthothioamide tetrahedral intermediates derived from conformationally heterogeneous imidates and headed toward an acetyl sink in relatively nonpolar media.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Registry No. **3**, 79568-46-0; **4**, 79568-47-1; **5**, 19964-07-9; **6**, 79568-48-2; **7**, 79568-49-3; **8**, 79568-50-6; **9**, 79568-51-7; **10**, 79568-52-8; **11**, 13070-07-0; **13**, 10441-57-3.

(10) Refluxing of **11** with $NaOCH_3$ in anhydrous methanol followed by treatment with AcCl/pyridine did not yield any of **8**; hence, thiolactam **11** is the thermodynamically favored product.

(11) For the **7** → **11** rearrangement, the sequences **7** → [3C] → **11** + **12** (Scheme II) and **7** → [**3C**]$^{\pm}$ → **11** + **12** (Scheme III) are equivalent. The latter sequence emphasizes the involvement of (partially) charged intermediates; the flow of charge that must accompany the rearrangement is represented here through an arbitrary sequence of fully charged intermediates (depicted in idealized zwitterionic form).

(12) Preadded acetic anhydride serves as an effective source of CH_3CO^+—the trapping species; hence, the entire reaction is led toward an "acetyl sink".

(13) The idealized representations [**3C**]$^{\pm}$ (+ on N, − on S) and [**3C**]$^{\pm}$ (+ on O, − on S) reflect the direction in which + and − charge buildup should occur and does not imply the exact timing of the proton transfer; a gradual change of charges is therefore equally acceptable.

(14) The absence of preadded trapping agent, in effect, corresponds to a "proton sink", and the most likely pathway is **7** → **15** → **8** (Scheme III).

(15) The lower (E)-**5** → [**3G**] → [**3F**] → [**3K**] → **11** + **12** pathway appears to be insignificant.

(16) Pseudorotation in a five-membered ring is a low-energy process [in THF it is 0.16 kcal/mol (cf. Engerholm, G. G.; Luntz, A. C.; Gwinn, W. D. *J. Chem. Phys.* **1969**, *50*, 2446].

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Hydrolysis of Cyclic Thioimidate Tetrafluoroborates at Sub-Zero Temperatures[1,2]

Summary: The hydrolyses of 2-phenyl-*N*-methyl-1,3-thiazolinium and 2-phenyl-*N*-methyl-5,6-dihydro-1,3-thiazinium tetrafluoroborates (**2a** and **2b**, respectively) under kinetic control (NaOH, 15-crown-5, anhydrous *n*-PrCN, Ac_2O, −78 °C) proceed by preferential cleavage of the C–N bond; under thermodynamic control (KOH, EtCN–H_2O, 0 °C for **2a**; KOH, H_2O, 45 °C for **2b**) exclusive C–S bond scission is observed.

Sir: Stereochemical studies on short-lived tetrahedral intermediates of the type $RC(OR')(OH)_2$, $RC(OR')_2OH$, $RC(OR')(NR''_2)OH$, $RC(OR')(NR''_2)SH$, and $RC(OR')_2SH$ have demonstrated that their breakdown is subject to the Deslongchamps effect.[3] We report here on the generation

(1) The Chemistry of Tetrahedral Intermediates. 8. Part 7: Kaloustian, M. K.; Nader, R. B. *J. Org. Chem.* **1981**, *46*, in press. Part 6: Kaloustian, M. K.; Khouri, F., *Tetrahedron Lett.* **1981**, *22*, 413–416.

(2) (a) Presented at the New York Academy of Sciences, New York, NY, June 10, 1980. (b) Taken in part from the M.S. Thesis of Liliane Khouri, Fordham University, 1979.

(3) (a) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463–2490. (b) Deslongchamps, P. *Pure Appl. Chem.* **1975**, *43*, 351–378. (c) Deslongchamps, P. *Heterocycles* **1977**, *7*, 1271–1317 and papers cited therein. (d) Kaloustian, M. K.; Aguilar-Laurents de Gutierrez, M. I.; Nader, R. B. *J. Org. Chem.* **1979**, *44*, 666–668. (e) Kaloustian, M. K.; Khouri, F. *J. Am. Chem. Soc.* **1980**, *102*, 7579–7581.

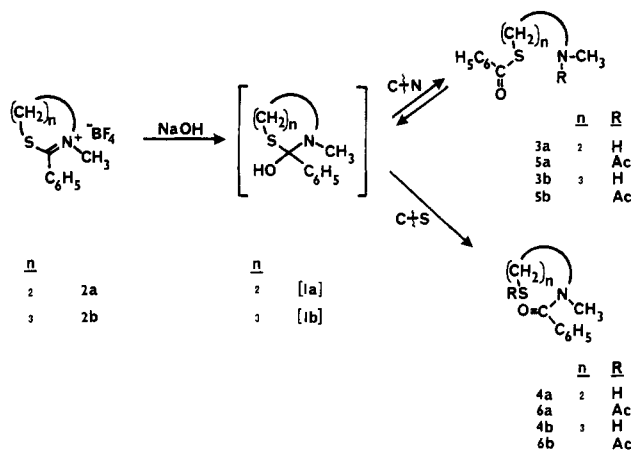
0022-3263/81/1946-5052$01.25/0

Table I. Hydrolysis of 2-Phenyl-*N*-methyl-1,3-thiazolinium and 2-Phenyl-*N*-methyl-5,6-dihydro-1,3-thiazinium Tetrafluoroborates (2a, 2b)

thio-imidate salt	entry	base (equiv)	solvent	trapping agent (equiv)	T, °C	% C-N cleavage[a]	% C-S cleavage[a]	% overall yield
2a	1	KOH (4)	EtCN-H_2O (94:6, v/v)		0	0	100	72
	2	KOH (5)	Me_2CO-H_2O (75:25, v/v)	AcCl (10)/py[b]	−78	28	72	7
	3	KOH (6)	Me_2CO-H_2O (80:20, v/v)	Ac_2O (5)[c]	−42	39	61	80
	4	KOH (1)[d]	MeCN	Ac_2O (2)[e]	0	50[f]	50[f]	[g]
	5	KOH (3)[h]	*n*-PrCN	Ac_2O (20)[i]	−78	55	45	[g]
	6	KOH (3)[d]	*n*-PrCN	Ac_2O (20)[i]	−78	60	40	100
	7	NaOH (3)[d]	*n*-PrCN	Ac_2O (20)[i]	−78	80	20	100
	8	NaOH (3)[d]	*n*-PrCN	Ac_2O (20)[i]	−78	86	14	69
2b	9	KOH (1)	H_2O		45	0	100	84
	10	NaOH (3)[d]	*n*-PrCN	Ac_2O (20)[i]	−78	75	25	78
	11	NaOH (3)[d]	*n*-PrCN	Ac_2O (20)[i]	−20	79	21	83
	12	NaOH (3)[d]	*n*-PrCN	Ac_2O (20)[i]	−78	80	20	88

[a] Product ratio (expressed as % molar ratio) was determined by isolation and weighing of C-N and C-S cleavage products. [b] Added after the reaction of **2a** with NaOH is complete. [c] Alkaline solution added to **2a** + Ac_2O. [d] 15-crown-5 added. [e] **2a** + Ac_2O added to alkaline solution. [f] Approximate product ratio determined by visual inspection of sprayed (0.5% $PdCl_2$) thin-layer chromatograms. [g] Not determined. [h] 18-crown-6 added. [i] **2a** added to alkaline solution + Ac_2O.

Scheme I



and breakdown of RC(SR′)(NR″$_2$)OH—an important class of tetrahedral intermediates that lie on the reaction paths of several plant, bacterial, and mammalian cysteine proteinases.[4]

Two such short-lived intermediates, [**1a**] and [**1b**] (Scheme I), were generated by the ion–ion combination reaction of thioimidate cations **2a** and **2b** with hydroxide ion in the presence of crown ethers over the −82–45 °C temperature range; their subsequent breakdown was studied in terms of competing cleavages of their C–N and C–S bonds (Scheme I). Table I summarizes the main results of our studies.

Treatment of 2-phenyl-1,3-thiazolinium tetrafluoroborate[5] (**2a**) with KOH in EtCN-H_2O at 0 °C gave only benzamido thiol **4a** (% C–N cleavage/% C–S cleavage = **3a**/**4a** = 0:100; Table I, entry 1).[6] At −78 °C, the reaction of **2a** with KOH in acetone–water followed by treatment with AcCl–pyridine yielded **5a** and **6a**[7,8] (% C–N cleavage/% C–S cleavage = **5a**/**6a** = 28:72; Table I, entry 2). When a precooled (−42 °C) solution of KOH/Me_2CO–H_2O was added to **2a** + Ac_2O,[9] the **5a**/**6a** ratio increased to 39:61 (Table I, entry 3). To enhance the hydrolytic breakdown in nonaqueous aprotic media,[10] we used crown ethers. At 0 °C, the **5a**/**6a** ratio increased to 50:50, when a solution of **2a** + Ac_2O was added to KOH + 15-crown-5 + MeCN (Table I, entry 4). At −78 °C, the rapid dropwise addition of **2a** (in *n*-PrCN) to KOH + 15-crown-5 + Ac_2O, followed by storage of the reaction mixture over dry ice for 3 days, led to a slight change in the **5a**/**6a** ratio, viz., to ca. 55:45 (Table I, entry 5). Considerably higher ratios were observed when cold (−78 °C) Ac_2O was added to the precooled alkaline mixture (KOH or NaOH + *n*-PrCN + 15-crown-5), followed by the rapid dropwise addition of **2a** in *n*-PrCN (Table I, entries 6–8). The optimum % C–N cleavage/% C–S cleavage ratio (=**5a**/**6a**) was found to be 86:14 (Table I, entry 8).[11] Similar hydrolytic studies of *N*-methyl-2-phenyl-5,6-dihydro-1,3-thiazinium fluoroborate[12] (**2b**) gave **4b**[13] (100% C–S cleavage; Table I, entry

(4) (a) Lowe, G. *Tetrahedron* **1976**, *32*, 291–302. (b) Angelides, K.; Fink, A. L. *Biochemistry* **1979**, *18*, 2363–2369.

(5) Prepared from 2-phenyl-1,3-thiazoline (cf. Wenker, H. *J. Am. Chem. Soc.* **1935**, *57*, 1079–80) and $Me_3O^+BF_4^-$ (CH_2Cl_2, 27 °C, N_2 atmosphere, 7 h); 80% yield (CH_2Cl_2–Et_2O). All new compounds gave satisfactory elementary (C, H) analyses.

(6) Benzamido thiol **4a**: R_f 0.45 ($CHCl_3$–CH_3CN, 5:1, v/v); IR ($CDCl_3$) 2950, 1630, 1400, 1070, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (1 H, br s, SH), 2.72 (2 H, m, CH_2S), 3.00 (3 H, s, NCH_3), 3.56 (2 H, m, CH_2N), 7.38 (5 H, s, aromatic H's).

(7) Acetamido thiol ester **5a**: R_f 0.40 ($CHCl_3$–CH_3CN, 5:1, v/v); IR (CCl_4) 2950, 1660, 1630, 1400, 1210, 910, 770, 680 cm^{-1}; NMR ($CDCl_3$) δ 2.08 and 2.16 (3 H, 2 s, $CH_3C{=}O$), 2.98, 3.10 (3 H, 2 s, NCH_3), 3.22 (2 H, m, CH_2S), 3.54 (2 H, m, CH_2N), 7.50 (3 H, m, aromatic H's), 7.90 (2 H, m, aromatic H's). This material was identical with the compound isolated from the sequence of reactions starting from 2,*N*-dimethylthiazolinium tetrafluoroborate:[19] (i) KOH, H_2O, 0 °C (84% yield); (ii) C_6H_5COCl/py, 0 °C (59% yield). Benzamido thiol ester **6a**: R_f 0.48 ($CHCl_3$–CH_3CN, 5:1, v/v); IR ($CDCl_3$) 2925, 1690, 1630, 1400, 1130, 1070, 790, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (3 H, s, $CH_3C{=}O$), 3.04 (3 H, s, NCH_3), 3.12 (2 H, br m, CH_2S), 3.56 (2 H, br m, CH_2N), 7.38 (5 H, s, aromatic H's). This compound was identical with the product obtained from the reaction of **4a** and AcCl/py (0 °C, 62% yield).

(8) The unusually low yield of this reaction is a consequence of the specific workup procedure used for this case in order to remove the excess pyridine; the material balance is unreacted **2a** (TLC).

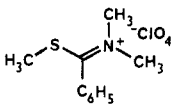
(9) In contrast to entry 1 (Table I), which corresponds to a "proton sink" for the reaction, preadded Ac_2O constitutes an "acetyl sink"; cf. ref 1, part 7, footnote 12.

(10) The hydrolysis of cationic intermediate **2a** (and **2b**) requires only the availability of HO^- rather than H_2O; hence, aprotic solvents *can* be used for the study of the hydrolytic breakdown of salts exemplified by **2a** and **2b**.

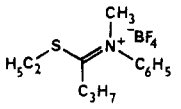
(11) The rate at which the reaction mixture is warmed up appears to be crucial. The optimum results were obtained by keeping the reaction mixture at −78 °C (2 h), over dry ice (6 days), −78 °C (1 h), −65 °C (2 h), and warming up to room temperature (over a 3-h period).

(12) Prepared from 2-phenyl-5,6-dihydro-1,3-thiazine (cf. Pinkus, G. *Chem. Ber.* **1893**, *26*, 1077–1084) by treatment with $Me_3O^+BF_4^-$ (CH_2Cl_2, 27 °C, N_2 atmosphere, 1.5 h); 96% yield (CH_2Cl_2–Et_2O).

9) under thermodynamic control. Under kinetic control, however, % C–N cleavage/% C–S cleavage ratios (=**5b**/**6b**)[14] were between 72:25 and 80:20 (Table I, entries 10–12).[15] According to Schmir and co-workers,[16] the hydrolysis of acyclic thioimidates yields thiol esters/amines (i.e., C–N cleavage) at pH < 2, but amides/mercaptans (C–S cleavage) at higher pH. Thioimidate **7**, at pH 8.6–12.3, was reported to result in <2% dimethylamine (≡ >98% C–S cleavage); at pH 9.0, *N,N*-dimethylbenzamide was found to be formed quantitatively (100% C–S cleavage);[16a] further, thioimidate **8**, at pH 11.8 in 10% MeCN–



7



8

H_2O (30 °C) was said to give 0.3% amine (99.7% C–S cleavage).[16b] In sharp contrast, the present study shows that, under *alkaline* conditions, albeit at sub-zero temperatures, the kinetic cleavage of cyclic intermediates [**1a**] and [**1b**], formed during the hydrolysis of **2a** and **2b**, respectively, proceeds by the dominant cleavage of the C–N bond (rather than the C–S bond, as in the cases **7** and **8** above). These results constitute yet another manifestation of the Deslongchamps effect.[17] The observed optimum ratios of C–N to C–S cleavages (86:14 for [**1a**], and 80:20 for [**1b**]) are, in all likelihood, lower limits since the intramolecular S→N acyl transfer[18] (e.g., **3a** → [**1a**] → **4a** or **3b** → [**1b**] → **4b**) may well be in competition with the intermolecular acetylation reaction utilized in the trapping of **3a** (or [**1a**]) and **3b** (or [**1b**]).[19]

These studies prove that the kinetically preferred route for the breakdown of RC(SR′) (NR''_2)OH in aprotic media and in the presence of an "acetyl sink" involves the cleavage of the C–N bond. To the extent that this preference is dictated by stereoelectronic factors, it is likely that the specificity and reaction rates of cysteine proteinases may also be governed by similar stereoelectronic restraints.

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Registry No. **1a**, 79593-63-8; **1b**, 79593-64-9; **2a**, 79593-65-0; **2b**, 79593-67-2; **4a**, 79593-68-3; **4b**, 79593-69-4; **5a**, 79593-70-7; **5b**, 79593-71-8; **6a**, 79593-72-9; **6b**, 79593-73-0; 2-phenyl-1,3-thiazoline, 2722-34-1; 2-phenyl-5,6-dihydro-1,3-thiazine, 6638-35-3.

(13) Benzamido thiol **4b**: R_f 0.47 ($CHCl_3$–CH_3CN, 3:1, v/v); IR (CDCl_3) 2950, 2525, 1630, 1400, 1075, 920, 790, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (3 H, br m, SH and CCH_2C), 2.52 (2 H, br m, CH_2S), 3.00 (3 H, s, CH_3N), 3.50 (2 H, br m, CH_2N), 7.36 (5 H, s, aromatic H's).

(14) Acetamido thiol ester **5b**: R_f 0.41 ($CHCl_3$–CH_3CN, 3:1, v/v); IR (film) 1660, 1630, 1400, 1205, 910, 765, 680 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (2 H, m, CCH_2C), 2.08 (3 H, s, $CH_3C{=}O$), 2.91, 3.00 (3 H, 2 s, NCH_3), 3.05 (2 H, m, CH_2S), 3.43 (2 H, m, CH_2N), 7.46, 7.90 (5 H, m, aromatic H's). This product was identical with the compound isolated from the sequence of reactions starting from 2,*N*-dimethyl-5,6-dihydro-1,3-thiazinium tetrafluoroborate:[19] (i) KOH, H_2O, 45 °C (66% yield); (ii) C_6H_5COCl/py, 0 °C (96% yield). Benzamido thiol ester **6b**: *Rf* 0.56 ($CHCl_3$–CH_3CN, 3:1, v/v); IR ($CDCl_3$) 2925, 1690, 1630, 1400, 1140, 1080, 790, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.86 (2 H, br m, CCH_2C), 2.30 (3 H, s, $CH_3C{=}O$), 2.95 (3 H, s, NCH_3), 3.00 (2 H, br s, CH_2S), 3.48 (2 H, br m, CH_2N), 7.38 (5 H, s, aromatic H's). This compound was identical with the product obtained from the reaction of **4b** and AcCl/py (0 °C, 74% yield).

(15) The optimum conditions were attained by adding neat, precooled (−78 °C) Ac_2O to a solution of NaOH (19.4 mg) and 15-crown-5 (0.48 mmol) in *n*-PrCN (1.5 mL), followed by the addition of a cold solution of **4b** (0.161 mmol) in *n*-PrCN (2.0 mL). After 15 min at −78 °C, the reaction mixture was warmed up to room temperature (over a 30-min period) and stirred at room temperature (45 min).

(16) (a) Chaturvedi, R. K.; MacMahon, A. E.; Schmir, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 6984–6993 (b) Chaturvedi, R. K.; Schmir, G. L. *Ibid.* **1969**, *91*, 737–746.

(17) See ref 3e, p 7581.

(18) (a) Martin, R. B.; Hedrick, R. I. *J. Am. Chem. Soc.* **1962**, *84*, 106–110. (b) Barnett, R.; Jencks, W. P. *Ibid* **1968**, *90*, 4199–4200.

(19) Analogous hydrolytic studies were also conducted on 2,*N*-dimethyl-1,3-thiazolinium and 2,*N*-dimethyl-5,6-dihydro-1,3-thiazinium tetrafluoroborates (prepared from 2-methyl-1,3-thiazoline (Aldrich Chem. Co.) and 2-methyl-5,6-dihydro-1,3-thiazine (Pinkus procedure, footnote 12), respectively, and $Me_3O^+BF_4^-$ (68% and 100% yield, respectively). However, owing possibly to the extremely rapid intramolecular S→N acetyl transfers, kinetic products from C–N cleavages could not be assessed.

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