OCH_3) enhance cinnamaldehyde formation, while those which favor path b (X = OCH_3 > CH_3 > H > Cl) increase indene selectivity.

In terms of the selective oxidation of propylene over bismuth molybdate catalysts, these results are consistent with and reinforce the mechanism formulated on the basis of previous studies.[1a] Rate-determining α-hydrogen atom abstraction from propylene results in the π- and σ-allylic intermediates analogous to **5** and **1** in Scheme II. A fast second hydrogen abstraction leads to formation and subsequent desorption of acrolein. In the presence of ammonia, condensation with Mo=O sites in **7** forms imido species Mo=NH, which leads to formation of the analogous N-π intermediate prior to the N-σ allylic species, which is the acrylonitrile precursor.

Conclusions

The selective oxidation of allylbenzene over bismuth molybdate catalysts at 320 °C produces cinnamaldehyde and indene as sole products at low conversion (<2.5%). Relative rates of selective oxidation of *p*-$XC_6H_4CH_2CH{=}CH_2$ under these conditions decrease in the order X = OCH_3 > Cl > CH_3 > H (radical substituent effects), while the X-indene–indene selectivity ratio in any pair-wise run decreases in the order OCH_3 > CH_3 > H > Cl (cationic substituent effects). Formation of cinnamaldehyde and indene proceeds via a π-allyl radical surface complex formed in the rate-determining step, which undergoes C–O bond formation to give σ-*O*-allyl molybdate **1** (Scheme II). Indene is produced by ring closure of the phenyl allylcarbonium ion, which results from heterolytic C–O cleavage of **1**. This process is favored by electron-donating groups X and catalysts of low α-hydrogen-abstracting strength (low Bi). Cinnamaldehyde is formed by 1,4-hydrogen shift in **1**, a process favored by electron-withdrawing X groups, catalysts of high H-abstracting strength (i.e., high Bi) and the presence of base.

By analogy, in selective oxidation and ammoxidation of propylene, the π-allylic surface complex is also radical-like. After conversion to the corresponding σ–O and σ–N allylic species, acrolein and acrylonitrile are formed, respectively.

Acknowledgment. We thank H. Z. Wang for preliminary experimental work and T. E. Hammond for GC/mass spectral analysis.

Registry No. Allylbenzene, 300-57-2; *p*-allylanisole, 140-67-0; *p*-allylchlorobenzene, 1745-18-2; *p*-allyltoluene, 3333-13-9; MoO_3, 1313-27-5; $Bi_2Mo_3O_{12}$, 13595-85-2; Bi_2MoO_6, 13565-96-3.

α-Keto Acid Dehydrogenases: A Chemical Model

William H. Rastetter*[1] and Julian Adams[2]

Department of Chemistry, Massachusettes Institute of Technology, Cambridge, Massachusetts 02139

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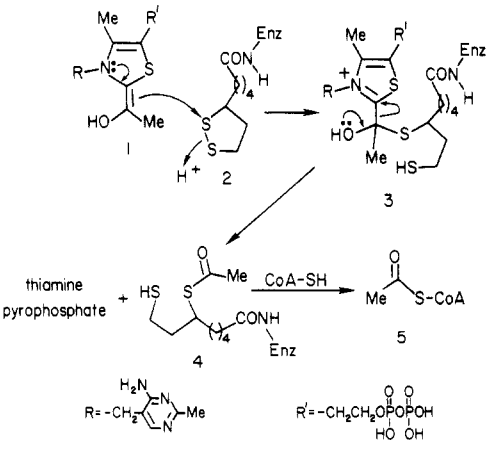
A model system for the involvement of lipoic acid in α-keto acid dehydrogenase systems is described. 2-(α-Hydroxyethyl)-3-benzyl-4-methylthiazolium tetrafluoroborate (**6**) serves as precursor for an analogue of the thiamine-bound active aldehyde **1** in the natural system. The model active aldehyde **7** reacts with linear disulfides, yielding thiols and thioesters. The 1,2-dithiolane, methyl lipoate (**14**), is unreactive under model reaction conditions. The tetrahedral intermediate which would be formed from methyl lipoate (**14**) plus an active aldehyde analogue **19** has been generated in a nonbiomimetic fashion. The synthetic tetrahedral intermediate **17** undergoes the reverse of the biological, disulfide reductive cleavage reaction.

The α-keto acid dehydrogenases[3,4] mediate the production of energy-rich thioesters of coenzyme A (e.g., acetyl coenzyme A, **5**, Scheme I) by oxidative decarboxylation of α-keto acids (e.g., pyruvate). Our preliminary report[5] of a model system for the formation of thioesters catalyzed by these enzyme systems supported the direct reductive acylation steps (**1** + **2** → **3** → **4**)[6] depicted in Scheme I. We were unable, however, to directly address the involvement of the 1,2-dithiolane, lipoic acid (see **2**), in the biological

Scheme I



(1) Firmenich Assistant Professor of Natural Products Chemistry; Alfred P. Sloan Fellow, 1980–1982.

(2) Natural Sciences and Engineering Research Council of Canada Predoctoral Fellow, 1980–1981.

(3) Reviews follow: (a) Reed, L. J. "Comprehensive Biochemistry"; Florkin, M., Stotz, F. H., Eds.; Elsevier: New York, 1966; Vol. 14, Chapter II; (b) Reed, L. J. "Organic Sulfur Compounds"; Kharasch, N., Ed.; Pergamon: New York, 1961; Vol. 1, Chapter 36; (c) Breslow, D. S.; Skolnik, H. "C_3S_2 Ring Systems"; Wiley-Interscience: New York, 1966; Part 1, Chapter 5; (d) Schmidt, U.; Grafen, P.; Altland, K.; Goedde, H. E. *Adv. Enzymol.* **1969**, *32*, 423–469.

(4) For model studies and the use of thiazolium salt derived acyl anion equivalents, see the following: (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719; (b) Breslow, R.; McNelis, F. *Ibid.* **1959**, *81*, 3080; (c) Crosby, J.; Stone, R.; Lienhard, G. E. *Ibid.* **1970**, *92*, 2891; (d) Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196; (e) Tagaki, W.; Hara, H. *J. Chem. Soc., Chem. Commun.* **1973**, 891; (f) Yasnimov, A. A.; Babicheva, A. F. *Ukr. Khim. Zh.* **1974**, *40*, 52; *Chem. Abstr.* **1974**, *80*, 145006; (g) Stetter, H.; Kuhlman, H. *Tetrahedron Lett.* **1974**, 4505; (h) Stetter, H. *Angew Chem., Int. Ed. Engl.* **1976**, *15*, 639; (i) Stetter, H.; Rämsch, R. Y.; Kuhlmann, H. *Synthesis* **1976**, 733; (j) Castells, J.; Llitjos, H.; Moreno-Mañas, M. *Tetrahedron Lett.* **1977**, 205. (k) Castells, J.; Duñach, E.; Geijo, F.; López-Calahorra, F.; Prats, M.; Sanahuja, O; Villanova, L. *Ibid.* **1980**, *21*, 2291.

(5) Rastetter, W. H.; Adams, J.; Frost, J. W.; Nummy, L. J.; Frommer, J. E.; Roberts, K. B. *J. Am. Chem. Soc.* **1979**, *101*, 2752.

(6) The direct reductive acylation of Scheme I was suggested by Breslow (*Ann. N.Y. Acad. Sci.* **1962**, *98*, 445) and by White and Ingraham (*J. Am. Chem. Soc.* **1962**, *84*, 3109).

0022-3263/81/1946-1882$01.25/0

Scheme II

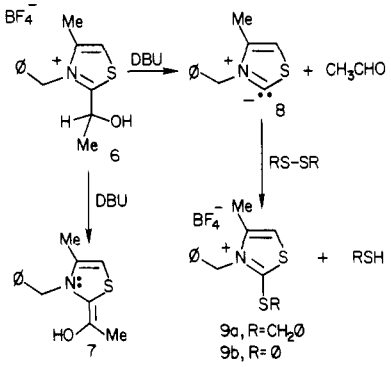


Table I. Reactions of Model Active Aldehyde 7[a] with Sulfur Electrophiles

electrophile	reaction time	product/yield, %
PhSPhth[b]	16 h	CH_3COSPh/42[c]
PhSSPh[d]	5 min	CH_3COSPh/32,[e] PhSH/74[e]
$PhCH_2SSCH_2Ph$[d]	5 min	CH_3COSCH_2Ph/13,[e] $PhCH_2SH$/88[e]
EtSSEt[d]	5 min	CH_3COSEt/33,[e] EtSH[f]

[a] Generated in tetrahydrofuran at ambient temperature from 6 plus 1.0 equiv of DBU (1,5-diazabicyclo[5.4.0]undec-5-ene). [b] *N*-(Phenylthio)phthalimide; 1.0 equiv used vs. 6. [c] Isolated yield. [d] 5.0 equiv of disulfide used vs. 6. [e] GLC yield (4.1% SE-30 on Chromosorb G, 7 ft) determined relative to hydrocarbon standard; product identity confirmed by coinjection and GLC/mass spectral comparison with an authentic sample. [f] EtSH yield not determined owing to interfering solvent peak in GLC run.

system. As its methyl ester, lipoic acid is completely unreactive in our model system under conditions which produce thioesters from linear disulfides.

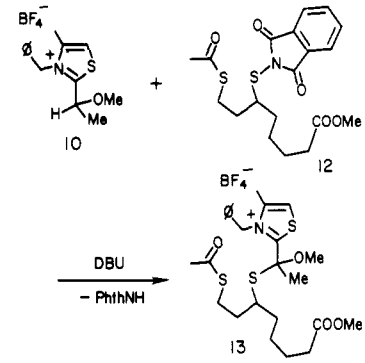
Herein we detail reactivity studies of thiazolium salt derived acyl anion equivalents (see 1, Scheme I) toward both linear and cyclic sulfur electrophiles. The atypical behavior of methyl lipoate (see 14, Scheme IV) in our model system is specifically addressed by a *nonbiomimetic* generation of an analogue of putative, enzyme-bound tetrahedral intermediate 3. The facile collapse of the analogue by disulfide formation to analogues of 1 and 2 is discussed in relation to the biological system.

Model System

Reactivity Studies. In our model system an equivalent of the biological active aldehyde (7, cf. 1) is generated by proton abstraction from the crystalline precursor 6 (Scheme II), made by a modification of Breslow's early route.[4b] As precedented,[4g] 7 serves as an acyl anion equivalent in the transfer of the acetyl moiety to methyl vinyl ketone.[5] The reactions of 7 with sources of electrophilic sulfur (Table I) mimic the pyruvate dehydrogenase mediated production of enzyme-bound acetyldihydrolipoic acid (4, Scheme I).

Competing, base-promoted reaction pathways exist for precursor 6 (Scheme II). Treatment of 6 with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) not only generates enamine 7 but also induces fragmentation of 6 to ylide 8 and acetaldehyde. Reaction of 7 with disulfides yields thioesters and thiols; competing reaction of 8 with disulfides yields sulfenylated products (e.g., **9a,b**) and thiols. Thus, the yield of thiols produced in the model reaction of 6 with disulfides substantially exceeds the yield of thioesters

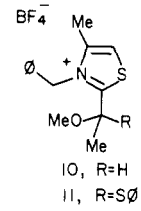
Scheme III



(Table I).[7] In an independent experiment, ylide 8, generated from 3-benzyl-4-methylthiazolium tetrafluoroborate[8] and DBU, reacted rapidly with benzyl disulfide, yielding benzylthiol (79%, GLC yield) and sulfenylated product **9a**; **9b** was isolated (74%) from the reaction of ylide 8 with *N*-(phenylthio)phthalimide.[9]

The facile sulfenylation of ylide 8 (Scheme II) precludes efficient generation of thioesters starting from ylide 8 plus acetaldehyde and disulfides. One equivalent of acetaldehyde reacts with 5.0 equiv of diphenyl disulfide in tetrahydrofuran (THF) containing 1.0 equiv of 3-benzyl-4-methylthiazolium tetrafluoroborate[8] and 1.0 equiv of DBU (cf. Table I), producing less than a 1% yield of acetylthiophenol but a 73% yield of thiophenol (GLC yields based on CH_3CHO and thiazolium salt, respectively).

The base-initiated fragmentation of precursor 6 can be blocked by using the methylated derivative 10. In situ enamine generation from 10 and trapping with *N*-(phenylthio)phthalimide[9] yields the crystalline adduct 11 (74%).

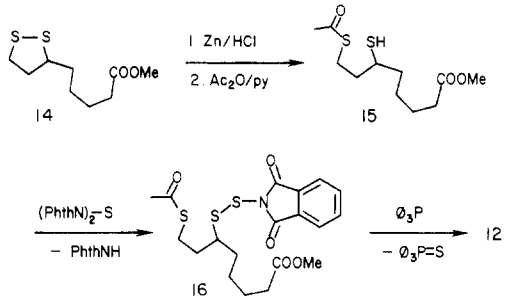


Reactions with Lipoate. Methyl lipoate (see 14, Scheme IV) is completely unreactive in a variety of solvents under conditions which produce thioesters from linear disulfides or from *N*-(phenylthio)phthalimide (Table I). The 1,2-dithiolane 14 is also stable to acetaldehyde/Et_3N/3-benzyl-4-methylthiazolium tetrafluoroborate[8] (45 °C) and to the enamine (see 19, Scheme V) derived from methylated precursor 10. We have also subjected the cyclic disulfides 1,2-dithiane, 1,2-dithiepane, and 1,2-dithiocane to the thioester-forming conditions of our model system. The six-membered-ring disulfide is stable to reaction conditions; the seven- and eight-membered-ring disulfides polymerize.[10]

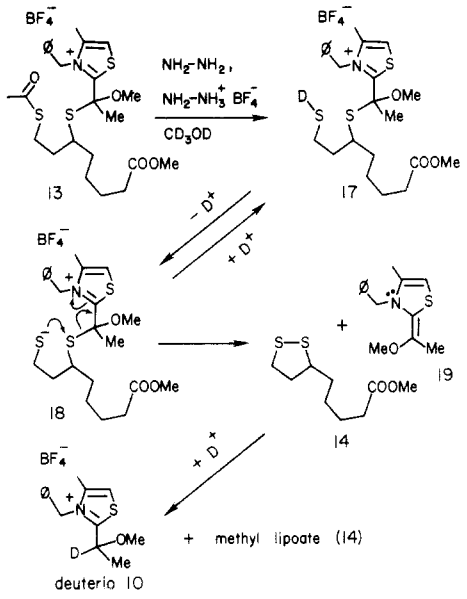
Faced with the unreactivity of methyl lipoate toward enamines 7 and 19, further examination of the behavior of cyclic disulfides in our model system was sought. Tetrahedral adduct 11 was easily produced from active aldehyde precursor 10 and *N*-(phenylthio)phthalimide (vide supra). The stability of the adduct from 10 and

(7) The thioesters are stable to reaction conditions.
(8) Conjugate acid of ylide 8, Scheme II.
(9) Behforouz, M.; Kerwood, J. F. *J. Org. Chem.* **1969**, *34*, 51.
(10) Polymerization may be initiated by attack of enamine 7 or thiazolium ylide 8 at the disulfide.

Scheme IV



Scheme V

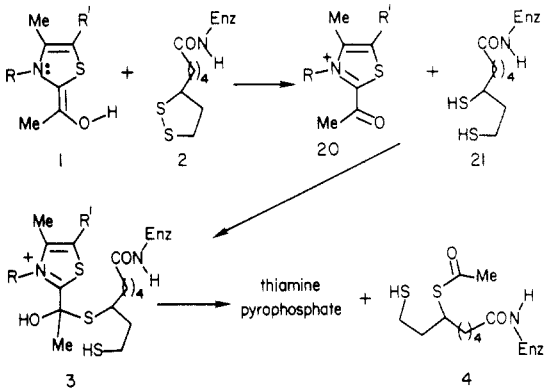


methyl lipoate (see **17**, Scheme V), however, remained in question. Thus, a nonbiomimetic assembly of an analogue of enzyme bound adduct **3** (Scheme I) was sought. By analogy to the successful sulfenylation **10** → **11**, a lipoate derived tetrahedral adduct might be constructed as depicted in Scheme III. Imide displacement from **12** (compare **10** + *N*-(phenylthio)phthalimide → **11**) would generate, without dithiolane ring opening, adduct **13**. Deacetylation of **13** would give the desired analogue of **3** (see **17**, Scheme V), *a product inaccessible (vide supra) from methyl lipoate plus methylated active aldehyde precursor* ***10***. The stability of **17** relative to **10** and methyl lipoate thus could be studied.

Sulfenamide **12** is produced as shown in Scheme IV. Reduction and acetylation of (±)-methyl lipoate (**14**) produces a mixture of acetylated (±)-dihydrolipoates.[11] The 8-acetyl isomer reacts smoothly with *N,N'*-thiobisphthalimide [$(PhthN)_2S$],[12] giving thioester phthalimido disulfide **16**. Desulfurization[13] of **16** by triphenylphosphine yields the desired sulfenamide **12**. Reaction of **12** with **10** proceeds in the presence of catalytic DBU in tetrahydrofuran. Adduct **13**, having two asymmetric centers, is produced as a racemic 1:1 mixture of diastereomers. The mixture of diastereomers can be purified by gel-permeation liquid chromatography.

Adduct **13** (Scheme V) is stable in methanol-d_4 in the presence of hydrazinium tetrafluoroborate. This mixture,

Scheme VI



immediately upon mixing with 2.5 equiv of NH_2NH_2/$NH_2NH_3{}^+BF_4{}^-$, gives rise to methyl lipoate (**14**) and deuterio-**10**.

Discussion

The formation of thioesters in our model system lends support to the mechanism[6] of Scheme I. An earlier, proposed mechanism[14] (Scheme VI) for the conversion **1** + **2** → **3** invoked two steps: (a) a redox reaction of **1** and **2**, yielding 2-acetylthiazolium salt **20** plus dihydrolipoate (**21**), and (b) collapse of these intermediates, giving **3**. In our model system such a mechanism is possible by starting from precursor **6** but not from methylated derivative **10**. On the basis of the similar conditions for reaction of **6** and for reaction of **10** in our model system we suggest that the biological generation of thioesters of coenzyme A from α-keto acids occurs via the direct reductive acylation of enzyme-bound lipoic acid by the active aldehyde **1**, as formulated by Breslow and by Ingraham (Scheme I) in 1962.[6]

Our model system, successful in thioester production from linear disulfides, fails in the reductive cleavage of methyl lipoate (**14**), an analogue of the natural, enzyme-bound 1,2-dithiolane **2**. Acyl dihydrolipoate (e.g., **4**) is known to accumulate in α-keto acid dehydrogenase systems[15] deprived of coenzyme A (see **4** → **5**, Scheme I). The overall reductive acylation of lipoate, at least in the natural system, thus, is favored thermodynamically. The chemical model system lacks some thermodynamic and/or kinetic factors which promote reaction in the α-keto acid dehydrogenases.

The experiment depicted in Scheme V helps to define some, though not all, of the thermodynamic and kinetic parameters for reaction of methyl lipoate (**14**) in our model system. We assume the conversion **13** → deuterio-**10** + **14** proceeds by deacetylation of **13** to thiol **17**, an analogue of tetrahedral intermediate **3** (Scheme I). Rapid ring closure, probably from thiolate **18**, *achieves the reverse of the biological, lipoate reductive cleavage* ***1*** → ***2*** → ***3***. The enforced proximity of the thiolate in **18** to the tetrahedral intermediate entropically favors disulfide formation. Under the conditions of Scheme V adduct **17** is thermodynamically disfavored relative to methyl lipoate and deuterio-**10**. Also, deuterio-**10** and methyl lipoate are kinetically accessible from **17** under very mild conditions.

The collapse of adduct **17** to methyl lipoate and deuterio-**10** establishes chemical precedent for the mechanism,

(11) Gunsalus, I. C.; Barton, L. S.; Gruber, W. *J. Am. Chem. Soc.* **1956**, *78*, 1736.
(12) Kalnins, M. V. *Can. J. Chem.* **1966**, *44*, 2111.
(13) This procedure appears generally applicable for the synthesis of sulfenamides; manuscript in preparation.
(14) Das, M. L.; Koike, M.; Reed, L. J. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 753.
(15) See, e.g.: (a) Collins, J. H.; Reed, L. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 4223; (b) Frey, P. A.; Ikeda, B. H.; Gravino, G. R.; Speckhard, D. C.; Wong, S. S. *J. Biol. Chem.* **1978**, *253*, 7234.

if not the direction, of the reductive cleavage of lipoate in the α-keto acid dehydrogenase systems. It is apparent from the experiment of Scheme V that methylated tetrahedral adduct 17 cannot accumulate in the forward model reaction of 10 plus methyl lipoate. Yet the enzymatic tetrahedral adduct 3 (Scheme I) need not accumulate in the natural system either; i.e., the natural process may be driven by thioester formation from 3. Intermediate 3, but not model adduct 17, can collapse to form thioester. *Un*methylated active aldehyde 7 and methyl lipoate, however, in principle can undergo both the reductive cleavage and the thioester-forming steps of Scheme I (1 + 2 → 3 → 4). Yet methyl lipoate is stable to model reaction conditions. It is not cleaved by enamine 7 nor by ylide 8 (cf. 8 → 9, Scheme II). The current data do not help distinguish between kinetic and thermodynamic barriers for reaction of methyl lipoate with model active aldehyde 7. An activation (kinetic) barrier may lie between starting materials and the methyl lipoate derived thioester; i.e., the tetrahedral adduct (from 7 plus 14) may not form, even reversibly, under model reaction conditions. Alternatively, the thioester and accompanying products actually may lie uphill in the model system, despite the accumulation of thioester observed in the natural system.[15]

Adduct 17 (Scheme V) collapses readily to model system starting materials, but *the activation barrier for the forward reductive cleavage of methyl lipoate (10 + 14 → 17 or 6 + 14 → adduct) remains unknown.* The natural reductive cleavage may be catalyzed by the protonation of developing thiolate as depicted in Scheme I (see 2). However, under the basic conditions of the model system the cleavage of methyl lipoate is unlikely to proceed directly to reduced thiol product (see 3 and 17, Scheme V). Rather, a substantial activation barrier may exist for ring opening to the strongly reducing dihydrolipoate thiolate anion (see anion 18, Scheme V). The thiolates formed in the model system upon reductive cleavage of linear disulfides are significantly less strongly reducing than thiolates from 1,3-dithiols such as dihydrolipoate.[16] The reduction potential of dihydrolipoate also may be responsible for the stability of methyl lipoate to ylide 8 which is rapidly sulfenylated by linear disulfides (Scheme II).

It is appealing to speculate that factors other than simple protonation at 1,2-dithiolane sulfur also may promote the enzymatic redox process of Scheme I. Active aldehyde 1, formed upon decarboxylation of the thiamine–pyruvate adduct,[3] may be bound at the enzyme active site in such a way to raise its reduction potential. During the conversion 1 + 2 → 3 a full positive charge develops on the thiazolium moiety. Stabilization of the developing charge at the active site (e.g., by a charge–charge or charge-transfer interaction[17]) would catalyze the reductive cleavage process and stabilize the reaction products (kinetic and thermodynamic benefits). Such a mechanism might not function in our model system which lacks the ordered enzyme binding of substrate and coenzymes.

Experimental Section

^{1}H NMR spectra were obtained on a Perkin-Elmer R-24B (60 MHz) or Varian T-60 (60 MHz) spectrometer and high-resolution ^{1}H NMR spectra were determined on a Bruker WM250 spectrometer. Chemical shifts downfield from tetramethylsilane are reported on the δ scale. Mass spectra were determined on a CEC 110B Mattauch Herzog (Du Pont instruments) high-resolution mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer 567 or 283B grating spectrophotometer. Melting points are uncorrected and were obtained in open capillaries (Mel Temp instrument). Gas chromatograms were obtained on a Varian 3700 instrument (4.1% Chromosorb G on SE-30, 7 ft). Liquid chromatography was performed on a Waters analytical LC system. Combustion analyses were performed by Robertson Laboratory, Florham Park, NJ.

The following abbreviations are used throughout this section: THF = tetrahydrofuran, DMF = *N,N*-dimethylformamide, DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene, DNP = dinitrophenylhydrazine.

3-Benzyl-2-(α-hydroxyethyl)-4-methylthiazolium Tetrafluoroborate (6). Active aldehyde precursor 6 was made by a modification of Breslow's route,[4b] using *tert*-butyllithium at −94 °C (rather than *n*-butyllithium at −78 °C) for the initial metalation of 4-methylthiazole. Condensation with acetaldehyde and quaternization with benzyl bromide were performed by following Breslow's procedures. Anion exchange was achieved by mixing 3-benzyl-2-(α-hydroxyethyl)-4-methylthiazolium bromide (0.55 g, 1.76 mmol) in absolute EtOH (25 mL) and $AgBF_4$ (0.35 g, 1.76 mmol) in absolute EtOH (5.0 mL). Precipitated silver salt was removed by filtration through Celite and 6 was obtained by removal of solvent in vacuo; yield 0.52 g, 92%. Recrystallization from 2-methyl-1-propyl alcohol/isopropyl alcohol (3:1) provided colorless needles: mp 79–80 °C; ^{1}H NMR (60 MHz, acetone-d_6) 1.65 (3 H, d, J = 7.5 Hz), 2.50 (3 H, s), 2.91 (1 H, s, exchangeable), 5.73 (1 H, q, J = 7.5 Hz), 5.97 (2 H, s), 7.1–7.6 (5 H, m), 8.14 (1 H, s); IR (CH_2Cl_2) 3480, 3030, 2995, 1595, 1426, 1328 cm^{-1}.

Reactions of 6 as an Acyl Anion Equivalent. The reaction of 6 with diphenyl disulfide is given as representative of the reactions of Table I. A solution containing 6 (64 mg, 0.20 mmol), diphenyl disulfide (218 mg, 1.0 mmol), and *n*-decane (18 μL, 0.09 mmol, internal GLC standard) in dry THF (0.5 mL) was freeze–thaw degassed. To the mixture under argon was added at ambient temperature DBU (30 μL, 0.20 mmol) in degassed THF (0.5 mL) solution. After 5 min, analysis of the red-brown reaction mixture by GLC revealed the presence of CH_3COSPh (32%) and PhSH (74%) (yields calculated from measured flame ionization detector response factors vs. internal *n*-decane). GLC–mass spectral analysis confirmed the identity of these products by comparison of fragmentation patterns to authentic samples.

Acetylthiophenol (CH_3COSPh) was isolated from a similar reaction of 6 (64 mg, 0.20 mmol), *N*-(phenylthio)phthalimide (51 mg, 0.20 mmol), and DBU (30 μL, 0.20 mmol) in THF (1.0 mL). After being stirred for 16 h at ambient temperature, the reaction mixture was evaporated to dryness in vacuo. The residue was partitioned between Et_2O and 2% aqueous HCl, and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. Trituration with $CDCl_3$ gave insoluble phthalimide, mp 231–233 °C. Acetylthiophenol (13 mg, 42%) was obtained by evaporation of solvent: ^{1}H NMR (60 MHz, $CDCl_3$) 2.39 (3 H, s), 7.2–7.6 (5 H, m); IR 1700 cm^{-1}.

Base-Induced Decomposition of 6. DNP Trapping of Acetaldehyde. A THF solution (1 mL) containing 6 (64 mg, 0.20 mmol) was treated with DBU (30 μL, 0.20 mmol) at ambient temperature. After 5 min the mixture was quenched with H_2O/CH_3CN (3:1) containing 1% NaOAc. LC analysis (C_{18} reverse phase) revealed a 30–40% loss of 6 and formation of protonated 8 (assignments confirmed by coinjection with authentic materials). TLC analysis of a similar reaction after 5 min showed 6 (R_f 0.39) and protonated 8 (R_f 0.09) (silica gel, pyridine/2-methyl-1-propyl alcohol/H_2O, 4:1:1).

Acetaldehyde produced from 6 upon treatment with DBU was trapped as its DNP derivative. A nitrogen stream was passed through a solution of 6 (64 mg, 0.20 mmol) and DBU (30 μL, 0.20 mmol) in THF (1 mL) and the volatile components were bubbled through a DNP solution (excess) cooled to 0 °C in a second flask. After 1 h the resulting orange solution was chromatographed (silica gel preparative TLC, CH_2Cl_2), giving the 2,4-dinitrophenylhydrazone of acetaldehyde (11 mg, 25%), mp 161 °C, mixture mp 161 °C.

(16) The reducing potential of an α,ω-dithiol is strongly influenced by the size of the cyclic disulfide formed on its oxidation (cf. 17 → 14 + 19, Scheme V). See: Szajewski, R. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2011.

(17) Aoki and Yamazaki have recently discussed a model for apoenzyme binding of thiamine pyrophosphate. These authors also reference earlier studies which implicate charge-transfer complexation upon binding of the coenzyme to transketolase; see: Aoki, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1980**, *102*, 6878 and references therein.

3-Benzyl-4-methylthiazolium Tetrafluoroborate. 3-Benzyl-4-methylthiazolium bromide[4a] (2.90 g, 10.7 mmol) was treated with $AgBF_4$ (2.10 g, 10.7 mmol) in absolute EtOH (50 mL). Insoluble AgBr was removed by filtration through Celite and the tetrafluoroborate salt (protonated 8) was obtained upon removal of solvent in vacuo: yield 2.70 g (92%); mp 89–91 °C; ^1H NMR (60 MHz, acetone-d_6) 2.60 (3 H, s), 5.86 (2 H, s), 7.39 (5 H, m), 8.06 (1 H, s), 10.01 (1 H, s).

Reactions of Ylide 8 with Benzyl Disulfide and with *N*-(Phenylthio)phthalimide. A solution of 3-benzyl-4-methylthiazolium tetrafluoroborate (70 mg, 0.25 mmol), benzyl disulfide (61 mg, 0.25 mmol), and *n*-decane (20 μL, 0.10 mmol, internal GLC standard) in THF (0.5 mL) was treated with DBU (37 μL, 0.25 mmol) in THF (0.5 mL) (both solutions freeze–thaw degassed). GLC analysis revealed a maximum yield of benzyl mercaptan (79%) after 40 min.

A solution of 3-benzyl-4-methylthiazolium tetrafluoroborate (110 mg, 0.40 mmol) and *N*-(phenylthio)phthalimide[9] (102 mg, 0.4 mmol) in THF (1.5 mL) was treated with a catalytic amount (3 μL, 0.02 mmol) of DBU in THF (0.5 mL) (both solutions freeze–thaw degassed). After 4 h the solvent was removed in vacuo and the solid residue triturated with $CHCl_3$. Insoluble phthalimide was removed by filtration and thiophenyl adduct **9b** was obtained by evaporation of the filtrate; yield 138 mg, 86%. Recrystallization from $CHCl_3/CCl_4$ (2:1) afforded white needles: mp 138–140 °C; ^1H NMR (60 MHz, $CDCl_3$) 2.47 (3 H, s), 5.66 (2 H, s), 6.7–8.2 (11 H, m); IR (KBr) 3020, 1585, 1447, 1345 cm^{-1}. Anal. Calcd for $C_{17}H_{16}NOS_2BF_4$: C, 53.00; H, 4.19; N, 3.64. Found: C, 52.78; H, 4.16; N, 3.52.

Reaction of Ylide 8 with Diphenyl Disulfide in the Presence of Acetaldehyde. 3-Benzyl-4-methylthiazolium tetrafluoroborate (56 mg, 0.20 mmol), diphenyl disulfide (218 mg, 1.0 mmol), acetaldehyde (9 mg, 0.20 mmol), and *n*-decane (20 μL, 0.10 mmol, internal GLC standard) in THF (0.5 mL) were treated with DBU (30 μL, 0.20 mmol) in THF (0.5 mL) (both solutions freeze–thaw degassed). Formation of thiophenol was apparent after 5 min (GLC yield 73% based on thiazolium salt). Acetylthiophenol was observed in less than 1% yield (based on acetaldehyde) after 5 min and did not increase over a period of 1 h.

Preparation of Methyl-Protected Analogue 10. To a suspension of NaH (18 mg, 0.77 mmol) in DMF (5 mL) at 0 °C was added 2-(α-hydroxyethyl)-4-methylthiazole[4b] (100 mg, 0.70 mmol). After the mixture was stirred for 1 h, methyl iodide (99 mg, 0.70 mmol) was added, and the reaction was allowed to warm to ambient temperature and stirred an additional 12 h. Extractive workup (Et_2O/H_2O), drying ($MgSO_4$), and removal of Et_2O in vacuo gave 2-(α-methoxyethyl)-4-methylthiazole as a clear oil (79 mg, 72%). In larger scale preparations the methyl ether was purified by distillation (32–36 °C, 0.8 mmHg): ^1H NMR (60 MHz, $CDCl_3$) 1.59 (3 H, d, J = 6.0 Hz), 2.50 (3 H, s), 3.46 (3 H, s), 4.75 (1 H, q, J = 6.0 Hz), 7.02 (1 H, s); IR (neat, NaCl) 3095, 2920, 2822, 1523, 1447, 1308, 1090 cm^{-1}.

2-(α-Methoxyethyl)-4-methylthiazole (2.0 g, 12.0 mmol) and benzyl bromide (11.0 g, 60.0 mmol) were heated in a sealed tube at 80 °C for 48 h. The reaction mixture was partitioned between H_2O and $CHCl_3$ and the aqueous layer evaporated to dryness in vacuo. The residue was foamed by evaporation from Et_2O in vacuo (yield 3.30 g, 79%). Without further purification the bromide salt was treated with $AgBF_4$ (1.95 g, 10.0 mmol) in absolute EtOH (50 mL) to achieve anion exchange. The resulting salt, **10** (3.10 g, 98%), was recrystallized from $CHCl_3/Et_2O$ (1:1): mp 79–80 °C; ^1H NMR (60 MHz, $CDCl_3$) 1.52 (3 H, d, J = 7.5 Hz), 2.42 (3 H, s), 3.41 (3 H, s), 5.01 (1 H, q, J = 7.5 Hz), 5.68 (2 H, s), 6.8–7.4 (5 H, m), 7.84 (1 H, s); ^1H NMR (250 MHz, CD_3OD) 1.40 (3 H, d, CH_3, J = 6.5 Hz), 2.32 (3 H, d, aromatic CH_3, J = 1 Hz), 3.33 (3 H, s, OCH_3), 5.01 (1 H, q, J = 6.5 Hz), 5.66 (2 H, s, benzyl CH_2), 7.0–7.4 (5 H, 2 m, aromatic), 7.87 (1 H, br s, thiazolium H); IR (KBr) 2995, 2948, 1580, 1450, 1305 cm^{-1}. Anal. Calcd for $C_{14}H_{18}NOSBF_4$: C, 50.17; H, 5.41; N, 4.18. Found: C, 50.02; H, 5.35; N, 4.17.

Reaction of 10 with *N*-(Phenylthio)phthalimide. A THF solution (1.5 mL) containing **10** (134 mg, 0.40 mmol) and *N*-(phenylthio)phthalimide (102 mg, 0.40 mmol) was treated with DBU (6 μL, 0.04 mmol) in THF (0.5 mL) (both solutions freeze–thaw degassed). A crystalline precipitate formed and was collected by filtration after 3 h, affording thiophenyl thiazolium adduct **11** (131 mg, 74%). Salt **11** was recrystallized from $CHCl_3/Et_2O$ (2:1), affording shiny white needles: mp 176–177 °C; ^1H NMR (60 MHz, $CDCl_3$) 1.89 (3 H, s), 2.32 (3 H, s), 3.66 (3 H, s), 5.7–6.6 (2 H, AB q, J = 18.5 Hz), 6.8–7.5 (10 H, m), 7.67 (1 H, s); IR ($CHCl_3$) 3039, 1590, 1442, 1060 cm^{-1}; exact mass calcd for $C_{19}H_{18}NS_2$ ($M^+ - BF_4^- - CH_3OH$) m/e 324.08807 (found m/e 324.08716), calcd for $C_{12}H_{11}NS_2$ ($M^+ - BF_4^- - CH_3OH - C_6H_5CH_2$) m/e 233.03330 (found m/e 233.03350). Anal. Calcd for $C_{20}H_{22}NOS_2BF_4$: C, 54.19; H, 5.00; N, 3.16. Found: C, 53.21, 53.23; H, 4.96, 4.95; N, 2.97, 2.96 (data from two separate samples of **11** recrystallized 3 and 6 times, respectively, and dried at 80 °C in vacuo).

Reactions with Methyl Lipoate (14). The reaction of **14** with active aldehyde precursor **6** and DBU in THF is given as representative of the lipoate reactions. Precursor **6** (30 mg, 0.93 mmol), methyl lipoate (**14**; 21 mg, 0.93 mmol), and DBU (15 μL, 0.10 mmol) were dissolved in freeze–thaw degassed THF (1 mL) and the reaction mixture was stirred at ambient temperature under N_2 atmosphere. The reaction was monitored by GLC vs. *n*-dodecane as internal standard. No mono- or diacetylated methyl dihydrolipoate could be detected nor was any loss of **14** observed over a 14-h period. Methyl lipoate was also stable in similar reactions in EtOH or *t*-BuOH as solvents, or in THF with Et_3N as base. The enamine derived from methylated precursor **10** (see **19**, Scheme V), generated in THF with 1.1 equiv of DBU, was also unreactive toward **14**. Conditions for condensation of acetaldehyde with methyl vinyl ketone catalyzed by ylide **8**[5] are also ineffective in the reductive acylation of **14**.

Synthesis of Sulfenamide 12. Thioester **15** was prepared by the literature[11] procedure and purified by silica gel chromatography (hexanes/EtOAc, 8:1); yield 29%. A solution of **15** (1.87 g, 7.10 mmol) in CH_2Cl_2 (50 mL) was added dropwise to *N,N'*-thiobisphthalimide[12] (4.60 g, 14.1 mmol) in refluxing CH_2Cl_2 (150 mL) under a N_2 atmosphere. After 30 min at reflux the solvent was removed in vacuo and the residue chromatographed (silica gel, hexanes/EtOAc, 5:2), affording disulfide **16** (R_f ~0.1) as a viscous oil (2.45 g, 78%): ^1H NMR (60 MHz, $CDCl_3$) 1.0–2.1 (8 H, m), 2.19 (2 H, m), 2.23 (3 H, s), 2.7–3.3 (3 H, m), 3.64 (3 H, s), 7.6–8.0 (4 H, m); IR (neat, NaCl) 2940, 2865, 1780, 1740, 1695, 1610, 1437, 1260, 1045 cm^{-1}; exact mass calcd for $C_{17}H_{20}NO_4S_3$ ($M^+ - CH_3CO$) m/e 398.05546 (found m/e 398.05570), calcd for $C_{11}H_{19}O_3S_2$ (M^+ – *S*-phthalimide) m/e 265.07336 (found m/e 265.07372). Anal. Calcd for $C_{19}H_{23}NO_5S_3$: C, 51.68; H, 5.25; N, 3.17. Found: C, 51.43; H, 5.29; N, 2.96.

Disulfide **16** (3.54 g, 8.00 mmol) in benzene (75 mL) was desulfurized by slow addition of triphenylphosphine (2.10 g, 8.00 mmol) in benzene (75 mL) at ambient temperature under a N_2 atmosphere. After 1 h the reaction mixture was concentrated and triturated with hexanes, and precipitated triphenylphosphine sulfide was removed by filtration. The filtrate was concentrated in vacuo and the residue chromatographed (silica gel, hexanes/EtOAc, 5:2), affording sulfenamide **12** (1.70 g, 52%) as a gum (R_f ~0.15). Crystallization from Et_2O yielded white needles: mp 56–57 °C; ^1H NMR (60 MHz, $CDCl_3$) 1.2–2.0 (8 H, m), 2.30 (2 H, m), 2.33 (3 H, s), 2.7–3.5 (3 H, m), 3.64 (3 H, s), 7.8–8.1 (4 H, m); IR ($CHCl_3$) 3050, 1780, 1760, 1735, 1490, 1335, 1100 cm^{-1}; exact mass calcd for $C_{17}H_{20}NO_5S_2$ ($M^+ - CH_3CO$) m/e 366.087 (found m/e 366.084). Anal. Calcd for $C_{19}H_{23}NO_5S_2$: C, 55.73; H, 5.66; N, 3.42; S, 15.66. Found: C, 55.67; H, 5.95; N, 3.12; S, 15.37.

Synthesis of Adduct 13. A freeze–thaw degassed, THF-d_8 solution (0.4 mL) of thiazolium salt **10** (67 mg, 0.20 mmol) and sulfenamide **12** (82 mg, 0.20 mmol) was treated with a catalytic amount (3 μL, 0.02 mmol) of DBU. The reaction was monitored by ^1H NMR which indicated complete reaction after 16 h. Removal of solvent in vacuo and trituration of the residue with CH_2Cl_2 served to remove insoluble phthalimide. The CH_2Cl_2 phase was diluted to ca. 40 mL with additional CH_2Cl_2 and washed with 1% HBF_4 (aqueous, 2 × 10 mL). Purification was achieved by gel-permeation chromatography (Waters μStyragel columns, 1 × 500 Å and 4 × 100 Å in series, CH_2Cl_2), affording adduct **13** (49 mg, 41%) as a viscous oil. ^1H NMR indicates that **13** is formed as a ~1:1 mixture of diastereomers: ^1H NMR (250 MHz, $CDCl_3$) 1.0–2.0 (16 H, m), 1.70 (3 H, s, CH_3), 1.73 (3 H, s, CH_3), 2.21–2.35 (4 H, m), 2.27 (3 H, s, CH_3CO), 2.29 (3 H, s, CH_3CO), 2.38 (6 H, br s, aromatic CH_3's), 2.7–3.0 (6 H, m), 3.449 (3 H, s, $COOCH_3$),

3.453 (3 H, s, $COOCH_3$), 3.62 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 5.8–6.5 (4 H, 2 AB q, benzyl CH_2's, J = 17.3 Hz), 6.8–7.4 (10 H, 2 aromatic m), 8.04 (1 H, q, thiazolium H, J = 0.7 Hz), 8.06 (1 H, q, thiazolium H, J = 0.7 Hz); ^1H NMR (250 MHz, CD_3OD) 0.7–1.8 (16 H, m), 1.68 (3 H, s, CH_3), 1.70 (3 H, s, CH_3), 2.18 (3 H, s, CH_3CO), 2.20 (3 H, s, CH_3CO), 2.22 (4 H, m), 2.29–2.30 (6 H, 2 d, aromatic CH_3's, J = 0.7 Hz), 2.7–2.8 (6 H, m), 3.43 (3 H, s, $COOCH_3$), 3.44 (3 H, s, $COOCH_3$), 3.54 (3 H, s, OCH_3), 3.57 (3 H, s, OCH_3), 5.5–6.5 (4 H, 2 AB q, benzyl CH_2's, J = 16.7 Hz), 6.8–7.4 (10 H, 2 aromatic m), 7.80 (1 H, q, thiazolium H, J = 0.7 Hz), 7.82 (1 H, q, thiazolium H, J = 0.7 Hz); IR (CH_2Cl_2) 2940, 1728, 1683, 1578, 1432, 1128, 1055 cm^{-1}; field-desorption mass spectrum calcd for $C_{25}H_{36}NO_4S_3$ ($M^+ - BF_4^-$) m/e 510 (found m/e 510). Anal. Calcd for $C_{25}H_{36}NO_4S_3BF_4$: C, 50.25; H, 6.47; N, 2.34; S, 16.10; F, 13.01. Found: C, 50.21; H, 6.33; N, 2.44; S, 16.21; F, 13.01.

Conversion of Adduct 13 into Deuterio-10 plus Methyl Lipoate (14). To adduct **13** (2.0 mg, 3.4 μmol) in CD_3OD (0.4 mL) was added an aqueous solution of $NH_2NH_3^+BF_4^-$ (0.7 μL, 5.0 μmol). This mixture was unchanged during the course of 30 min as monitored by ^1H NMR. A second aqueous solution (1.5 μL) containing NH_2NH_2 (8.6 μmol) and $NH_2NH_3^+BF_4^-$ (8.6 μmol) was added to the ^1H NMR sample. Reintroduction of the sample to the spectrometer and ^1H NMR observation indicated rapid conversion (elapsed time ca. 10 min) of **13** into methyl lipoate (**14**), deuterio-**10**, and $CH_3CONDND_2$. The ^1H NMR of the mixture clearly showed absorptions attributable to these products as compared to spectra of authentic samples in CD_3OD. The ^1H NMR absorptions for deuterio-**10** are consistent with its monodeuteration by solvent: ^1H NMR (250 MHz, CD_3OD) 1.40 (3 H, s, CH_3), 2.32 (3 H, d, aromatic CH_3, J = 1 Hz), 3.33 (3 H, s, OCH_3), 5.66 (2 H, s, benzyl CH_2), 7.0–7.4 (5 H, 2 m, aromatic) 7.87 (1 H, br s, thiazolium H) (cf. ^1H NMR (CD_3OD) of **10** above). ^1H NMR (CD_3OD) for methyl lipoate (**14**), authentic sample and mixture with deuterio-**10** plus $CH_3CONDND_2$: 1.34 (2 H, complex m), 1.54 (4 H, complex m), 1.77 (1 H, 6-line m), 2.24 (2 H, t), 2.35 (1 H, 6-line m), 3.02 (2 H, complex m), 3.46 (1 H, 8-line m), 3.55 (3 H, s). ^1H NMR (CD_3OD) of $CH_3CONDND_2$, authentic sample and mixture with deuterio-**10** plus **14**: 1.79 (s).

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Registry No. **6**, 70625-03-5; **7**, 70625-04-6; **8**, 70625-05-7; **8** protonated, 4356-66-5; **9b**, 70625-09-1; **10**, 70625-11-5; **11**, 70625-84-5; **12**, 76756-41-7; **13** (isomer 1), 76756-43-9; **13** (isomer 2), 76756-45-1; **14**, 46236-19-5; **15**, 925-33-7; **16**, 76756-46-2; PhSSPh, 882-33-7; $PhCH_2SSCH_2Ph$, 150-60-7; EtSSEt, 110-81-6; CH_3COSPh, 934-87-2; PhSH, 108-98-5; $PhCH_2SH$, 100-53-8; CH_3COSEt, 625-60-5; *N*-(phenylthio)phthalimide, 14204-27-4; 4-methylthiazole, 693-95-8; acetaldehyde 2,4-dinitrophenylhydrazone, 1019-57-4; 3-benzyl-4-methylthiazolium tetrafluoroborate, 76756-47-3; 2-(α-hydroxyethyl)-4-methyl-thiazole, 7586-99-4; 2-(α-methoxyethyl)-4-methylthiazole, 76756-48-4; *N,N'*-thiobisphthalimide, 7764-29-6; 3-benzyl-2-(α-hydroxyethyl)-4-methylthiazolium bromide, 13079-87-3.

Kinetics and Mechanism of the Thermolysis of a Five-Membered-Ring Peroxide, 3,3,5,5-Tetramethyl-1,2-dioxolane

William H. Richardson,* Ronald McGinness, and H. Edward O'Neal*

Chemistry Department, San Diego State University, San Diego, California 92182

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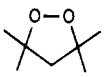
The kinetics of the thermolysis of 3,3,5,5-tetramethyl-1,2-dioxolane (**1**) was studied in benzene solution with a free-radical chain inhibitor (2,6-di-*tert*-butyl-*p*-cresol) in the gas phase. The peroxide **1** was susceptible to induced decomposition both in solution without the inhibitor and in the gas phase without conditioned reactor walls. However, under optimum conditions, first-order kinetics were observed in both the gas phase and in solution. Activation parameters for the thermolysis of **1** in benzene solution with the inhibitor at 500 K are E_a = 44.6 ± 0.9 kcal/mol, log A = 15.85 ± 0.42, $\Delta H^\ddagger$ = 43.6 ± 0.9 kcal/mol, and $\Delta S^\ddagger$ = 11.0 ± 1.9 eu. In the gas phase, the parameters at 500 K are E_a = 45.5 ± 0.3 kcal/mol, log A = 15.72 ± 0.13, $\Delta H^\ddagger$ = 44.5 ± 0.3 kcal/mol, and $\Delta S^\ddagger$ = 10.4 ± 0.6 eu. These parameters closely approach calculated activation parameters for **1** which are based on a stepwise biradical decomposition mechanism: E_a = 48.6 kcal/mol, log A = 16.55, $\Delta H^\ddagger$ = 47.6 kcal/mol, and $\Delta S^\ddagger$ = 14.2 eu at 500 K. Considering the susceptibility of **1** to induced decomposition, which will lower the activation parameters, the close approach of the experimental to the calculated parameters indicates that **1** undergoes decomposition by a stepwise biradical route. Thus, there is no mechanistic discontinuity between the stepwise biradical mechanism observed with simply substituted 1,2-dioxetanes (four-membered-ring peroxides) and the five-membered-ring peroxide **1**.

Thermolysis of the four-membered-ring peroxides, 1,2-dioxetanes, is well accommodated in most instances by a stepwise decomposition process.[1,2] Activation parameters for the thermolysis of many substituted dioxetanes fall within a limited range, and these experimental parameters are usually in good agreement with calculated values, based on a stepwise process.[2]

We expected that 1,2-dioxolanes, the next higher homologue from 1,2-dioxetanes, would also undergo thermolysis in a stepwise manner. Yet, the calculated activation parameters for 3,3,5,5-tetramethyl-1,2-dioxolane (**1**),



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based on a stepwise process, differed considerably from

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