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COMMUNICATION

Simultaneous synthesis of thioesters and iron-sulfur clusters in water: two universal components of energy metabolism

Sebastian A. Sanden [a,b]*, Ruiqin Yi [a], Masahiko Hara [a,b] and Shawn E. McGlynn [a,c,d]*

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Thioesters are important intermediates in both synthetic organic, and biosynthetic reaction pathways. Here we show that thioesters can be synthesized in an aqueous reaction between thioacetic and thiols. The reaction can be coupled to a second reaction between sulfide and either ferrous or ferric iron, which drives the reaction forward. We furthermore demonstrate that sulfide released during thioester formation can be used in the synthesis of peptide bound [Fe-S] clusters, which like thioesters, are ancient components of metabolism. Together our results reveal a primordial linkage between high-energy ester formation and redox chemistry.

A key question of the emergence of life is to understand how prebiotically available molecules could have been assembled into self-replicating systems. Biology today replicates by coupling otherwise energetically unfavorable, endergonic reactions to energy yielding reactions, but how such an energy coupling scheme may have worked in the earliest life remains unclear. A large component of the energetic cost of cell replication is derived from polymerization reactions, where monomers must be activated so that dehydration can proceed in water.[1,2] These reactions are typically powered by the hydrolysis of phosphoesters such as adenosine triphosphate (ATP), which today are sustainably regenerated in the cell mainly through electron transfer processes in metabolism.[3] Thioesters are a frequently invoked alternative to ATP in abiotic processes: (i) Both have similar standard free energies of hydrolysis, making them exchangeable from an energetic perspective.[4] (ii) Since thioester formation often precedes phosphoester formation in metabolism, for example in glycolysis[5] and in the Wood–Ljungdahl pathway, [6] it is tempting to consider them as primordial, having operated before phosphoesters in metabolisms.[7] (iii) Recent computational studies employing network extension algorithms have indicated the possibility of a phosphate-free core metabolic network, where coupling of endergonic reactions to thioesters is sufficient for driving components of the reductive-TCA cycle, amino acid biosynthesis, and the hydroxypropionate bi-cycle.[8] An early thioester enabled metabolism may have been privileged compared to those using phosphoesters, due solubility issues of phosphates in the ferruginous Archean ocean.[9]

Several prebiotically relevant synthetic routes for thioesters have been reported, for example the synthesis of iminothioesters from malononitrile, which can subsequently hydrolyze producing a thioester, [10] thioester synthesis from acetaldehyde and a thiol via UV-irradiation[4], through the exergonic dehydration of glyceraldehyde[11], with carbonyldiimidazole as a condensing agent[12], and also from CO under hydrothermal conditions[13]. Thioacids are possible precursors to thioesters, and can be synthesized by thiolysis of nitriles in water, with subsequent hydrolysis of the produced thioamide,[14] or produced by the reaction of primary amines with carbonyl sulfide.[15] Thioacetic acid (TAA) in particular has been found to be an efficient acetylating agent for amino acids producing peptide bonds in the presence of an oxidant.[14,16] In addition to these synthetic reactions, thioacetate would also have likely had important roles in energy transfer reactions in a prebiotic metabolism: if thioesters could be produced from thioacetate in non-peptide forming reactions, they might be able to form a link between anabolic peptide forming reactions and catabolic energy harvesting reactions. However, information on direct thioester formation from thioacetate in aqueous solution is lacking.

In this work, thioacetate was investigated as a thiol-acylating agent, and the reaction yields and rates of thioacetate with two different thiols were surveyed at different pH. Promotion of the reaction by sequestering sulfide in iron sulfide was investigated, as was the utilization of liberated sulfide in the formation of peptide bound iron sulfur clusters. Thioester formation from thioacetate and a thiol could potentially occur with or without ferrous iron, and in an oxidative process in the presence of ferric iron (Scheme 1). [16,17] Given that the free energy of hydrolysis of thioacetic acid has been calculated to be -15.2 kJ mol^{-1} whereas thioester hydrolysis is generally more negative ($\Delta G^{0\prime}_{Hyd}$ = -35.3 kJ mol^{-1} for methyl-thioacetate), [18] we first considered if thiol-acetylation via thioacetic

[a] Earth Life Science Institute, Tokyo Institute of Technology
2-12-1 I7E Ookayama, Meguro, Tokyo 152-8550, Japan.
[b] School of Materials and Chemical Technology, Tokyo Institute of Technology
4259 G1-7 Nagatsuta, Midori-ku, Yokohama, Kanagawa 226-8502, Japan.
[c] Center for Sustainable Resource Science, RIKEN
2-1 Hirosawa. Wako, Saitama 351-0198, Japan.
[d] Blue Marble Space Institute of Science, Seattle, Washington 98154, United States
Email: mcglynn@elsi.jp, sanden@elsi.jp
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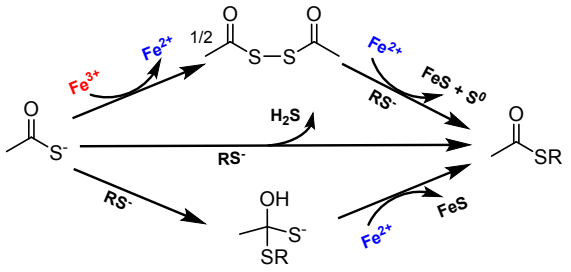
acid could be enhanced by coupling to a redox reaction with Fe^{3+} or with non-redox formation of iron(II) sulfide (ΔG^0 = -93.6 kJ mol^{-1}), [19] with sulfide originating from TAA as shown in Scheme 1. In such a way, low energy TAA could be converted into a high energy thioester, representing a possible route of prebiotic energy conservation between organic chemistry and mineral formation.



Scheme 1 Overview of the proposed reaction mechanisms of thioester synthesis from thioacetate in iron independent and iron dependent reactions. On the top, oxidation of thioacetate to diacetyldisulfide by Fe^{3+} precedes thioester formation, and is followed by formation of the thioester along with FeS and S^0 with hydrogen disulfide as the leaving group.[20] In the middle, the non-iron dependent reaction involves degassing of H_2S, and on the bottom, sulfide is sequestered through the formation of iron sulfide (FeS) with Fe^{2+}.

The reaction between TAA and a model thiol compound of mercaptoethanesulfonate (also known as Coenzyme M, CoM) at 70°C follows initially pseudo-zeroth order rate kinetics (Fig. 1). The addition of 5 mM Fe^{2+} does not alter the initial reaction rate significantly, but ferric iron (5 mM) increases the reaction rate by a factor of 3 at pH 5.5, and shows a 1.6-times faster reaction at pH 7.5. During separate experiments which ran for several days (Fig. S11, ESI), reactions with the addition of Fe^{3+} at pH 5.5 exhibited maximum thioester yields of 39% at 1.7 days, compared to 35% yield at 4.8 days with the addition of Fe^{2+} (the percent yields are given with respect to the starting thiol concentration, and are averages from duplicate experiments measured by UPLC, with ranges in % yield between duplicates given in Table S2, ESI). With no metal addition, the maximum yield observed was 29%. At pH 7.5, the highest thioester yields were 19% in the presence of 5 mM Fe^{3+} at 0.9 days, 13% with Fe^{2+} at 1.7 days, and 9% at 0.9 days with no added metal.

Triethylamine has been employed previously during the acetylation of alcohols and is expected to act as an auxiliary base.[21] With an altered experimental setup using lower concentrations of starting materials (Fig. 1c), we found that the addition of triethylamine accelerated the formation of thioesters with and without the addition of Fe^{2+}/Fe^{3+} (Fig. 1**c** and **d**).

Using a tertiary amine containing thiol (2-diethylamino)ethanethiol; Et_3NS) as the starting compound, a drastic increase in reaction rate was observed (Fig. 2), and the reaction characteristics varied between the two pH conditions investigated. The highest yields were observed at pH 5.5, the highest concentration of acetylated Et_3NS ($AcEt_3NS$) was measured after 1h reaction time (within the time frame of the experiment and analysis via UPLC) at both pH values in the case of $FeCl_3$ or no metal addition. At pH 5.5, the addition of Fe^{2+} changed the production curve markedly, and in the case of ferric iron or no addition, the hydrolysis of the thioester followed pseudo zeroth order kinetics within the first 10h. The hydrolysis of the thioester methyl-thioacetate was previously determined to follow a pseudo first order[18,22] but for $AcEt_3NS$ only the times series obtained with $FeCl_3$ at pH 7.5 showed a similar trend (Fig. 2b).

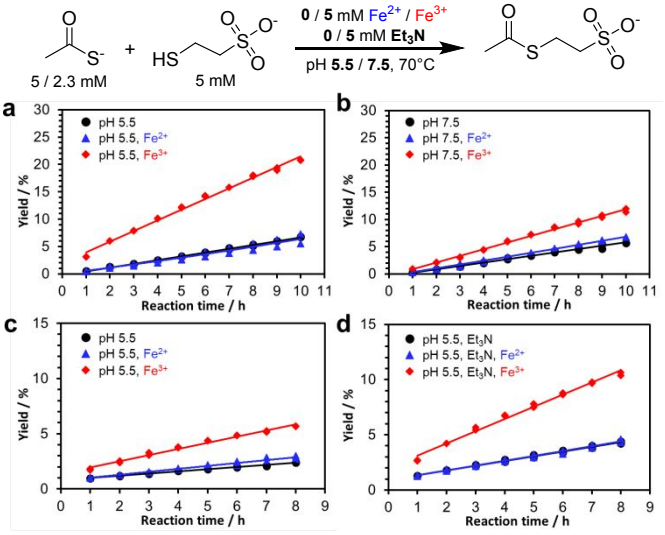


Figure 1 Time course measurement of the synthesized CoM thioester (AcCoM) from 5 mM thioacetate at 70°C expressed in percent yield in respect to 5 mM CoM as starting material (Panel **a** and **b**). Each time point for the respective experiment shows data from experimental duplicates and a regression with the least square fit. The red trace shows the reactions in which $FeCl_3$ was added, blue with $FeCl_2$ and black with no iron. Panel **c** and **d** had an initial concentration of 2.3 mM thioacetic acid and 5 mM of thiol and Fe^{2+}/Fe^{3+}. Panel **d** contained 5mM triethylamine in addition to the components in **c**. The y-axis scale is different for panels **c** and **d** where lower concentrations were used compared to **a** and **b**. Additional reaction rate measurements at lower TAA concentrations are given in Fig. S12, ESI.

In aqueous solution, thioester synthesis competes with the hydrolysis of both the starting compound TAA and the product thioester. An investigation of the hydrolysis rates of methyl-thioacetate at different pH found the highest stability of the thioester at pH 4,[22] which would favor a more acidic pH for a higher yield of acetylated CoM and Et_3NS (AcCoM and $AcEt_3NS$). In line with this, only traces of the expected thioester could be found in a 100 mM carbonate buffer at pH 10, suggesting rapid hydrolysis of any AcCoM produced.

At longer time periods, the concentration of AcCoM decreased only marginally at pH 5.5 over the course of five days compared to pH 7.5 where up to half of the thioester produced hydrolyzed (Fig. S11, ESI). At the lower pH, the reaction equilibrium is expected to shift towards thioester formation, due to the continuous removal of H_2S to the vapor phase (pKa = 7). This – in addition to differences in stability against hydrolysis – could account for the highest yields obtained for $AcEt_3NS$: in the absence of Fe^{2+}/Fe^{3+}, a threefold higher $AcEt_3NS$ concentration was measured at pH 5.5 (21% yield) than at pH 7.5 (6%) within the first hour of the experiment (Fig. 2a). For AcCoM, the highest yields are found at longer time intervals, and the highest average thioester concentration was also associated with the lower pH either with or without the addition of iron (Fig. S11, ESI). Importantly, heating a pH 5.5 acetate buffer with Et_3NS at 70°C did not yield any detectable thioester, indicating that acetate in solution did not lead to acetylation of the thiol.

Other than sulfide removal by degassing, the formation of FeS by reaction with ferrous iron provides another way to sequester sulfide and shift the reaction equilibrium towards the formation of thioesters. Using Et_3NS, a black iron sulfide precipitate is formed

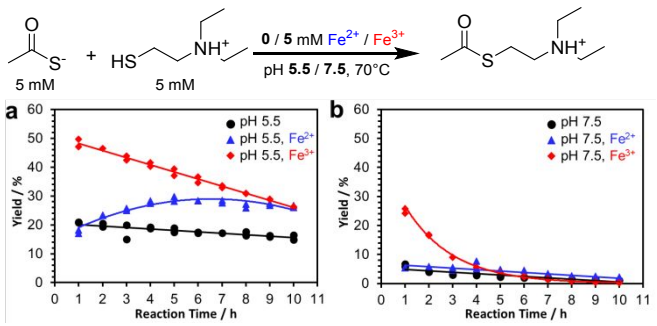
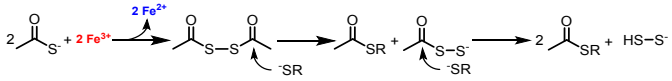


Figure 2 Time course measurement of the production of the $AcEt_3NS$ thioester at 70°C is displayed as % yield in respect to the initial amount of Et_3NS at pH 5.5 (**a**) and pH 7.5. (**b**) with 5mM Fe^{2+} (blue), Fe^{3+} (red) or no metal added (black). Duplicates were performed for each reaction and are shown at the time point.

within a few hours of reaction at 70°C when either Fe^{2+} or Fe^{3+} were in the reaction. At pH 5.5 and with the addition of $FeCl_2$, the highest yields of thioester increased by 9% and 5% for Et_3NS and AcCoM respectively (Fig. 2b, Fig. S11, ESI). At pH 7.5, a 4% yield increase of AcCoM was observed with the addition of $FeCl_2$, which at these lower yields with respect to the starting thiol corresponds to a 1.4-fold concentration increase in respect to the no metal addition (Fig. S11, ESI). However, at pH 7.5 thioester formation was insignificantly increased by $FeCl_2$ using the Et_3NS thiol. In the presence of ferric iron, the highest yield of $AcEt_3NS$ of 48% was obtained after 1h reaction at pH 5.5. Indeed, Fe^{3+} was associated with the maximum yields observed in all of the experiments (Fig. 1, Fig. 2, S11, S12). The enhancement of both reaction rate and yield with Fe^{3+} suggests that the oxidation of thioacetate is involved as previously reported in the case of amines and peptide bond formation[16,23] and depicted in Scheme 2 in the case of thiols.



Scheme 2 Proposed reactions scheme for oxidation of thioacetate by Fe^{3+} to diacetyldithiol and subsequent thioester formation. The leaving hydrogen persulfide likely reacts with Fe^{2+} produced in the reaction to form FeS and elemental sulfur as reported earlier.[20]

The energetic efficiency of thioester formation can be assessed by considering the reaction thermodynamics: Acetic anhydride, a commonly used compound for acetylation in organic synthesis,[24] has a standard free energy of hydrolysis of -65.9 kJ mol^{-1},[25] whereas thioacetate amounts to only -15.2 kJ mol^{-1}. [18] In the case of thioester formation from iminothioesters[10] and nitriles, the standard free energy of hydrolysis of acetonitrile and hydrogen cyanide to the corresponding amide is calculated to be -27.0 kJ mol^{-1} and -69.3 kJ mol^{-1} respectively.[26] With fair yields of thioesters obtained at mild conditions in water, thioacetate thus presents an energy efficient route for the acetylation of thiols. As the toxic sulfide produced during the acetylation by thioacetate can be sequestered away as FeS, this reaction scheme might be applicable to green chemistry due to its energy efficiency and the usage of water as the sole solvent.

Peptide bound [Fe-S] clusters have prominent and diverse roles in biological metabolism[27,28] and likely emerged early in metabolism bound by short peptides.[29,30] Understanding how [Fe-S] clusters may form in plausible prebiotic conditions requires research into the availability of thiols, ferric iron, and sulfide.[30] Since thioester formation from thioacetate involves the release of sulfide, we investigated peptide bound [Fe-S] cluster synthesis during thioester forming reactions.

Using a previously characterized peptide as a model [4Fe-4S] cluster binding sequence,[31] a reaction with Et_3NS, thioacetate, and $FeCl_3$ at 70°C produced an absorbance spectrum characteristic of [Fe-S] clusters (Fig. 3, Fig. S10). Absorbance features at ~384nm, and 447nm, which are characteristic of the ligand to metal charge transfer bands in iron-sulfur clusters,[32] bleached with the addition of dithionite, demonstrating redox activity (Fig. S10, ESI). Water soluble thiols such as 2-mercaptoethanol can serve as ligands for [4Fe4S] clusters produced from $FeCl_3$ and Na_2S,[33] but while working on a similar timescale as with the peptide, no appreciable amount of [FeS] clusters were self-assembled from reactions that lacked the peptide (Fig. 3). Instead, in the absence of the peptide an increase in absorbance across the spectrum after 6.5h was observed, likely resulting from FeS nanoparticle derived turbidity[34] followed by precipitation by 15h (Fig. S10, ESI).

After 6.5h, the measured yield of $AcEt_3NS$ was 1.2% compared to 2.3% under the same reaction conditions but without the addition of the peptide. Thioacetate can thus serve as a source of both thioesters and sulfide in [Fe-S] cluster formation. Besides the prebiotic implications of this, molecular release of sulfide from thioacetate may be of use in laboratory chemical reconstitution schemes, where sulfide is usually added slowly in a dropwise manner.[35]

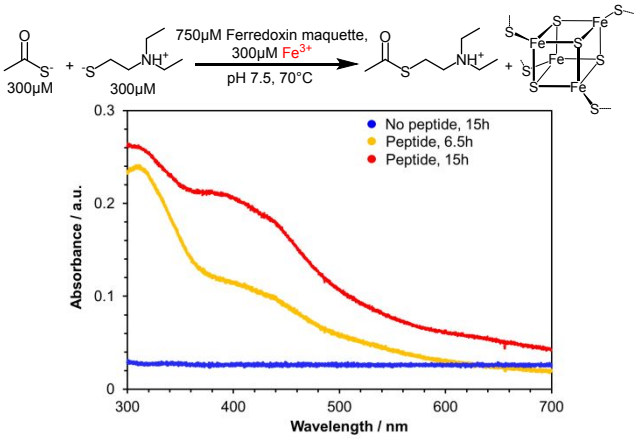


Figure 3 UV-Vis spectrum of the reaction of 300 µM Et_3NS, thioacetate and $FeCl_3$ in the presence of 750 µM Ferredoxin peptide maquette at 70°C after 6.5h (yellow), after 15h (red) and without the maquette after 15h (blue).

Iron sulfur derivatives have featured prominently in origins of life research[36,37] and both synthetic [Fe-S] clusters and iron sulfide minerals have been shown experimentally to facilitate CO_2 reduction. Reductive carboxylations and amino acid synthesis have been performed with synthetic [Fe-S] clusters[38] and pyruvate has been synthesized from CO_2 on a greigite (Fe_3S_4) working electrode[39] and in reactions involving metallic iron and also iron minerals and hydrogen.[40,41] With the availability of pyruvate for prebiotic chemistry assured, a synergistic process between thioesters and Fe-S clusters can be conceived regarding the work presented here. The enzyme pyruvate ferredoxin-oxidoreductase (PFOR) catalyzes the synthesis of the thioester acetyl-coenzyme A (CoA) from pyruvate via oxidative decarboxylation and uses [4Fe-4S] clusters as electron

mediators.[6] If the acetylation of a thiol by thioacetate and the concomitant formation of [4Fe-4S] clusters were to be connected to the reconstitution of a proto-PFOR, a catalytic feedback could be envisioned, in which continued thioester formation could now be synthesized from both thioacetate and prebiotically available pyruvate. Thus, thioacetate and abiotically produced pyruvate could work synergistically to produce high energy thioesters through two different reactions in an early metabolism.

PFOR, [Fe-S] clusters, and thioesters adopt a central position in the metabolism of bacteria and archaea, connecting the Wood-Ljungdahl (WL) CO_2 fixation pathway with the tricarboxylic acid cycle.[42] The WL pathway itself is thought to be the most ancient autotrophic pathway,[43] and in concert with a complete rTCA cycle as is found in *Thermovibrio Ammonificans,*[44] a hybrid WL-rTCA pathway may have been a robust primordial metabolism due to redundancy in the formation of thioesters as a central metabolite.[45]

The formation of both thioesters and soluble [FeS] clusters from thioacetate thus presents an intriguing prebiotic entry point into both the WL Pathway and the rTCA cycle. Thioester formation with TAA as the acetylating agent and Fe^{3+} as an oxidant is reminiscent of oxidative thioesterification reactions in metabolism, such as that in glycolysis and in the decarboxylation of alpha-keto acids. The biological finding of an ancient thioester driven core metabolism[8] enriched in coenzymes that utilize [Fe-S] clusters as catalytic centers, points towards thioacetate being a possible substrate for a metabolic network that also generates both, the necessary catalysts and redox mediators.

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Conflicts of interest

There are no conflicts to declare.

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Simultaneous synthesis of thioesters and iron-sulfur clusters in water: two universal components of energy metabolism

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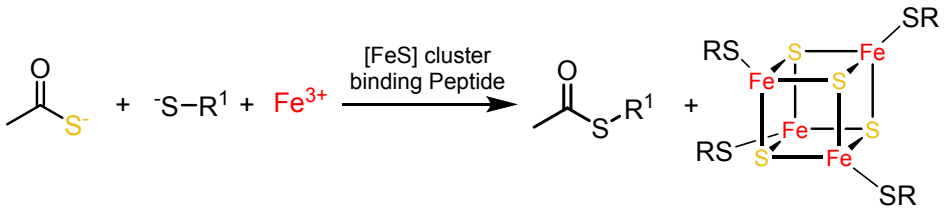

Thioesters and peptide ligated [Fe-S] clusters can be synthesized simultaneously from thioacetic acid in an aqueous one-pot reaction.