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SHORT COMMUNICATION

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Theoretical Study, Synthesis, and Reactivity of Five-Membered-Ring Acyl Sulfonium Cations

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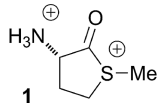
The feasibility of the cyclization of γ-alkylthiobutyric acid derivatives to form previously unknown five-membered-ring acyl sulfonium cations was studied. Experimental results were in good agreement with our DFT calculations that predicted such cyclizations to be easy if starting with acyl iodides and mixed anhydrides of triflic acid. Particularly efficient were the reactions of γ-alkylthiobutyryl fluorides with trimethylsilyl triflate in $CDCl_3$ solution, which led to cyclic acyl sulfonium triflates. In some cases, the observed acyl sulfonium salts were stable enough to be characterized by NMR spectroscopy. They were found to be both alkyl-transfer reagents and acylating agents. They react with amines to form amides. These findings lend some weight to our hypothesis that the acyl sulfonium derived from methionine may have played a major role in the prebiotic synthesis of the first peptides on the primitive Earth.

Introduction

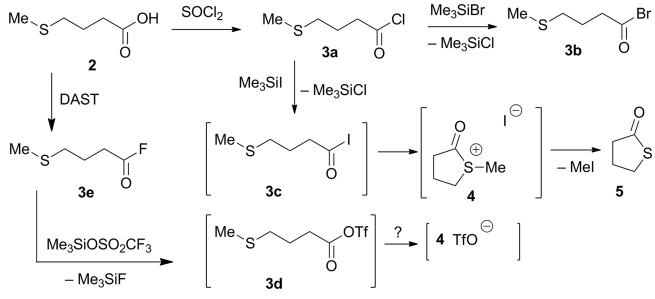
In 1993, Jakubowski[1] reported that cyclic acyl sulfonium compound **1** was formed from methionine during tRNA aminoacylation catalyzed by *E. coli* methionyl tRNA synthetase (editing process). He stated that **1** was stable in acidic water and proposed that it could have been a possible methyl donor in the primitive ocean at a time when *S*-adenosyl-methionine and folate cycles did not exist, and thus it may have played an important prebiotic role. However, the pieces of evidence presented in support of the existence of **1** were rather weak and consisted of TLC spots and the argument that the compound producing these spots reversed to methionine after basic hydrolysis. No spectroscopic data of **1** were presented, and from an organic chemist point of view, the realness of such an acyl sulfonium cation could be regarded as questionable.



1

In fact, acyl sulfoniums are poorly known compounds, and most of those that have already been described or proposed as intermediates are very reactive. In 1963, the intermediacy of a five-membered cyclic acyl sulfonium was postulated by Truce and Abraham[2] to explain the formation of a thiolactone upon heating 4-alkylthiobutyryl chlorides (i.e., the transient acyl sulfoniums were found to be readily dealkylated). In 1977, Minato et al.[3] reported that the *S*-alkylation of an aromatic thiol ester gave a sulfonium cation that was detected by ^1H NMR spectroscopy. Later, very reactive three- and four-membered cyclic acyl sulfoniums, observable only at low temperature, were described by Lebedev et al.[4] In 2005, Kozhevnikov et al.[5] reported the isolation of two stable solid acyl sulfonium chlorides, the stability of which was probably due to the bulky aromatic groups surrounding their sulfonium function.

We were thus intrigued by the possible existence of compound **1**. Had it existed in the primitive ocean, it could have played a role not only as a methyl donor (as proposed by Jakubowsky[1]) but also as an activated amino acid, able to react with other amino acids to give dipeptides, in the absence of any catalyst.[6–8]



Scheme 1. Synthesis and cyclization of acyl halides derived from acid **2**. DAST = diethylaminosulfur trifluoride, TfO = CF_3SO_3.

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To demonstrate that five-membered-ring acyl sulfonium cations can be stable species, we study herein the synthesis of simple analogues of **1**, for example **4**, and demonstrate that they can be both alkylating and acylating reagents (Scheme 1).

Results and Discussion

Our DFT calculations (see Table 1, Figure 1, and the Supporting information) predicted that acyl chloride **3a** and bromide **3b** should not undergo cyclization (in solution at room temperature). In contrast, we expected iodide **3c** to cyclize readily to form the iodide salt of sulfonium **4**. However, in this case easy dealkylation of **4** was predicted, and the probable final products would then be methyl iodide and thiolactone **5**. Cyclization was also anticipated to be easy and quick with mixed anhydride **3d** as the starting material. Furthermore, the stabilities of **4**-triflate and **5** + MeOTf were predicted to be similar. As the activation energy for this last transformation was calculated to be quite high, we anticipated that the triflate salt of **4** could be stable.

These predictions were confirmed by our synthesis of compounds **3a**–**d** from acid **2**.[9] As expected, **3a** and **3b** were found to be stable compounds, but iodide **3c** (^{13}C NMR: C=O at δ = 161.7 ppm), observed after treatment of **3a** with TMSI (a method known to yield acyl iodides from chlorides[11]), was unstable at room temperature in $CDCl_3$ solution and was transformed into methyl iodide (^{13}C NMR: δ = –22.5 ppm) and thiolactone **5**.[12]

However, even if we did not observe any trace amount of MeOTf, we were unable to identify **4** as a product of the reaction of fluoride **3e**, obtained by the reaction of the corresponding acid with DAST,[13] with Me_3SiOTf (even though the formation of Me_3SiF was clearly demonstrated by ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopy).[14] In place of the singlet at about δ = 3.15 ppm[3] expected for sulfonium **4**, we observed a signal at δ = 2.94 ppm, not compatible with structure **4**, but rather with a trialkylated sulfonium species that we were unable to identify [$Me_2S^+(CH_2)_3C(O)X$?] but probably indicating migration of the methyl group of **4** onto a sulfide. Similar migrations will be presented later in this communication.

Table 1. Standard free-energy change (ΔG) and activation energy ($\Delta G^{\ddagger}$) for cyclization and demethylation reactions.

Reaction	ΔG[a] [kcal mol^{-1}]	$\Delta G^{\ddagger}$[a] [kcal mol^{-1}]
3a → **4**-Cl$^-$	5.5	12.9
3b → **4**-Br$^-$	2.7	10.9
3c → **4**-I$^-$	–0.1	10.2
3d → **4**-TfO$^-$	–9.6	9.7
4-I$^-$ → **5** + MeI	–14.4	16.7
4-TfO$^-$ → **5** + MeOTf	–0.3	30.1

[a] Solvent (continuum): acetonitrile (ε = 35.688).[10]

As **4** was not observed, we envisaged to replace the methyl substituent of **2** by bigger groups (Scheme 2). Treatment of fluoride **6** with Me_3SiOTf[15] resulted in the formation of a new species. At room temperature, its ^{1}H NMR spectrum consists mainly of a series of broad signals, but at –20 °C, the spectrum is clearer and indicates the presence of a stereogenic sulfur atom.

Both the chemical shifts and the splitting of the observed signals are in agreement with structure **7** (Figure 2, a), accompanied with some thiolactone **5**. In the ^{13}C NMR spec-

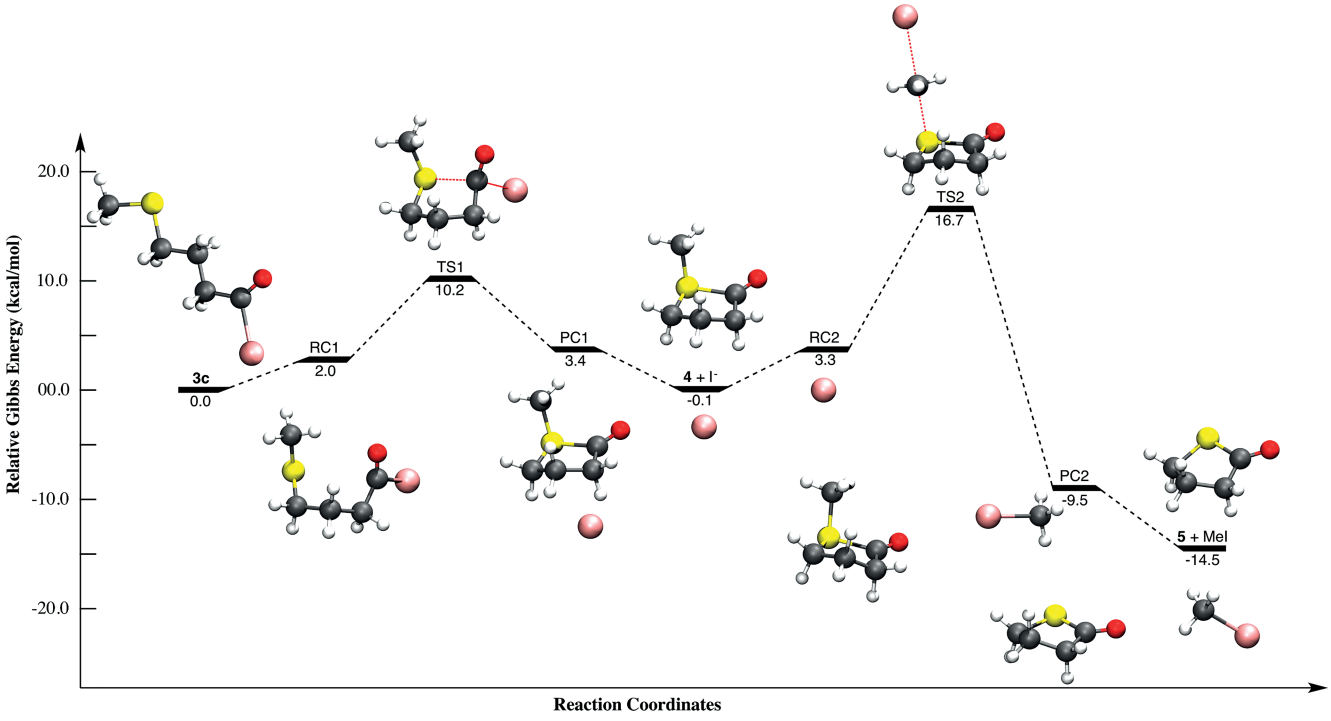
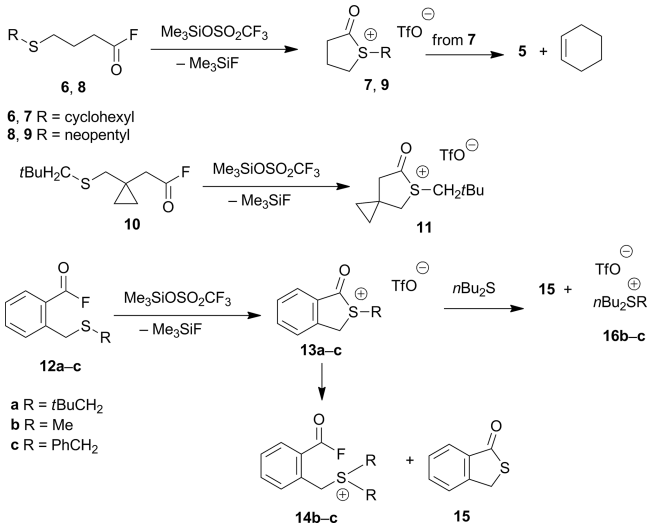


Figure 1. Energy diagram for the reaction pathway from **3c** to **5** (cyclization and demethylation).



Scheme 2. Synthesis and evolution of acyl sulfonium cations.

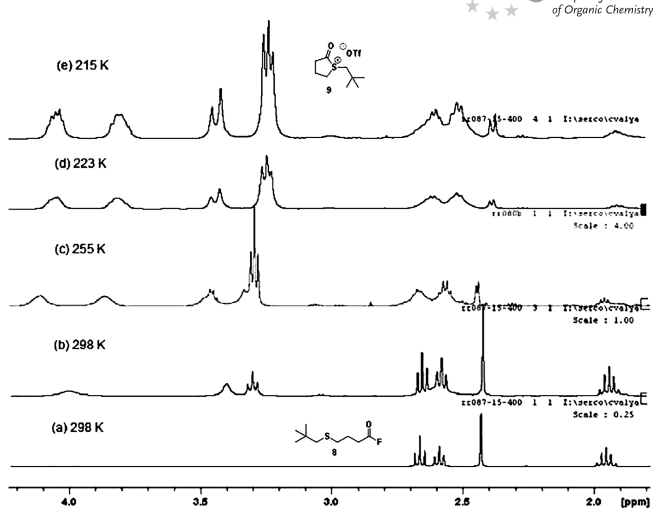


Figure 3. ^{1}H NMR spectroscopy study of the formation of **9** from **8** with time and at various temperatures: (a) **8**; (b) just after the addition of TMSOTf; (c) at 255 K after 1 h; (d) at 223 K; (e) at 215 K.

trum, the C=O carbon atom is observed at δ = 187.1 ppm. However, **7** has only a half-life of about 2 h at room temperature, and it is cleaved into **5** and cyclohexene.[16] Under similar conditions, from **8**, chosen because in this case no β-elimination would be possible from the expected sulfonium cation, a new species for which we assumed structure **9** was obtained. Even though its ^{1}H NMR spectrum is not completely resolved, even at low temperature, chemical shifts and observable splitting patterns (Figure 3) added to the signals observed in its ^{13}C NMR spectrum (C=O at δ = 187.6 ppm) made us confident that the main species in solution was **9**. This was further ascertained by the synthesis of spiro derivative **11** from **10**.[17] Here, the structure is rigidified, and the lack of a β-CH_2 moiety simplifies the spectrum. Even though some impurities were present, the three AB systems expected for **11** are clearly observed at –20 °C (Figure 2, b). Compounds **9** and **11** are stable at least for days in $CDCl_3$ solution at room temperature.

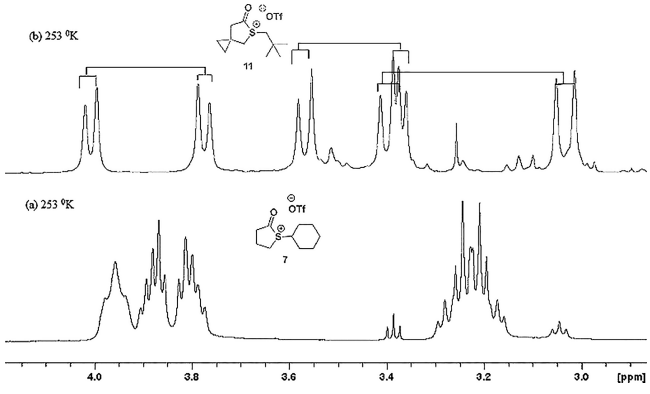
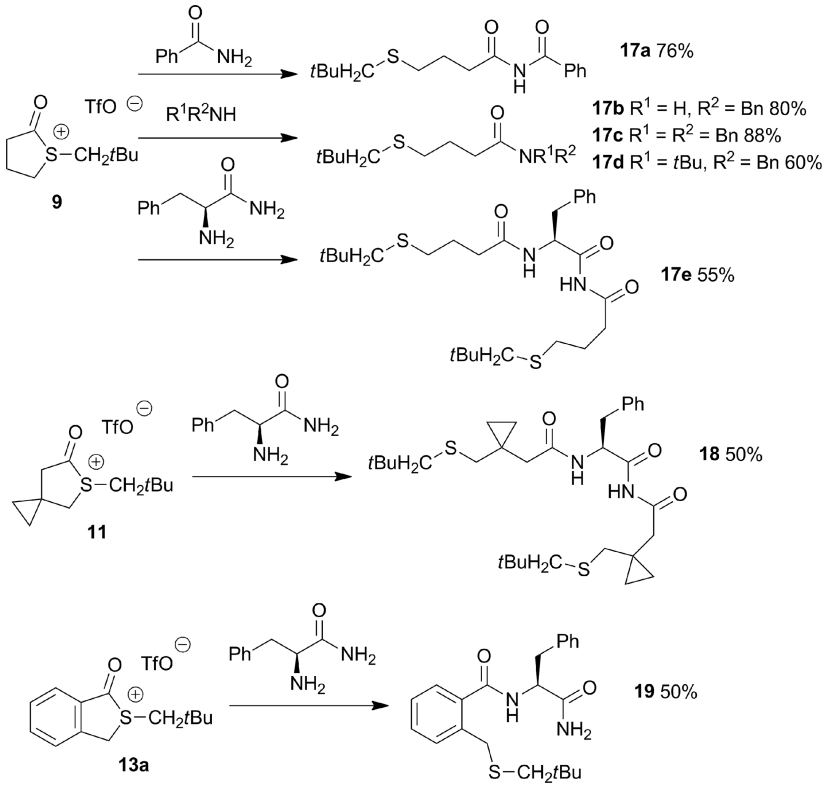


Figure 2. ^{1}H NMR spectra of **7** and **11** at 253 K.

Further evidence for the existence of stable cyclic acyl sulfonium cations was obtained with aromatic analogues of **4**. Thus, **13a** was found to be stable in $CDCl_3$ solution. Even methyl derivative **13b** was clearly obtained (^{1}H NMR: SMe at δ = 3.15 ppm). However, it was accompanied by two other products that we identified as thiolactone **15**[18] and sulfonium **14b** (^{13}C NMR: C=O at δ = 156.4 ppm, ^{19}F NMR: δ = 27.0 ppm; ^{1}H NMR: SMe_2 at δ = 3.07 ppm, CH_2S at δ = 5.05 ppm). The final ratio (reached after 5 h at room temp.) of **13b** and **15** was found to be about 1:1. This is an unambiguous example of a cyclic acyl sulfonium cation acting as a methyl donor. Another example of this behavior was observed if the reaction was run in the presence of dibutyl sulfide. In this case, **15** and **16b**[19] were obtained in a nearly 1:1 ratio (a trace amount of **14b** was also present).

Similar results were obtained from **12c**. However, benzyl migration was quicker than the previous methyl migration. Thus, **13c** was not observed, and **14c** and **15** were obtained in a 1:1 ratio. If dibutyl sulfide was present in the reaction mixture, **15** and **16c**[20] were the major products (≈1:1 ratio, with some amount of **14c**).

Having demonstrated that acyl sulfonium cations are alkyl-transfer reagents, we tested their ability also to be acylating reagents. Indeed, the LUMO that we calculated for **4** (Figure 4) had its biggest coefficient on the carbon atom of the carbonyl group ring, a strong argument in favor of easy ring-opening reactions by nucleophilic species. Representative results with amines and amides are presented in Scheme 3.[21] Alicyclic sulfonium cations were found to react with both types of nucleophiles, but aromatic cation **13a** was less reactive and reacted only with the amino group of phenylalanine amide. These results confirm our prediction and assumption that if methionine derivative **1** was present on the early Earth, it could not only be a methyl donor but also a good starting material for the synthesis of dipeptides. However, the stability of **1** in water is still far from certain.[6]



Scheme 3. Reactions of stable acyl sulfonium triflates with amines and amides.

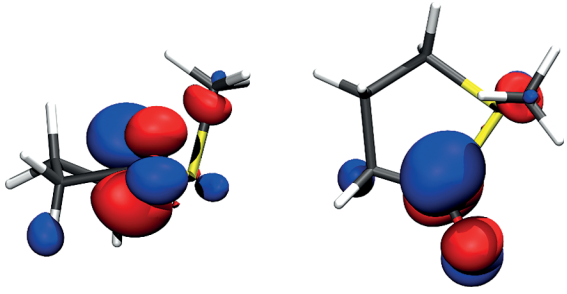


Figure 4. Calculated LUMO for cation **4**. (Left) Side view; (right) top view.

Acknowledgments

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complexes energies were similar to those calculated with acetonitrile (within 5 kcal mol^{-1}). However, separated charged species (**4**, Cl^-, Br^-, I^-, and TfO^- at an infinite distance) were poorly described in implicit $CHCl_3$, because the scheme is mostly a function of the dielectric constant of the solvent, ε. Calculations in acetonitrile were kept for their accuracy.
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[17] Compound **10** was obtained in two steps from commercially available 1-(mercaptomethyl)cyclopropaneacetic acid: (1) alkylation of thiol with neopentyltriflate, (2) fluorination with DAST.
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[21] Crystals of **17a** were obtained after recrystallization from ethanol. CCDC-1055644 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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