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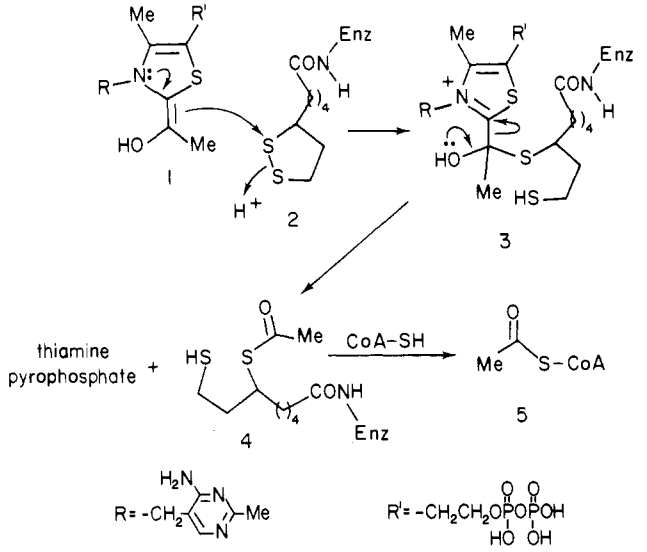
On the Involvement of Lipoic Acid in α-Keto Acid Dehydrogenase Complexes

Sir:

Herein we report the reactivity of thiazolium salt derived acyl anion equivalents (see **1**, Scheme I) toward sulfur electrophiles and provide a model for the thioester-forming step catalyzed by the lipoic acid containing enzymes (**2**), the α-keto acid dehydrogenases.[1,2] This class of enzymes mediates the production of energy-rich thioesters of coenzyme A (e.g., acetyl coenzyme A, **5**) by oxidative decarboxylation of α-keto acids (e.g., pyruvate). Our work, detailed below, focuses on the formation of the intermediate thioester **4** and supports the direct reductive acylation step[3] depicted in Scheme I.

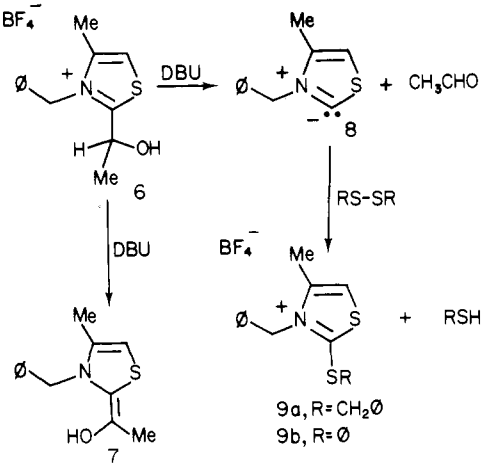
Scheme I



In our model system an equivalent of the biological "active aldehyde" (**1**) is generated by proton abstraction from the crystalline precursor **6** (Scheme II).[4] Table I shows results of the trapping of in situ generated enamine **7** by a variety of electrophiles. As precedented,[2g] **7** transfers the acetyl moiety to methyl vinyl ketone (entries 1 and 2). The reactions of **7** with sources of electrophilic sulfur (entries 3-6) 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, as well, induces fragmentation of **6** to ylide **8** and acetaldehyde.[5] 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 (Table I, entries 4 and 5).[6] In an independent experiment, the ylide **8**, generated from 3-benzyl-4-methylthiazolium tetrafluoroborate[7] and DBU reacted rapidly with benzyl disulfide yielding benzylthiol (79%, GLC yield) and sulfenylated product **9a; 9b** was isolated[8] (74%) from the reaction of ylide **8** with *N*-(phenylthio)-phthalimide[9] (PhS-Phth).

Scheme II



The facile sulfenylation of ylide **8** (Scheme II) precludes efficient generation of thioesters starting from ylide **8** plus acetaldehyde and disulfides. One (1.0) equivalent of acetaldehyde reacts with 5.0 equiv of diphenyl disulfide in tetrahydrofuran (THF) containing 1.0 equiv of 3-benzyl-4-methylthiazolium tetrafluoroborate[7] and 1.0 equiv of DBU (cf. Table I, entry 4) producing <1% yield of acetylthiophenol but a 73% yield of thiophenol (GLC yields based on CH_3CHO).

The base-initiated fragmentation of precursor **6** can be blocked using the methylated derivative **10**.[10] In situ enamine generation from **10** and trapping with *N*-(phenylthio)-

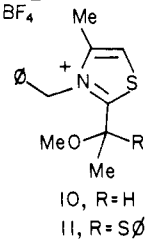


Table I. Reactions of 2-(α-Hydroxyethyl)-3-benzyl-4-methylthiazolium Tetrafluoroborate (**6**) as an Acyl Anion Equivalent

entry	electrophile	solvent, base	conditions, time (temp)	product (% yield)
1	methyl vinyl ketone[a]	EtOH, DBU[b]	0.5 h (ambient temp)	2,5-hexanedione (40)[c]
2	methyl vinyl ketone[a]	EtOH, Et_3N[d]	15 h (reflux), plus 20 h (ambient temp)	2,5-hexanedione (49)[e]
3	PhS-Phth[a]	THF, DBU[b]	16 h (ambient temp)	CH_3COSPh (42)[f,i]
4	PhS-SPh[g]	THF, DBU[b]	5 min (ambient temp)	CH_3COSPh (32),[c,i] PhSH (74)[c,i]
5	$PhCH_2S$-SCH_2Ph[g]	THF, DBU[b]	5 min (ambient temp)	CH_3COSCH_2Ph (13),[c,i] $PhCH_2SH$ (88)[c,i]
6	EtS-SEt[g]	THF, DBU[b]	5 min (ambient temp)	CH_3COSEt (33),[c,i] EtSH[h]

[a] 1.0 equiv used vs. **6**. [b] 1.0 equiv of DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) used vs. **6**. [c] GLC yield (4.1% SE-30 on Chromosorb G, 7 ft), determined relative to hydrocarbon standard. [d] 7.2 equiv of Et_3N used vs. **6**. [e] Isolated yield as bisoxime, mp 129-132 °C. [f] Isolated yield. [g] 5.0 equiv of disulfide used vs. **6**. [h] EtSH yield not determined owing to interfering solvent peak in GLC run. [i] Identity confirmed by GLC-mass spectrum (comparison with authentic sample).

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phthalimide[9] yields the crystalline adduct **11**[11] (74%). The formation of **11** directly parallels the biological formation of tetrahedral intermediate **3** (Scheme I) and lends support to the mechanism[3] of Scheme I. An earlier proposed mechanism[12] for the conversion **1** + **2** → **3** invoked two steps: (a) an oxidation-reduction of **1** and **2**, yielding 2-acetylthiazolium salt plus dihydrolipoate, and (b) collapse of these intermediates, giving **3**. In our model system this possibility is ruled out by the blocking methyl group. Based on our results, 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," as first formulated by Ingraham (Scheme I).[3]

Although the reactions summarized above lend further credence to the mechanisms of Scheme I, they do not directly address the involvement of the 1,2-dithiolane, lipoic acid, in the biological system. As its methyl ester, lipoic acid is completely unreactive under conditions[13] which produce thioesters from linear disulfides or from *N*-(phenylthio)phthalimide. It remains to be established whether thermodynamic or kinetic factors govern the lack of reactivity of enamine **7** toward methyl lipoate. Schmidt et al.[1d] discuss ring strain and geometrical factors which may render 1,2-dithiolanes kinetically more reactive than linear disulfides toward nucleophiles (e.g., **7**). Thermodynamic factors may then govern the stability of methyl lipoate in our model system. The enforced proximity of the thiol (thiolate) in a tetrahedral intermediate such as **3** could well drive the equilibrium **1** + **2** ⇄ **3** (Scheme I) toward the 1,2-dithiolane and enamine.[14,15] The position of the equilibrium should be pH dependent, however. In particular, in our model system the tertiary amine (DBU) present ensures an appreciable concentration of thiolate anion (conjugate base of intermediate **3**). At the pyruvate dehydrogenase active site, the reductive acylation of enzyme-bound lipoic acid could be driven by protonation of the dihydrolipoate intermediate (see **3**). We currently pursue a synthesis of a blocked (O-methylated) version of **3** (cf. **11**) as a model to study the facility and possible pH dependence of the conversion **3** → **1** + **2**.

Acknowledgment is made to the Research Corporation and to the National Science Foundation for support of this work. We thank M. Cutrera and D. Roberts for their technical assistance during the early phase of this work and the Undergraduate Research Opportunities Program (Massachusetts Institute of Technology) for support to them and K.B.R.

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(3) The direct reductive acylation of Scheme I was first suggested by White, F. G.; Ingraham, L. L. *J. Am. Chem. Soc.* **1962**, *84*, 3109.

(4) Made by a modification of Breslow's route (ref 2b). We use *t*-BuLi (−94 °C) rather than *n*-BuLi (−78 °C) and achieve anion exchange with $AgBF_4$ (overall yield from 4-methylthiazole, 70%; mp 79–80 °C.

(5) A nitrogen stream was passed through a solution of **6** + DBU in THF and the volatile components were bubbled through a 2,4-dinitrophenylhydrazine solution in a second flask; the 2,4-dinitrophenylhydrazone of acetaldehyde, mp 161 °C, was formed in 25% isolated yield (preparative TLC); see also ref 2b. LC (C-18 reverse phase, 3:1 H_2O/CH_3CN, 1% NaOAc) of the mixture **6** + DBU shows formation of 3-benzyl-4-methylthiazolium salt (protonated ylide).

(6) The thioesters are stable to reaction conditions (see Table I).

(7) Made by benzylation of 4-methylthiazole with excess benzyl bromide at 80 °C, followed by anion exchange with $AgBF_4$, mp 89.5–91.0 °C. Satisfactory spectral data were obtained.

(8) Only a catalytic amount of DBU was used to form the ylide. Isolation was accomplished by precipitation of the phthalimide byproduct and recrystallization of **9b** (mp 138–140 °C); yield reported is of analytically pure material. Anal. Calcd for $C_{17}H_{16}NS_2BF_4$: C, 53.00; H, 4.19; N, 3.64. Found: C, 52.78; H, 4.16; N, 3.52. Satisfactory spectral data were obtained. The product **9a** was not isolated; its structure is assumed by analogy to **9b**.

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(10) Made by methylation of 2-(α-hydroxyethyl)-4-methylthiazole[2b,4] followed by benzylation and anion exchange (overall yield from 4-methylthiazole, 52%), mp 79–80 °C. Anal. Calcd for $C_{14}H_{18}NOSBF_4$: C, 50.02; H, 5.35; N, 4.17. Found: C, 50.17; H, 5.41; N, 4.18. Satisfactory spectral data were obtained.

(11) **11** had mp 176–177 °C. 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 samples of **11** recrystallized (three and six times, respectively). Satisfactory spectral data were obtained.

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(13) Reactions were monitored by GLC (4.1% SE-30 on Chromosorb G, 7 ft). No loss of methyl lipoate was detected in THF, EtOH, or *t*-BuOH with **6** plus DBU or in THF with **6** plus Et_3N. Methyl lipoate is also stable to acetaldehyde–Et_3N–3-benzyl-4-methylthiazolium tetrafluoroborate (45 °C) and to the enamine derived from methylated precursor **10**.

(14) Our thermodynamic argument is strongly supported by studies of α,ω-dithiol reducing potentials by R. P. Szajewski and G. M. Whitesides (private communication). The reducing potential of an α,ω-dithiol is strongly influenced by the size of the cyclic disulfide formed on its oxidation. Further, 1,3-dithiols are significantly more strongly reducing than simple thiols. We thank R.P.S. and G.M.W. (Massachusetts Institute of Technology) for communicating their results prior to publication.

(15) We have also reacted 1,2-dithiane, 1,2-dithiepane, and 1,2-dithiocane in our model system. The six-ring disulfide is stable to reaction conditions; the seven- and eight-ring disulfides polymerize. The polymerization may be initiated by attack of enamine **7** or thiazolium ylide **8** at the disulfide.

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Mechanism of Photosubstitution of $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_4$ by Triphenylphosphine and Triisopropyl Phosphite. Direct Observation of a Binuclear Intermediate, $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_4\{P[OCH(CH_3)_2]_3\}$, a Molecule with a Carbonyl Bridge but No Metal–Metal Bond

Sir:

Very little is known about the mechanisms of photochemical reactions of polynuclear complexes containing bridging carbonyl ligands.[1] For this reason, we have been investigating the photochemistry of $Cp_2Fe_2(CO)_4$ (Cp = η^5-C_5H_5), a molecule in which the Fe–Fe unit is bridged by two carbonyls.[2] We communicate here the results of experiments that strongly suggest that the photosubstitution mechanism employed by $Cp_2Fe_2(CO)_4$ is quite different from that[3,4] of unbridged metal–metal-bonded binuclear complexes, a difference that can be attributed to the presence of the bridging groups.

Irradiation of $Cp_2Fe_2(CO)_4$ in the presence of PPh_3[1e] or $P(O\text{-}i\text{-}Pr)_3$ in cyclohexane solution at room temperature leads to quantitative or near-quantitative conversion to $Cp_2Fe_2(CO)_3(PR_3)$ (Figure 1):

$$Cp_2Fe_2(CO)_4 + PR_3 \xrightarrow{h\nu} Cp_2Fe_2(CO)_3(PR_3) + CO \quad (1)$$

$$R = Ph, O\text{-}i\text{-}Pr$$

Of particular mechanistic significance is our observation that photolysis of a solution of $Cp_2Fe_2(CO)_4$ and $P(O\text{-}i\text{-}Pr)_3$ in ethyl chloride (or THF) solution at −78 °C yields a yellow intermediate. Formation of this intermediate does not occur in the absence of $P(O\text{-}i\text{-}Pr)_3$. The yellow solution containing the intermediate turns green upon warming to room temperature, and infrared and electronic spectroscopic measurements show that conversion to $Cp_2Fe_2(CO)_3[P(O\text{-}i\text{-}Pr)_3]$[5] has occurred.

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