S–S Bond Cleavage of Polymerization Resistant 1,2-Dithiolanes by Acetylides: Intrinsic Reactivity of Enzyme-bound Lipoic Acid toward Stable, Localized Carbanions

Masato Tazaki,*[a] Masayoshi Kumakura,[a] Shizuo Nagahama[a] and Makoto Takagi[b]

[a] *Department of Industrial Chemistry, Kumamoto Institute of Technology, Ikeda 4-22-1, Kumamoto 860, Japan*
[b] *Department of Chemical Science and Technology, Faculty of Engineering, Kyushu University, Hakozaki 6-10-1, Higashiku, Fukuoka 812, Japan*

The S–S bond of polymerization-resistant 1,2-dithiolanes **2** was cleaved cleanly by acetylides **4**, giving the corresponding ring-opened products **5** in aprotic THF (quenched as silylsulfide **6**) and their re-cyclized products 6,7-dihydro-1,4-dithiepins **3** in protic Bu^{t}OH in excellent yields. The reactivity of **2** is discussed in relation to the reductive acylation of the enzyme-bound lipoic acid (Lip-E_2).

Coenzyme lipoic acid[1] (Lip) is covalently bound to the pyruvate dehydrogenase complex and reductively acetylated at the start of the Krebs cycle by hydroxyethylidenethiamine diphosphate (HET), an active form of the coenzyme thiamine diphosphate (TDP). The similar reductive succinylation is involved in the 2-oxoglutarate dehydrogenase complex within the Krebs cycle. Two controversial mechanisms were proposed for the reductive acetylation of Lip-E_2 (Scheme 1): one involves a redox process producing acetyl TDP (Ac-TDP) and dihydro Lip-E_2, which combine to give the tetrahedral intermediate A (Route 1, redox mechanism[2]). The other mechanism involves simple S–S cleavage of Lip-E_2 by HET to produce directly the same intermediate A (Route 2, carbanion mechanism[3]). The detection of Ac-TDP in the *in vitro* enzyme system[4] and the related results using pyruvate dehydrogenase complex[5] may be considered significant evidence for the redox mechanism.

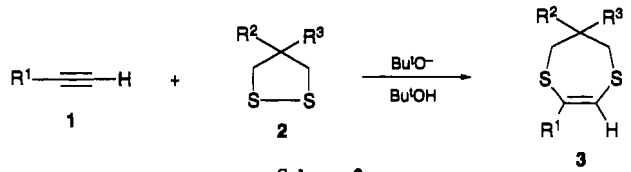
Since the rapid equilibrium between the intermediate A and Ac-TDP (plus dihydro Lip-E_2) was well demonstrated enzymologically,[5] the detection of Ac-TDP does not necessarily mean the reaction proceeds *via* the Ac-TDP as a transient intermediate. Therefore, the reactivity of Lip-E_2 towards carbon nucleophiles as well as its redox properties should be elucidated in order to resolve the enzyme mechanism.

Non-enzymic lipoyl derivatives may have structures closely related to Lip-E_2, but they are not suitable as model compounds, since they are highly polymerizable and are much less reactive towards carbon nucleophiles[6] than expected from their intrinsic ring-strain.[7] However, polymerization resistant 1,2-dithiolanes **2** are highly reactive towards the carbon nucleophile EtMgBr in diethyl ether,[8] and they are the most appropriate models for estimating the chemical properties of Lip-E_2.

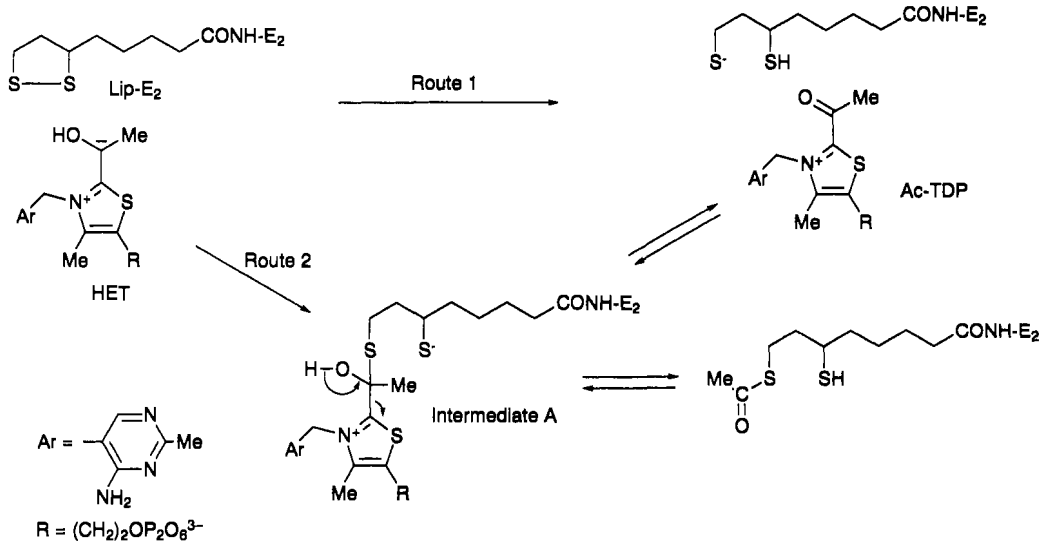
HET is a carbanion stabilized by the thiazolium ring.[9] Thus, we were interested in the behaviour of the model 1,2-dithiolanes **2** towards a stable carbanion of phenylacetylene **1a** (pK_a 23.2)[10] in the protic solvent *tert*-butyl alcohol. The observed result was not simple ring opening but rather novel vinylene insertion into the cyclic disulfides **2** (see Scheme 2).

In a typical experiment, a solution of 4,4-diethyl-1,2-dithiolane **2a** (3 mmol), ethynylbenzene **1a** (4 mmol) and Bu^{t}OK (1 mmol) in Bu^{t}OH (10 ml) was stirred under argon at room temperature for 1 d. After the mixture was diluted with water and extracted with hexane, the product 6,6-diethyl-2-phenyl-6,7-dihydro-1,4-dithiepin **3a** was obtained by a Kugelrohr distillation in excellent yield (97%).

The ring enlargement by vinylene insertion is not well documented so far.[11] Other polymerization resistant 1,2-dithiolanes reacted similarly with various alkyl and aryl acetylenes to give the corresponding dihydro-1,4-dithiepins in high yields as summarized in Table 1. Since no by-product was found in the mixture, the product was readily obtained by simple distillation in high yield and purity. The reaction could provide a facile route to the cyclic *cis*-1,2-bis(alkylthio)ethenes, whose role in organic synthesis as masked acyl anion equivalents have not yet been fully developed.[12]



Scheme 2



Scheme 1 Mechanisms proposed for reductive acetylation of enzyme-bound lipoic acid by hydroxyethylidenethiamine diphosphate. Route 1: redox mechanism; Route 2: carbanion mechanism; E_2: dihydrolipoamide acetyltransferase (EC 2.3.1.12); HET: hydroxyethylidenethiamine diphosphate; Lip-E_2: Lipoic acid bound to E_2; TDP: thiamine diphosphate; Ac-TDP: acetyl TDP.

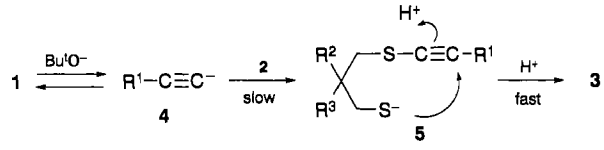
A catalytic amount of *tert*-butoxide was required for the reaction but excess methoxide, ethoxide and DBU were not effective. The yield of **3** was unaffected by the presence of oxygen (dry air) and hydroquinone, showing that no radical nor electron-transfer process is involved. The strain-assisted nature of the reaction was typically shown by the fact that the linear disulfide BuSSBu was completely unreactive under similar conditions. The polymerization-resistant nature[8] of the model dithiolanes **2** is also important, for highly polymerizable lipoic acid and lipoamide gave only unidentifiable polymeric materials under similar conditions.

The reaction mechanism shown in Scheme 3 involves the initial ring-opening of **2** by the acetylide **4** and the subsequent re-cyclization of the intermediate **5**. This was derived from the following evidence. (i) Deuterium in the starting acetylene PhCCD ([$^2H_1$]-**1a**) was lost much faster than the product **3a** was produced. (ii) The intermediate **5** was proved to be stable in an aprotic solvent THF as shown in Scheme 4: **5a** could be prepared *in situ* by reaction of **2a** with lithium phenylacetylide **4a**, and then trapped as a silyl sulfide **6**. (iii) Both the addition of MeOH to the THF solution of **5a** (**4a** plus **2a**) and the regeneration of **5a** in MeOH by the desilylation of **6** resulted in the rapid formation of **3a** (Scheme 4).

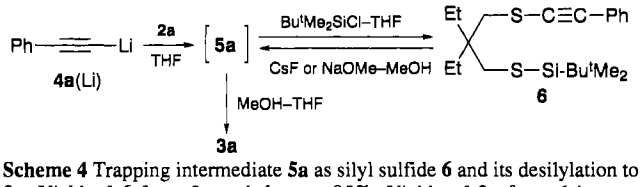
Table 1 Reaction of 1,2-dithiolanes **2** with acetylenes **1** in Bu^{t}OH[a]

R^1	R^2, R^3	R^1, R^2, R^3	Yield (%)
1a Ph	**2a** Et, Et	**3a** Ph, Et, Et	97
b H[b]	**a** Et, Et	**b** H, Et, Et	95
b H	**b** Et, Me	**c** H, Et, Me	96
b H	**c** $(CH_2)_5$	**d** H, $(CH_2)_5$	94
b H	**d** $(CH_2)_4$	**e** H, $(CH_2)_4$	92
c Et[b,c]	**a** Et, Et	**f** Et, Et, Et	93
d $MeOCH_2$ (MOM)	**c** $(CH_2)_5$	**g** MOM, $(CH_2)_5$	92
e C_5H_{11}[c]	**a** Et, Et	**h** C_5H_{11}, Et, Et	94

[a] Reaction described in Scheme 2. Conditions: $[1]_0$ = 0.3 mol dm^{-3}, $[2]_0$ = 0.4 mol dm^{-3}, $[Bu^tOK]_0$ = 0.1 mol dm^{-3}, Bu^{t}OH (10 ml) at room temp. for 1 d unless otherwise noted. [b] Excess gaseous alkynes **1b,c** were supplied from gas cylinder (1 atm). [c] Enforced conditions: $[Bu^tOK]_0$ = 0.2 mol dm^{-3}, reaction for 2 d.



Scheme 3 Mechanism proposed for formation of 1,4-dithiepine **3**



Scheme 4 Trapping intermediate **5a** as silyl sulfide **6** and its desilylation to **3a**. Yield of **6** from **2a** and **4a** was 95%. Yields of **3a** from **6** by two desilylations were quantitative.

These results show that a class of stable carbanions can cleave the S–S bond of 1,2-dithiolanes regardless of their method of generation or whether protic or aprotic solvents are used. This is the first observation that a stable carbanion cleaves the S–S bond of 1,2-dithiolane ring in a quantitative manner. Thus, Lip-E_2 is much more reactive to stable carbanions than previous studies suggested.[6] The reactivity is strain-accelerated and in line with the carbanion mechanism[3] proposed for the reductive acetylation of Lip-E_2.

It should not be overlooked that the S–S cleavage proceeds without electron transfer, which is essential to the alternative redox mechanism.[2] Acetylide, as a localized carbanion, is one of the most resistant to an electron transfer process, and the resistance of 1,2-dithiolane to one-electron reduction in the absence of transition metals have been well documented.[13] Thus the observed S–S cleavage by acetylide would be a normal S_N2 type reaction similar to the S–S cleavage of linear disulfides by stable carbanions[14] without any electron transfer or radical process. Thus, we can conclude that the 1,2-dithiolane ring of Lip-E_2 is cleaved by stable carbon nucleophiles even if any redox process is prohibited.

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