

Stability of Terpenoid-Derived Secondary Ozonides in Aqueous Organic Media

Published as part of *The Journal of Physical Chemistry virtual special issue "Advances in Atmospheric Chemical and Physical Processes"*.

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Cite This: *J. Phys. Chem. A* 2022, 126, 5386–5397



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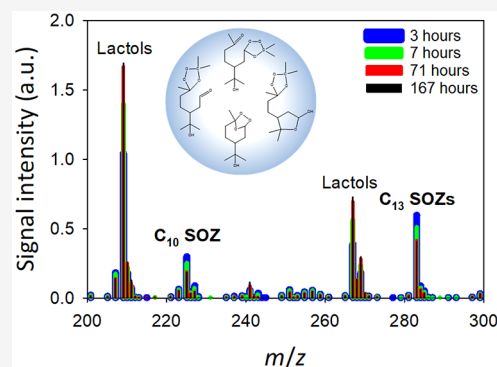


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ABSTRACT: 1,2,4-Trioxolanes, known as secondary ozonides (SOZs), are key products of ozonolysis of biogenic terpenoids. Functionalized terpenoid-derived SOZs are readily taken up into atmospheric aerosols; however, their condensed-phase fates remain unknown. Here, we report the results of a time-dependent mass spectrometric investigation into the liquid-phase fates of C_{10} and C_{13} SOZs synthesized by ozonolysis of a C_{10} monoterpene alcohol (α -terpineol) in water:acetone (1:1 = vol:vol) mixtures. Isomerization of Criegee intermediates and bimolecular reaction of Criegee intermediates with acetone produced C_{10} and C_{13} SOZs, respectively, which were detected as their Na^+ -adducts by positive-ion electrospray mass spectrometry. Use of CD_3COCD_3 , D_2O , and $H_2^{18}O$ solvents enabled identification of three types of C_{13} SOZs (aldehyde, ketone, and lactol) and other products. These SOZs were surprisingly stable in water:acetone (1:1) mixtures at $T = 298$ K, with some persisting for at least a week. Theoretical calculations supported the high stability of the lactol-type C_{13} SOZ formed from the aldehyde-type C_{13} SOZ via intramolecular rearrangement. The present results suggest that terpenoid-derived SOZs can persist in atmospheric condensed phases, potentially until they are delivered to the epithelial lining fluid of the pulmonary alveoli via inhaled particulate matter, where they may exert hitherto unrecognized adverse health effects.



INTRODUCTION

Ozonolysis is a major oxidation process in the atmosphere. Volatile organic compounds possessing one or more carbon–carbon double bond(s) ($C=C$) in their structures readily undergo reaction with ozone to produce a variety of oxygenated products.¹ These reactions are mediated by carbonyl oxides known as Criegee intermediates (CIs), which can undergo intramolecular rearrangement to form 1,2,4-trioxolanes, known as secondary ozonides (SOZs). Bimolecular reaction of CIs with carbonyl species such as formaldehyde and acetone can also produce SOZs.^{1–4} The formation of SOZs occurs not only in the gas phase but also in bulk liquid phases⁵ and at gas–liquid/solid interfaces.^{6–8} SOZs are categorized as both organic peroxides and reactive oxygen species.⁹ Because of their ubiquity, SOZs are deemed to play key roles in atmospheric, environmental, and biological chemistry.¹⁰

The fates and roles of SOZs in the atmosphere are poorly understood.¹¹ The thermal decomposition of SOZs in the gas phase is negligibly slow. For example, the SOZ derived from propene ozonolysis undergoes unimolecular decomposition with a rate coefficient (k) of approximately $4 \times 10^{-8} \text{ s}^{-1}$ at 295 K in the gas phase.¹² Theoretical calculations have predicted

that the reactions between C_2 SOZ and water molecules leading to the production of $2HCHO + H_2O_2$ are endothermic and endergonic.¹³ Therefore, the fate of SOZs in the atmosphere should depend on their reaction with OH radicals or their uptake into atmospheric condensed phases such as aerosol particles, fogs, and cloud droplets. The latter process is expected to occur especially for large, functionalized, and hence low-volatility terpenoid-derived SOZs.

The lifetimes and fates of SOZs in condensed phases depend on the structure, solvent, and temperature.^{9,14–16} A previous study has revealed that neat SOZs derived from ozonolysis of β -pinene were stable for months when kept at 243 K, whereas they decomposed within 24 h when kept in $CDCl_3$ at room temperature, and within 30 h when kept in C_6D_6 at 313 K.⁵ The decomposition of the SOZs in these organic solutions produced a mixture of nopinone (C_9 ketone) and formic acid.⁵

Received: June 13, 2022

Revised: July 19, 2022

Published: August 3, 2022



Other studies have suggested that thermal decomposition of neat SOZs derived from ozonolysis of 1-alkenes occurs only at ≥ 379 K.¹⁷ From a study of multiphase reactions under dry vs wet conditions, Heine et al. reported that the hydrolysis of SOZs produced from ozonolysis of squalene was not a fast process.¹⁸ Since the lifetimes of organic hydroperoxides derived from terpenoid CIs are dramatically shortened by the presence of water,^{19–21} one may expect that the lifetimes and fates of SOZs also differ in neat organic vs aqueous solutions. This is important because the fates of SOZs likely influence the oxidative and toxicological potentials of atmospheric particles.

Elucidation of the fates of SOZs in condensed phases is important for understanding the adverse health effects of air pollutants. If SOZs can survive sufficiently long in atmospheric aerosol particles, inhalation of these particles would deliver the SOZs to the airways, where they can perturb the redox balance of the epithelial lining fluid, and cause adverse health effects. Furthermore, inhalation of gaseous ozone may transform aqueous ascorbic acid, uric acid, and α -tocopherol, essential antioxidants possessing C=C bonds, into potentially harmful SOZs and other reactive oxygenated species.^{6,22,23} Recent experimental studies demonstrated that SOZs can be formed not only during ozonolysis but also OH reactions of lipid molecules.^{24,25} On the other hand, artificially synthesized SOZs are recently being explored as promising antiparasitic drugs due to their functional similarity to artemisinin, a plant-derived antimalarial chemical compound possessing an endoperoxide moiety.²⁶ Therefore, elucidation of the fate of SOZs in condensed phases will be important not only for the field of atmospheric chemistry but also for various biological applications.

Here, we report the first results of a time-dependent mass spectrometric investigation of the liquid-phase fates of functionalized C₁₀ and C₁₃ SOZs synthesized by ozonolysis of a C₁₀ cyclic terpene-alcohol (α -terpineol; α -Tp) in water:acetone mixtures. These mixtures were used as surrogates of environmental aqueous organic aerosols. Isomerization and reaction of CIs with acetone produced a C₁₀ SOZ and C₁₃ SOZs, respectively, that were directly detected as their Na⁺-adducts by positive-ion electrospray mass spectrometry. These α -Tp-derived SOZs were unexpectedly stable, and specific isomers survived for more than a week. In addition, the present results suggest that persistent SOZs in aerosol particles may be delivered to the epithelial lining fluid of the pulmonary alveoli, resulting in hitherto unrecognized adverse health effects.

EXPERIMENTAL SECTION

Mass Spectrometry. The experimental setup and procedure used in this study were similar to those reported previously.^{19,20,27} The key feature of the present experiment is that we utilized positive-ion mass spectrometry to detect the generated SOZs. α -Tp (2 mM) and NaCl (0.4 mM) were dissolved in 10 mL of neat acetone in a 25 mL glass vial (Figure S1). Separately, aqueous O₃ solutions were prepared by sparging water (10 mL) in a 25 mL vial for 20 s with O₃(g) generated by means of a commercial ozonizer (KSQ-050, Kotohira, Japan) fed with ultrahigh-purity O₂(g) (>99.999%). The initial O₃ concentration in the solutions, [O₃]₀, was 0.06 \pm 0.01 mM, as determined with a UV-vis spectrometer (Agilent 8453) using the reported O₃ molar extinction coefficient at 258 nm of 3840 M⁻¹ cm⁻¹ in water.²⁸

Ozonolysis reactions were initiated by mixing the acetone solution of α -Tp and NaCl and the aqueous O₃ solution (10 mL each) in a 25 mL glass vial in a Peltier-type circulating water bath (AS ONE corporation, CTB-1) kept at 298 \pm 1.0 K (Figure S1). In the water:acetone (1:1 = vol:vol) solutions, the concentrations of water and acetone were 27.8 and 6.8 M, respectively. The [α -Tp]₀/[O₃(aq)]₀ ratio was maintained above 17 to avoid unwanted secondary reactions; under these conditions, O₃ was consumed exclusively by α -Tp ([α -Tp]₀ = 1 mM, $k = 9.9 \times 10^6$ M⁻¹ s⁻¹) with a lifetime ($\tau_{1/e}$) of around 0.1 ms.²⁹ The reaction of acetone with O₃ in the aqueous phase is too slow ($k = 0.032$ M⁻¹ s⁻¹)³⁰ to influence the fates of SOZs and other products. Given that the gas-phase rate constant for CH₂O₂ + acetone is 4 $\times 10^{-13}$ cm³ molecule⁻¹ s⁻¹ (at 298 K) and the value is applicable to the liquid-phase value for the reaction of α -Tp CIs + acetone,^{1,10} the reaction of α -Tp CIs with acetone should have occurred within 1 ns under the present conditions. Note that the concentrations of the SOZs and reaction products were always less than [O₃]₀ (=0.06 mM).

Next, a glass syringe (5 mL, Agilent, covered with aluminum foil to avoid photodegradation) and a syringe pump (Pump 11 Elite, Harvard Apparatus) were used to immediately inject the reaction mixture (100 μ L min⁻¹) into an electrospray mass spectrometer (Agilent 6130 Quadrupole LC/MS Electrospray System housed at the National Institute for Environmental Studies, Japan). We started measuring the mass spectra of the solution at approximately 5 min after the start of ozonolysis. For longer-term measurements (>24 h), the solutions in vials were kept in the dark at room temperature (298 \pm 3 K).

Online positive-ion electrospray mass spectrometry of solutions containing submillimolar amounts of NaCl was used to detect sodium cation (Na⁺) adducts of the SOZs and other products such as lactols.^{31,32} The temporal profiles of the ion signals for the Na⁺ adducts of the SOZs and other products were determined with the electrospray mass spectrometer and a digital stopwatch. The following conditions were used for the electrospray mass spectrometer: dry nitrogen gas flow rate, 12 L min⁻¹; dry nitrogen gas temperature, 340 $^{\circ}$ C; inlet voltage, -3.5 kV relative to ground; fragmentor voltage, 60 V. All solutions were prepared in purified water (resistivity ≥ 18.2 M Ω -cm at 298 K) prepared with a Milli-Q water purification system (Merck, Direct-Q 3UV).

The following chemicals were used as received: α -terpineol (>95%, Tokyo Chemical Industry), acetone ($\geq 99.5\%$, Wako), acetone-d₆ (CD₃COCD₃, 99.9 atom % D, Sigma-Aldrich), D₂O (99.9 atom % D, Sigma-Aldrich), H₂¹⁸O ($\geq 97\%$, Cambridge Isotope Laboratories), and NaCl ($\geq 99.999\%$, Sigma-Aldrich).

Theoretical Calculations. Quantum chemical calculations were performed within the Gaussian 16 (rev C.01) program.³³ The geometries of the reactants, products, and transition states were optimized at the M06-2X³⁴/6-311++G(d,p)/SCRF = (SMD, solvent = water) level of theory. Transition states were extensively searched for, and if found, an intrinsic reaction coordinate calculation was conducted. The energies of the corresponding molecules were evaluated using a CBS-QB3³⁵ method. In the CBS-QB3//M06-2X method used herein, the potential energies and other thermochemical data obtained were corrected for by using frequency analysis results calculated at the M06-2X/6-311++G(d,p) level with zero point energy and frequency scaling factors of 0.970 and 0.943, respectively, determined by using the method reported by

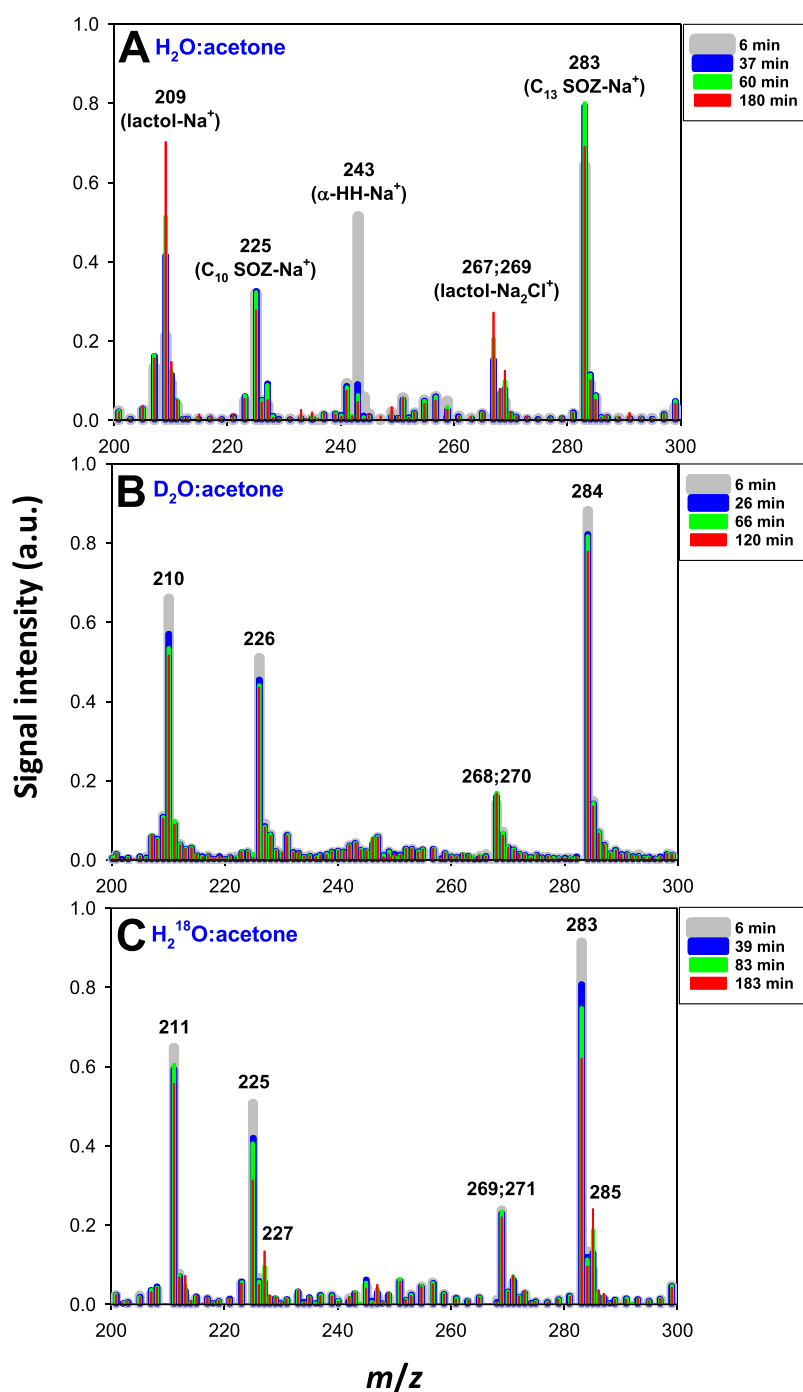


Figure 1. Time-dependent positive-ion mass spectra of 1 mM α -terpineol + 0.2 mM NaCl + 0.06 mM O₃ in H₂O:acetone (A), D₂O:acetone (B), or H₂¹⁸O:acetone (C) (all 1:1 = vol:vol). Background spectra obtained in the absence of O₃ were subtracted.

Alecu et al.³⁶ Solvent effects were included by application of the self-consistent reaction field with the integral-equation-formalism polarizable continuum model and the solvation model based on density³⁷ options within the Gaussian 16 rev C program when investigating aqueous reactions.

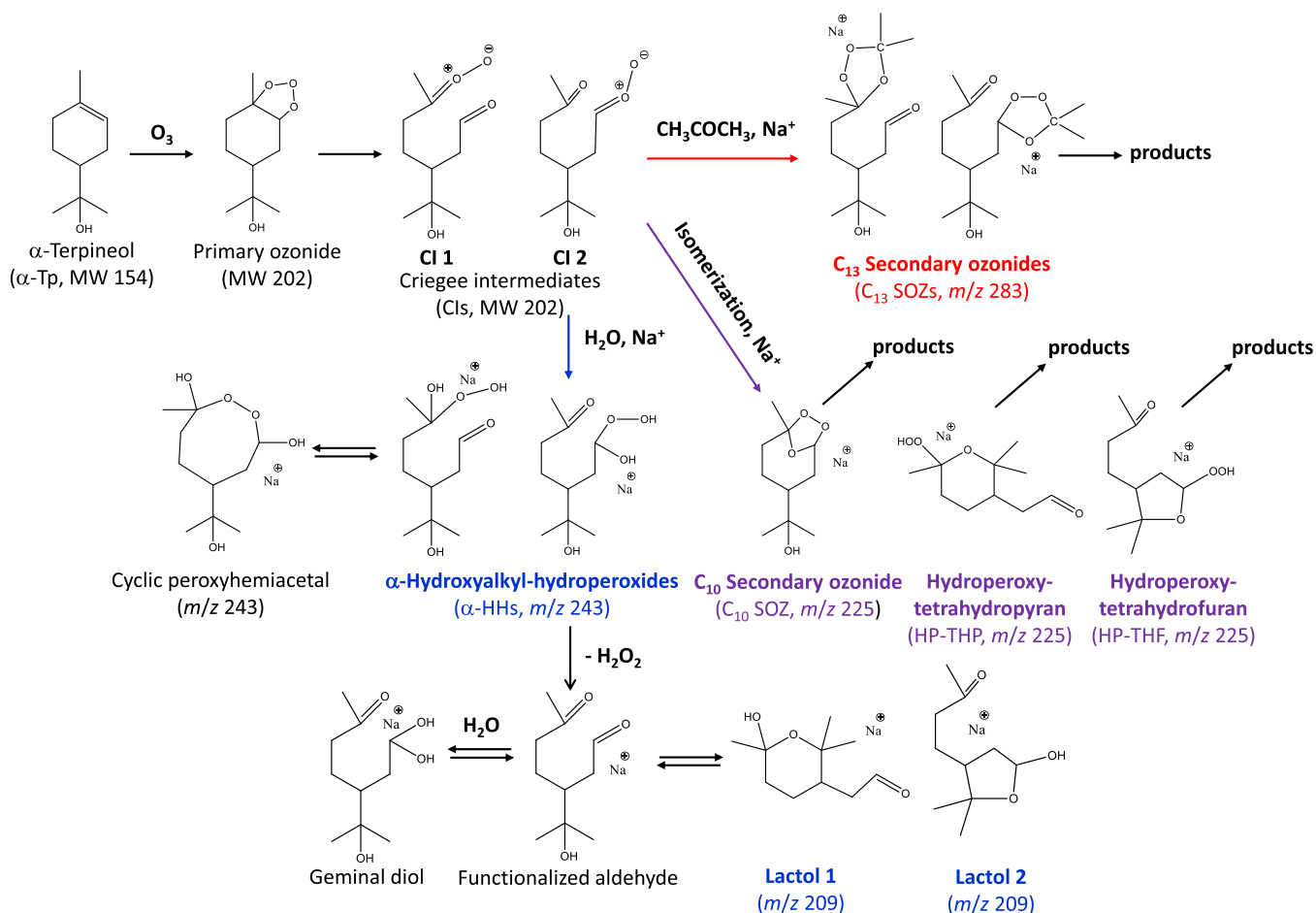
The rate coefficient (k_{TST}) for the generic reaction $A + B \rightarrow P$ (products in solution) can be calculated based on traditional transition state theory (TST) using the following formula:

$$k_{\text{TST}} = \frac{k_{\text{B}} T Q_{\text{TS}}}{h \Pi Q_{\text{react}}} \exp\left(-\frac{\Delta E_0}{k_{\text{B}} T}\right) \quad (1)$$

where k_{B} is the Boltzmann constant, T is the temperature, h is Planck's constant, Q_i is the partition function of the reactant and transition state, and ΔE_0 is the energy barrier to activation. The calculations were performed using the GPOP software package developed by Miyoshi.³⁸ The resulting rate coefficients were fit to the modified Arrhenius equation:

$$k(T) = A \cdot T^n \exp\left(-\frac{E_a}{RT}\right) \quad (2)$$

Here A is the preexponential factor, E_a is the activation energy, and R is the universal gas constant.

Scheme 1. Ozonolysis of α -Terpineol in Water:Acetone Solution^a

^aLikely isomers are shown.

RESULTS AND DISCUSSION

Ozonolysis of α -Terpineol in H_2O :Acetone, D_2O :Acetone, and $H_2^{18}O$:Acetone. Positive-ion mass spectra were obtained as a function of time for the liquid-phase ozonolysis of (α -Tp + NaCl) in H_2O :acetone, D_2O :acetone, or $H_2^{18}O$:acetone (1:1 = vol:vol) solution at $[\alpha\text{-Tp}]_0 = 1$ mM and $[O_3]_0 = 0.06$ mM (Figure 1A–C). Some background signals appeared and persisted in the mass spectra obtained from the mixture of α -Tp + NaCl in these solvents in the absence of O_3 (Figure S2). These signals likely originated from autoxidation products or impurities in the α -Tp sample. Given that these products were inert and did not affect the fates of the SOZs, these background signals were omitted from the presented spectra for clarity.

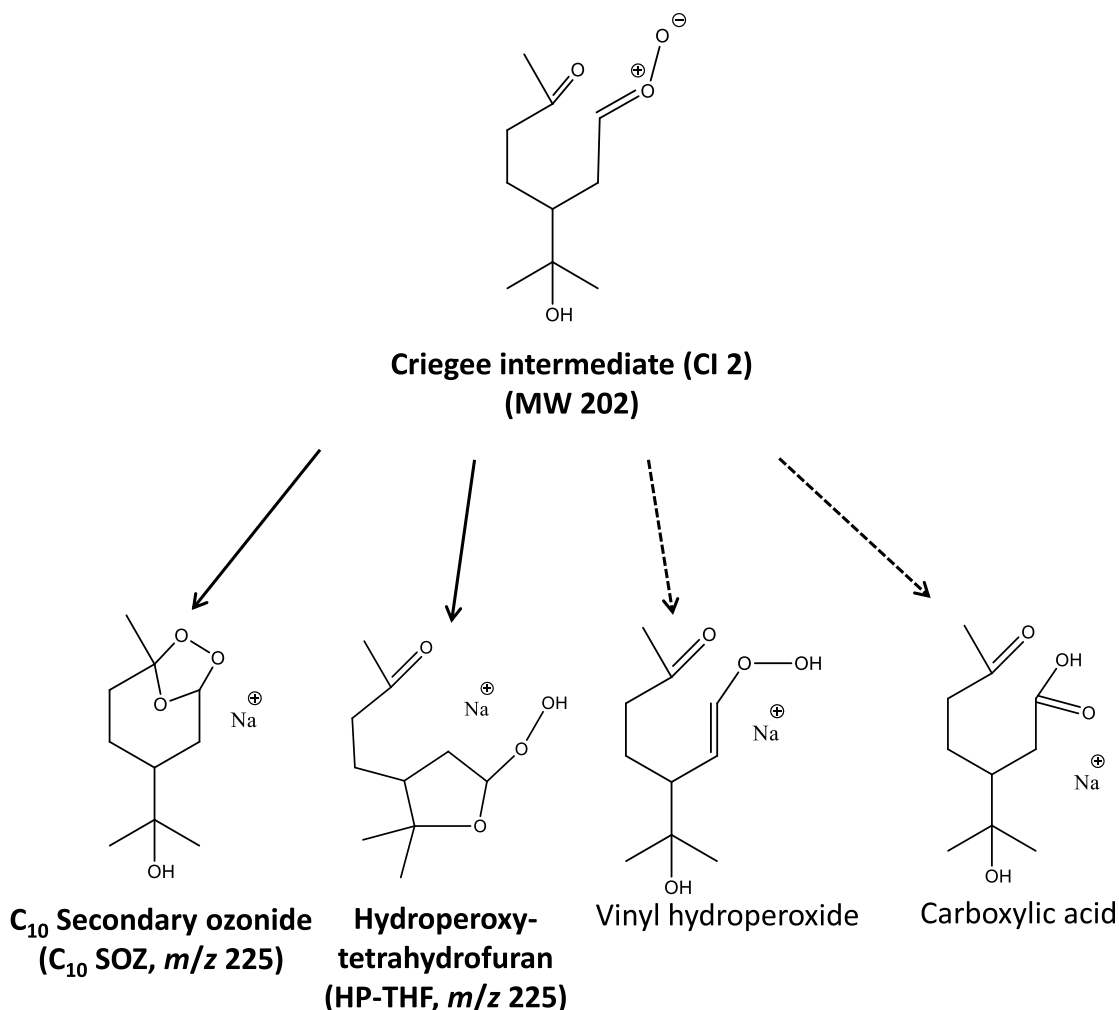
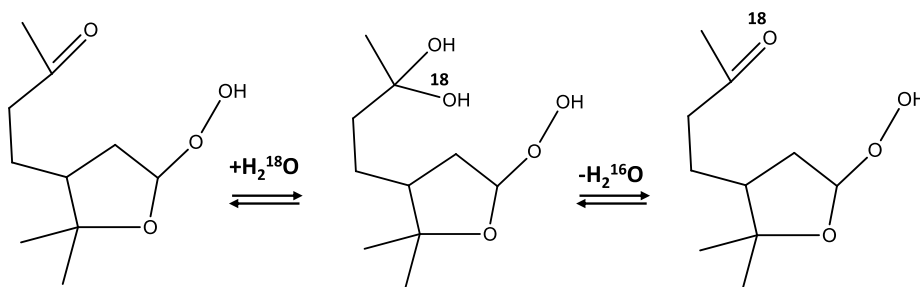
Based on Figure 1 and previous studies,^{19,27,39} we propose the following ozonolysis mechanism (Scheme 1). As the first step, O_3 is added to the double bond of α -Tp, producing a primary ozonide,³² which opens up into two stabilized CIs. In the solutions, three major reactions of CIs proceeded: isomerization to a C_{10} SOZ and other products, reaction with water to produce α -hydroxyalkyl-hydroperoxides (α -HHs), and reaction with acetone to produce C_{13} SOZs.

In the spectrum for the ozonolysis in H_2O :acetone (Figure 1A), the intense peaks at m/z 225 and 283 were attributable to the Na^+ adducts of the C_{10} and C_{13} SOZs: m/z 225 = 154 (α -Tp) + 48 (O_3) + 23 (Na^+) and m/z 283 = 154 (α -Tp) + 48

(O_3) + 58 (acetone) + 23 (Na^+). Note that two types of C_{13} SOZ possessing either an aldehyde or ketone group can be formed via the reaction of each CI with acetone (Scheme 1). Our theoretical calculations show that the formation of the aldehyde-type CI (CI 1 in Scheme 1) is more feasible than that of the ketone-type CI (CI 2), implying preferable formation of aldehyde-type SOZs; these aldehyde-type SOZs would then undergo further intramolecular rearrangement into stable lactol-type SOZs (vide infra).

Interestingly, we could not detect chloride (Cl^-) adducts of the C_{13} SOZs by means of negative-ion mode spectrometry under identical conditions, which should have appeared at m/z 295;297 (Figure S3). It is known that Cl^- can form an adduct with ROOH/ROH due to interaction between an H atom of $-OOH/-OH$ and a Cl atom.⁴⁰ On the other hand, Na^+ has an affinity for the O atom of species possessing $R-O-R'$ such as ethers.⁴¹ Therefore, the C_{13} SOZs were silent to mass spectrometry in negative-ion mode but detectable in positive-ion mode due to the favorable interaction between the O atom of the ozonide $R-O-R'$ moiety and Na^+ . This result is consistent with a previous report in which SOZs were detected by mass spectrometry as Na^+ adducts.⁷

Since α -Tp CIs can isomerize into multiple isomers, alternative assignments for the peak at m/z 225 were explored (Scheme 2). Given that CIs react with both carbonyls and alcohols with similar rate constants in the gas-phase,¹ we proposed that the reactive $-C=O^+-O^-$ moiety of α -Tp CIs

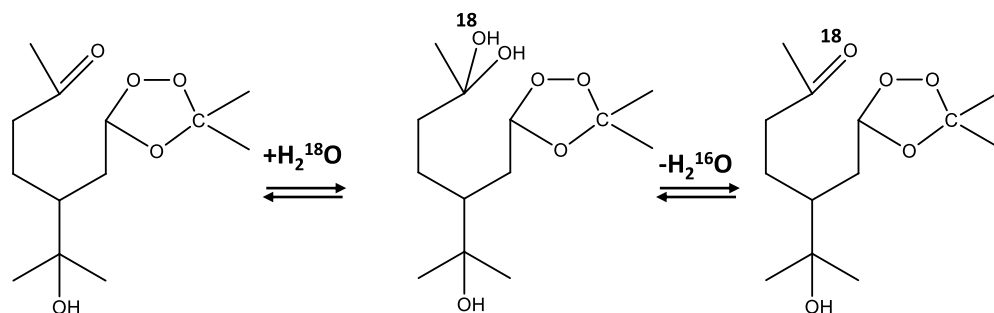
Scheme 2. Isomerization Pathways of an α -Terpineol Criegee IntermediateScheme 3. O-Atom Exchange between HP-THF and $H_2^{18}O$ in $H_2^{18}O$:Acetone Solution

competitively reacted with intramolecular $-C=O$ and $-OH$ to form SOZs and hydroperoxytetrahydropyran/tetrahydrofuran (HP-THP/THF), respectively, in the liquid phase (Scheme 1). A recent theoretical calculation study revealed that an intramolecular insertion of the $-C=O^+-O^-$ into the $O-H$ bond leading to the formation of cyclic ethers with an α -OOH substitution (e.g., HP-THP/THF) is a fast process with $k(298\text{ K})$ ranging from 10 to 10^7 s^{-1} .⁴²

The possibility of formation of vinyl hydroperoxides possessing an $-OOH$ and an $-OH$ from the isomerization of CIs (Scheme 2) was excluded because of the observed $+1$ Da shift to m/z 226 in D_2O :acetone solution (Figure 1B); it is known that the H atoms of $-OOH$ and $-OH$ are

exchangeable with the D atom of D_2O while the compounds are in the mass spectrometer.^{19,20} For the same reason, we excluded the formation of carboxylic acids possessing two $-OH$ groups. On the other hand, the $+1$ Da shift to m/z 226 in D_2O :acetone (Figure 1B) is consistent with the formation of C_{10} SOZ and HP-THP/THF.

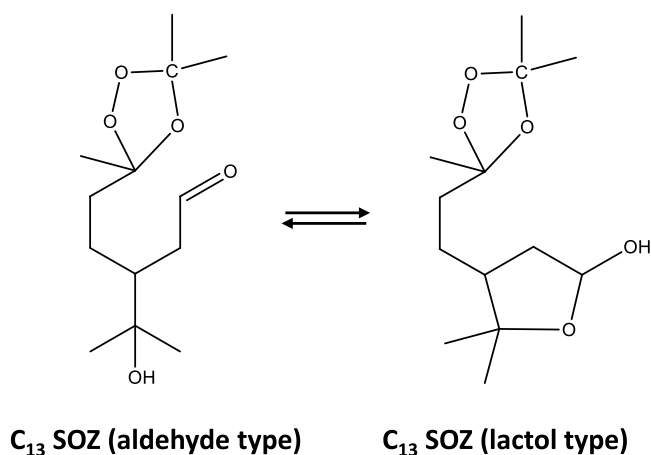
The fact that the peak at m/z 227 ($+2$ Da shift from 225) in the mass spectrum obtained from the ozonolysis in $H_2^{18}O$:acetone evolved as a function of time (Figure 1C) indicated exchange of the O atom of the carbonyl group $C=O$ of HP-THP/THF via addition of $H_2^{18}O$ (Scheme 3). Note that the C_{10} SOZ did not contain a carbonyl moiety that could exchange the O atom from water. The fact that the C_{13} SOZs

Scheme 4. O-Atom Exchange between C₁₃ SOZ and H₂¹⁸O in H₂¹⁸O:Acetone Solution

possessing a carbonyl exchanged only one ¹⁸O atom from water (Figure 1C) suggests that the trioxolane moiety of SOZs could not contribute to the exchange of the O atom from water. Therefore, we concluded that the products of the CI isomerization that appeared as a signal at *m/z* 225 (Figure 1A) included not only C₁₀ SOZ but also HP-THP/THF possessing a carbonyl group and an –OOH. The important implication is that similar intramolecular cyclization reactions occur for the ozonolysis of multifunctionalized alkenes (e.g., oxygenated terpenes) in ambient atmospheric condensed phases, resulting in accumulation of compounds possessing R–O–R' ether groups, as observed in field measurements.⁴³

The ion signal at *m/z* 283 shifted to *m/z* 284 in the experiment with D₂O:acetone (Figure 1B), which is consistent with the structure of C₁₃ SOZs containing a single –OH. Furthermore, the mass spectrum obtained using H₂¹⁸O:acetone showed +2 Da shift from *m/z* 283 after a few hours (Figure 1C), in accordance with the structures of C₁₃ SOZs possessing carbonyl groups (Scheme 4).

Importantly, the temporal profiles of the ion signal at *m/z* 283 showed a rise-and-decay behavior (Figure 1A). This observation implies the existence of isomers of C₁₃ SOZs that were formed at different rates. Since the reaction of the α -Tp CIs with acetone should have finished irreversibly within 1 ns at [acetone] = 6.8 M (see EXPERIMENTAL), we attribute the increase of the signal at *m/z* 283 to an intramolecular rearrangement of a C₁₃ SOZ possessing an aldehyde moiety into a lactol-type C₁₃ SOZ (Scheme 5). The implication is that a lactol-type C₁₃ SOZ is more surface-active and hence more electrospray-mass-spectrometry sensitive than the aldehyde-

Scheme 5. Intramolecular Rearrangement of an Aldehyde-Type C₁₃ SOZ to a Lactol-Type C₁₃ SOZ

ketone-type SOZs, resulting in the observed increase of signal intensity at *m/z* 283 within an hour. Since a higher signal intensity from electrospray mass spectrometry was obtained with more surface-active species in equimolar solutions,⁴⁴ the transformation of the –CH(=O) moiety of the aldehyde-type C₁₃ SOZ into the R–O–R' moiety of a lactol-type C₁₃ SOZ explains the increase of the signal intensity at *m/z* 283. A similar rise-and-decay pattern has been reported for the mass spectrum signal for the conversion of acyclic α -alkoxyalkyl-hydroperoxides to cyclic peroxyhemiacetals formed by the ozonolysis of α -Tp in water:1-propanol mixture.⁴⁵ Thus, three different C₁₃ SOZs—two rapidly (≤ 1 ns) formed SOZs possessing an aldehyde or a ketone and a slowly (≤ 1 h) formed SOZ possessing a lactol moiety—all contributed to the signal at *m/z* 283. This hypothesis is consistent with the temporal profiles of the signal at *m/z* 283 and theoretical calculations (vide infra).

The peak at *m/z* 243, which rapidly decayed as a function of time, was attributed to the Na⁺ adducts of the α -HHs and/or the isomer cyclic peroxyhemiacetals: *m/z* 243 = 154 (α -Tp) + 48 (O₃) + 18 (H₂O) + 23 (Na⁺) (Scheme 1). Based on previous studies,^{27,46} α -HHs decompose via H⁺- and water-catalyzed mechanisms in aqueous media into their corresponding aldehydes and H₂O₂. The absence of α -HH signals in Figures 1B and 1C implies that the α -HHs had decomposed within 6 min in the D₂O:acetone and H₂¹⁸O:acetone solvents. The aldehydes then further reacted with water to form geminal diols or isomerized into the functionalized lactols (Scheme 1). In fact, we detected species at *m/z* 209 [= 243–34 (H₂O₂)] and *m/z* 267;269 as major signals that emerged as a function of time (Figure 1A). These signals were attributed to the Na⁺ adducts and (Na₂Cl)⁺ adducts of the functionalized lactol products, respectively. These functionalized lactols were able to be detected in positive-ion mode due to the presence of R–O–R' moieties that favorably interact with Na⁺, but they were silent to mass spectrometry in negative-ion mode (Figure S3). In experiments with D₂O:acetone solvent (Figure 1B), the ion signals at *m/z* 209 and 267;269 shifted to 210 and 268;270, which is consistent with the formation of lactols containing an –OH. In the experiments with H₂¹⁸O:acetone (Figure 1C), the ion signals at *m/z* 209 and 267;269 shifted to 211 and 269;271, consistent with the proposed mechanism of the formation of lactols via the functionalized aldehyde that contains an ¹⁸O atom delivered from H₂¹⁸O (Scheme 1). The mechanism in which a water molecule is incorporated into the α -Tp CIs to form α -HHs, followed by rapid decomposition into the corresponding aldehyde and isomerization into lactols is in agreement with our previous results obtained from negative-ion mass spectrometry.^{27,46} The fact that the signals attributed to lactols kept increasing even after that of α -HH-

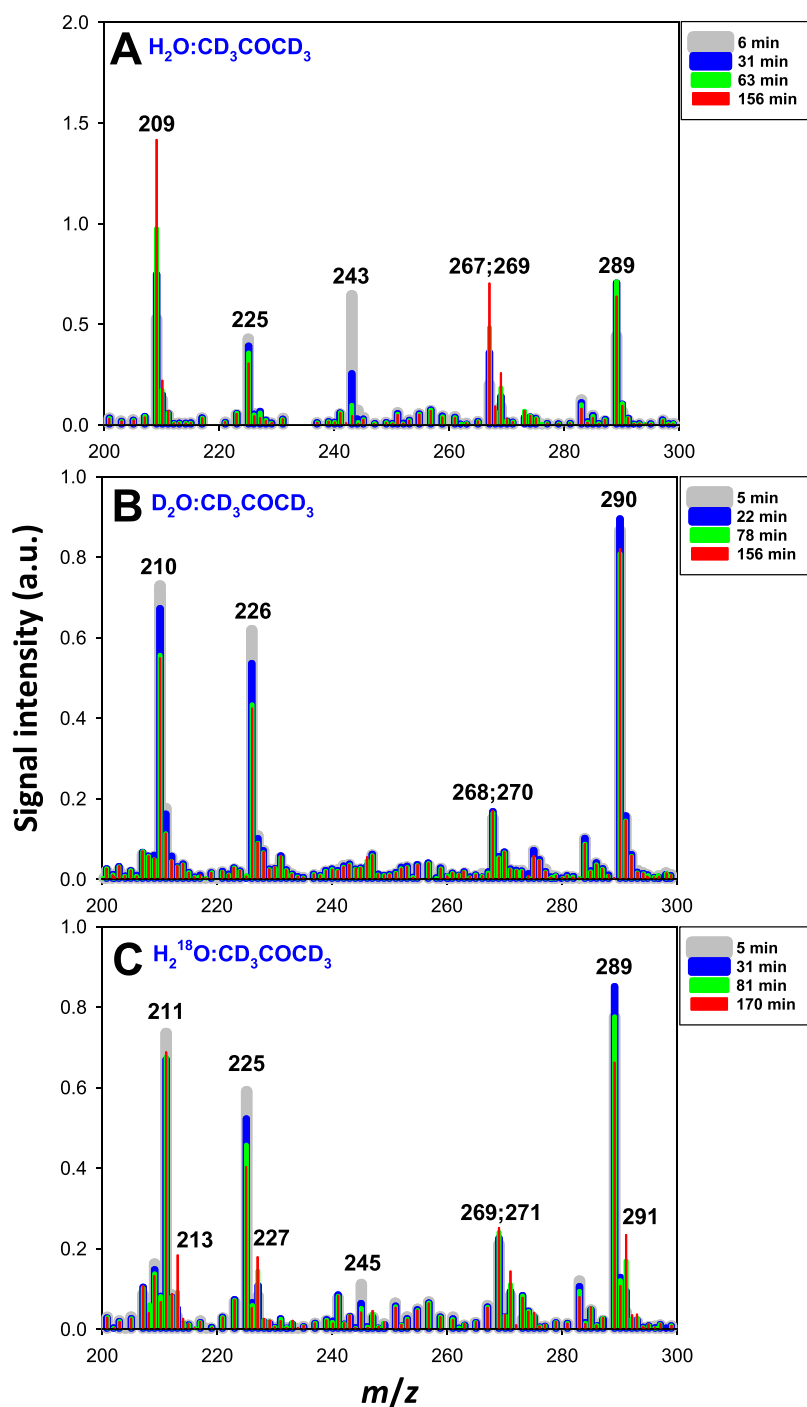


Figure 2. Time-dependent positive-ion mass spectra of 1 mM α -terpineol + 0.2 mM NaCl + 0.06 mM O_3 in (A) $H_2O:CD_3COCD_3$, (B) $D_2O:CD_3COCD_3$, or (C) $H_2^{18}O:CD_3COCD_3$ (all 1:1 = vol:vol). Background spectra obtained in the absence of O_3 were subtracted.

Na^+ had disappeared (Figure 1A) implies that the aldehyde was MS-silent and acted as a reservoir that slowly isomerized into the lactols (Scheme 1). Furthermore, we note the possibility that these lactols were also produced from the decomposition of HP-THP/THF (the conversion of ROOH to ROH) as observed in the cases of α -alkoxyalkyl hydroperoxides^{45,47–49} and other ROOH.⁹ Based on the fact that the ion signals at m/z 267;269 also appeared in water: CD_3COCD_3 solvent (see below) and the increase of the signals as a function of time was not correlated with the decay of m/z 283, we concluded that these lactols were not a decomposition product of C_{13} SOZs.

Ozonolysis of α -Terpineol in $H_2O:CD_3COCD_3$, $D_2O:CD_3COCD_3$, or $H_2^{18}O:CD_3COCD_3$. To confirm the product assignments, we repeated the experiments using acetone- d_6 (CD_3COCD_3) as a substitute for acetone. Figure 2 shows the positive-ion mass spectra obtained as a function of reaction time for the liquid-phase ozonolysis of (α -Tp + NaCl) in $H_2O:CD_3COCD_3$, $D_2O:CD_3COCD_3$, or $H_2^{18}O:CD_3COCD_3$ (1:1 = vol:vol) solution at $[\alpha\text{-Tp}]_0 = 1$ mM and $[O_3]_0 = 0.06$ mM.

In the experiment using $H_2O:CD_3COCD_3$ (Figure 2A), the signal attributed to the C_{13} SOZs appeared at m/z 289 = 154 (α -Tp) + 48 (O_3) + 64 (CD_3COCD_3) + 23 (Na^+), as

expected. In the experiment using $D_2O:CD_3COCD_3$ (Figure 2B), the signal attributed to the C_{13} SOZs at m/z 289 shifted to m/z 290, which is consistent with the proposed structures possessing a single H or D atom exchangeable $-OH$. In the experiment using $H_2^{18}O:CD_3COCD_3$ (Figure 2C), the ion signal at m/z 289 gradually shifted to m/z 291, which is consistent with the proposed mechanism of the exchange of an O atom between the carbonyl group of the C_{13} SOZs and $H_2^{18}O$. These results are consistent with the proposed structures of the aldehyde, ketone, and lactol C_{13} SOZs (Schemes 1 and 3). The formation of signals at m/z 209 and m/z 267;269 in the spectrum for the experiment using $H_2O:CD_3COCD_3$ (Figure 2A) is further evidence that these products are functionalized lactols that originated from the α -HHs rather than the C_{13} SOZs (Scheme 1).

Kinetics of Products Obtained from Ozonolysis of α -Terpineol in H_2O :acetone. Figure 3 shows the temporal

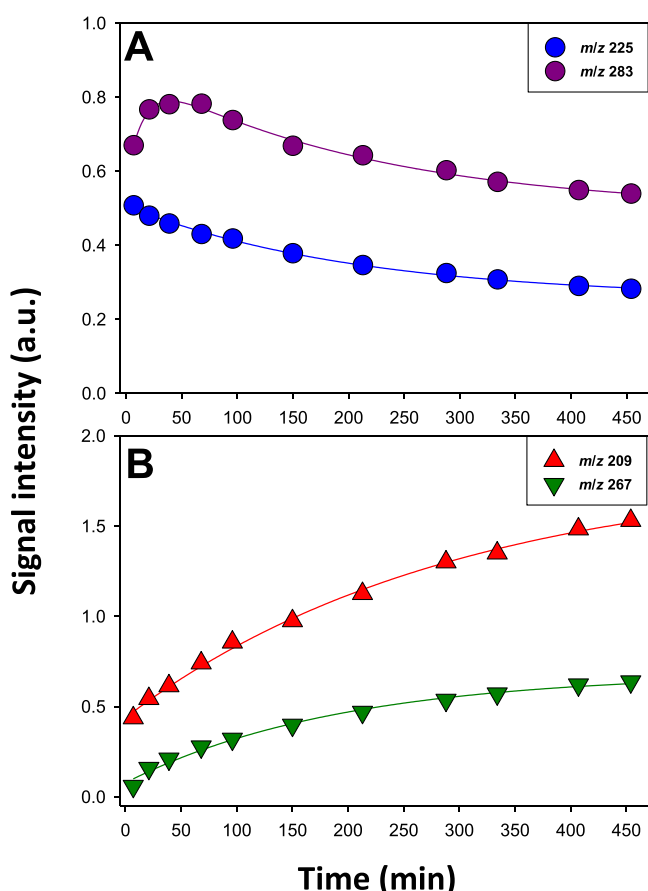


Figure 3. Temporal profiles of the signals for the products (A, m/z 225, 283; B, 209, 267) of reaction of 1 mM α -Tp + 0.2 mM NaCl + 0.06 mM O_3 in water:acetone (1:1 = vol:vol) at 298 K. Background signals obtained from mass spectra in the absence of O_3 were subtracted.

profiles of the product signals obtained from the liquid-phase ozonolysis of (α -Tp + NaCl) in water:acetone (1:1 = vol:vol) solution at $[\alpha\text{-Tp}]_0 = 1$ mM and $[O_3]_0 = 0.06$ mM at 298 K. The decay of the ion signal at m/z 225 (C_{10} SOZ/HP-THP/THF) was fit by a single-exponential function with a baseline of $S = S_0 + A \exp(-k_{225,\text{decay}}t)$ that yielded $k_{225,\text{decay}} = (7.0 \pm 1.1) \times 10^{-5} \text{ s}^{-1}$. k values are presented here and below as means \pm SDs of three independent experiments. $k_{225,\text{decay}}$

corresponds to the first-order rate coefficient for the decay of C_{10} SOZ and/or HP-THP/THF. In general, hydroperoxides (ROOH) are more reactive than alkylperoxides (ROOR').⁹ Therefore, the decay of the m/z 225 signal may be attributed to HP-THP/THF possessing a hydroperoxide moiety, while the baseline to C_{10} SOZ. Notably, the $k_{225,\text{decay}}$ is smaller by 1 or 2 orders of magnitude than those obtained for α -HHs or α -alkoxyalkylhydroperoxides/ α -acyloxyalkylhydroperoxides in the liquid-phase under similar experimental conditions.^{19,21,45}

The time profile of the ion signal at m/z 283 (C_{13} SOZs) was fit by a biexponential function with a baseline of $S = S_0 - A \exp(-k_{283,\text{rise}}t) + B \exp(-k_{283,\text{decay}}t)$ that yielded $k_{283,\text{rise}} = (9.9 \pm 2.7) \times 10^{-4} \text{ s}^{-1}$ and $k_{283,\text{decay}} = (6.8 \pm 2.3) \times 10^{-5} \text{ s}^{-1}$. As mentioned above, we attributed $k_{283,\text{rise}}$ to the conversion of aldehyde-type C_{13} SOZs into lactol-type C_{13} SOZs (Scheme 5), whereas the decay of all three types of C_{13} SOZ contributed to $k_{283,\text{decay}}$. Interestingly, once the SOZ signals reached plateaus, they appeared to stay constant for at least 1 week (Figure 4). Since background signals obtained from mass spectra in the absence of O_3 were subtracted, the persistent signals clearly originated from products formed by the ozonolysis. This observation demonstrates the extraordinary stabilities of the C_{10} SOZ and C_{13} SOZs in water:acetone solution. The implication is that terpenoid-derived SOZs are able to survive with their endoperoxide moieties in atmospheric condensed phases that are a mixture of water and organic compounds.⁵⁰ It is conceivable that the lactol-type C_{13} SOZ (Scheme 5) survived much longer than the aldehyde/ketone C_{13} SOZs and therefore contributed to the persistent signal at m/z 283.

We also determined the rate constants for the increase of the ion signals at m/z 209 and 267 (functionalized lactols). From a single-exponential rise to a maximum regression with a baseline of $S = S_0 + S_{\text{max}}[1 - \exp(-k_{\text{rise}}t)]$, we derived $k_{209,\text{rise}} = (6.6 \pm 0.8) \times 10^{-5} \text{ s}^{-1}$ and $k_{267,\text{rise}} = (8.4 \pm 2.4) \times 10^{-5} \text{ s}^{-1}$. The determined k values for m/z 209 and 267 were identical within the experimental error, as would be expected for species from the same origin, *i.e.*, the species are functionalized lactols (Scheme 1). The baselines observed for the temporal profiles of the signals at m/z 209 and 267 (Figure 3B) should have originated from the existence of two isomers of lactols (lactol 1 and 2 in Scheme 1) that formed at different rates, and these lactols should be at equilibrium with the functionalized aldehyde. As mentioned above, it is possible that these lactols were also formed from the decomposition of HP-THP/THF. In that case, the fast components appeared as the baselines may originate from α -HHs, while the slowly evolving components from HP-THP/THF. This hypothesis is consistent with the close value between $k_{209,267,\text{rise}}$ and $k_{225,\text{decay}} = (7.0 \pm 1.1) \times 10^{-5} \text{ s}^{-1}$.

The lack of signals attributable to decomposition products from the SOZs in both the positive- and negative-ion spectra was revealing. If organic acids were formed during the reactions, they should have appeared as corresponding carboxylate anions on negative-ion mass spectrometry (*cf.* Figure S3). This finding is at odds with previous reports that thermal decomposition of SOZs in neat organic solvents produces corresponding carboxylic acids.^{5,17} The implication is that the decomposition products of α -Tp SOZs in water:acetone solution are different from those of thermal decomposition in neat organic solvents, implying that water plays an important role in the decomposition process. The decay of the C_{13} SOZ signal in Figure 3A was therefore

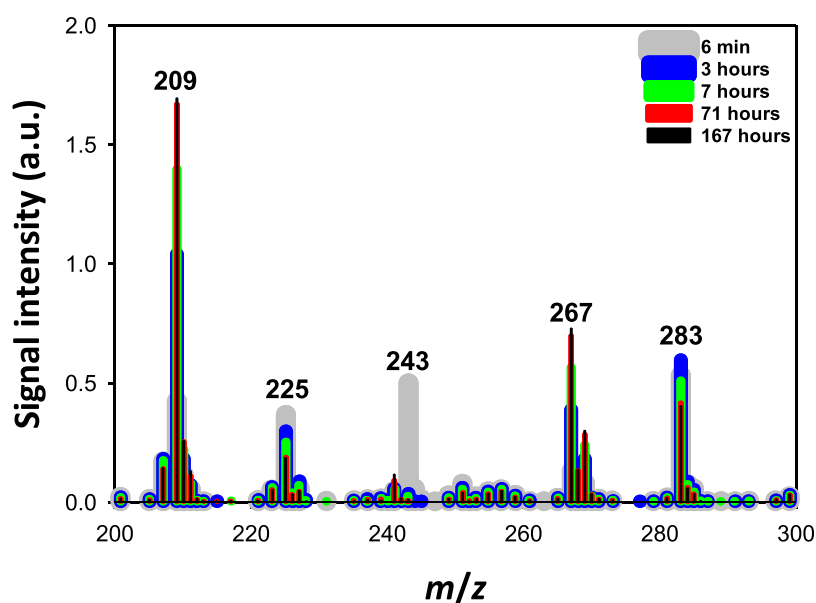
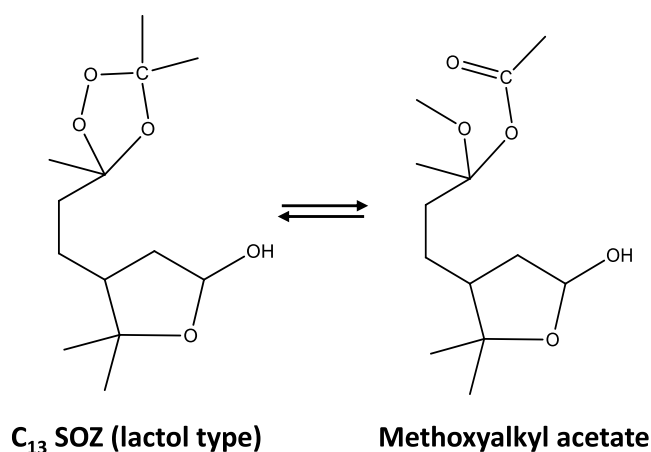


Figure 4. Extended time-dependent positive-ion mass spectra of (1 mM α -terpineol + 0.2 mM NaCl + 0.06 mM O_3) in water:acetone (1:1 = vol:vol) at $T = 298 \pm 3$ K. Background signals obtained in the absence of O_3 were subtracted.

attributed to the formation of products silent to mass spectrometry. Previous studies have suggested that the isomerization of SOZs derived from the reaction of CH_2OO + acetone in the gas-phase partly yielded methoxymethyl acetate via cleavage of the endoperoxide O–O bond.^{12,51} However, the possibility that C_{13} SOZs isomerized into the corresponding C_{13} methoxyalkyl acetate species (Scheme 6) was excluded here because of the lack of corresponding negative-ion signals that should have appeared at $m/z = 295$; 297 as the chloride adduct.

Scheme 6. Intramolecular Rearrangement of a Lactol-type C_{13} SOZ into a Methoxyalkyl Acetate That Did Not Occur under the Present Conditions



Also, the positive-ion signals of the corresponding hydroxyalkyl acetate at m/z 225 from the C_{10} SOZ isomerization that possesses two H or D atom exchangeable –OH groups should have shifted by +2 Da in D_2O :acetone solvent, which is at odds with the spectrum shown in Figure 1B. Together, these findings indicate that the isomerization of the C_{13} and C_{10} SOZs into the corresponding acetates did not occur under the present conditions.

Theoretical Calculations on α -Tp CIs and SOZs. Gibbs free-energy barrier and reaction kinetics for the formation of the two CIs, the aldehyde- and ketone-types, from the primary ozonide of α -Tp in water were compared. The Cartesian coordinates for the structural geometry used in the calculations can be found in Table S1. The Gibbs free-energy diagram is shown in Figure 5. The reactions that produced the aldehyde- and ketone-type CIs had relatively low free-energy barriers of 47.4 and 50.0 kJ mol^{-1} , respectively. Comparison of the reaction rates at 298 K determined by transition state theory (Table 1) revealed that the reaction rate of the aldehyde-type CI (CI 1 in Scheme 1) was 3.6 times faster than that of the ketone-type CI (CI 2). Hence, in an atmospheric environment, the main component of this reaction is considered to be the aldehyde-type CI. This suggests that the aldehyde type will also be the predominant type in the SOZs formed when this CI reacts with acetone.

The free-energy diagram of the reaction in which C_{13} SOZ undergoes intramolecular rearrangement from the aldehyde to the lactol type is shown in Figure 6. This diagram shows that the lactol type is more stable than the aldehyde type, and that this rearrangement should be a spontaneous process, which is consistent with the experimental results described above. However, the energy barrier for the rearrangement reaction pathway is rather high at 120.1 kJ mol^{-1} , suggesting that other reaction pathways, including an H^+ -catalyzed rearrangement, likely proceed.

Atmospheric and Environmental Implications. The formation of SOZs in the atmosphere is mediated by CIs that are formed during the ozonolysis of unsaturated organic compounds possessing one or more $C=C$ bonds. Biogenic terpenoids, which are emitted at a rate of 10^{14} g/year,⁵² are the predominant source of SOZs. Whether ozonolysis of a volatile organic compound results in the formation of SOZs largely depends on the steric constraint of the chemical structure.⁵³ In addition to reaction with OH radical, the uptake of SOZs into atmospheric condensed phases is considered an important sink. Functionalized SOZs originating from $C_{\geq 10}$ terpenoids are less volatile and hence more easily taken up into aerosols.⁵⁴

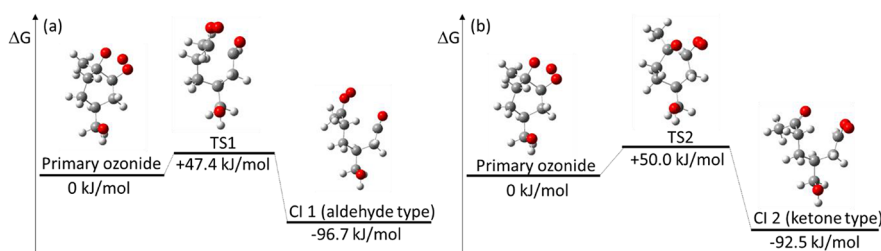


Figure 5. Gibbs free-energy diagram for the production of (a) aldehyde- and (b) ketone-type Criegee intermediates (CIs) from the primary ozonide of α -Tp in water.

Table 1. Kinetic Parameters for the Production of Criegee Intermediates (CIs) from the Primary Ozonide of α -Tp Using the Modified Arrhenius Equation: $k(T) = A \cdot T^n \exp(-E_a/RT)$

Product	A/s^{-1}	n	$E_a/kJ\ mol^{-1}$	$k_{298\ K}/s^{-1}$
CI 1 (aldehyde type)	8.16×10^9	1.14	52.7	3215
CI 2 (ketone type)	6.55×10^9	1.13	55.1	889

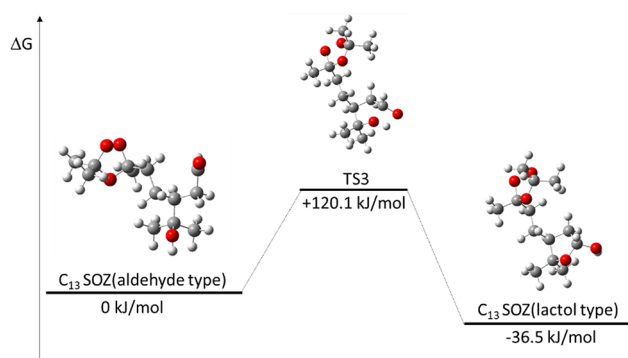


Figure 6. Gibbs free-energy diagram for the intramolecular rearrangement of C_{13} SOZ.

Multiphase ozonolyses and OH oxidations of unsaturated organic compounds possessing C=C bond(s) also produce SOZs, resulting in accumulation of SOZs in condensed phases.^{6–8,18,24,25,55} However, the fates and lifetimes of atmospherically relevant terpenoid-derived SOZs in aqueous organic media are largely unknown.

Here, we examined the liquid-phase fates of functionalized C_{10} and C_{13} SOZs synthesized by ozonolysis of C_{10} α -Tp in the presence of acetone. Direct mass spectrometric detection of these SOZs as their Na^+ adducts and isotope labeling experiments enabled us to identify the three forms of C_{13} SOZs produced. Of these C_{13} SOZs, our results suggested that the aldehyde-type C_{13} SOZ was converted into the lactol-type C_{13} SOZ within an hour and that the lactol-type C_{13} SOZ survived for more than a week. A lack of evidence for the formation of carboxylic acids in both positive- and negative-ion mass spectra was at odds with the expected products of thermal decomposition. The present results suggest that once gaseous SOZs are taken up into aerosols or directly formed in or at the gas–liquid interface of aerosols, they may persist as a stealth oxidant without losing their endoperoxide moieties. A recent study that has shown that the lifetimes of organic peroxides in SOA derived from α -pinene ozonolysis are highly isomer dependent.⁵⁶ Our results suggest that SOZs may account for the inert peroxides that survived even at high relative humidity conditions. The environmental implication is that inhalation of aerosols containing SOZs and transition

metal ions may induce oxidation of antioxidants in the epithelial lining fluid.^{6,57} This would result in disruption of the redox balance of the human respiration system. Furthermore, the present demonstration that terpenoid-derived SOZs can be stable in the aqueous phase hints at the potential use of rationally designed SOZs as antibacterial drugs.^{26,58} Further work on the effects of coreactants (H^+ , antioxidants, and transition metals) on the fates of SOZs in condensed phases is underway in our laboratory.

The present results also indicated that ozonolysis of α -Tp produced not only SOZs but also HP-THP/THF via intramolecular reaction between $-C=O^+-O^-$ and $-OH$ in the liquid phase.⁴² In addition, marked formation of lactols originated from acyclic α -HHs appeared in the liquid phase. The implication is that intramolecular cyclization reactions preferentially occur for the ozonolysis of multifunctionalized alkenes such as oxygenated terpenes in ambient atmospheric condensed phases.²⁹ The conversions of acyclic to cyclic and of $-OOH$ to $-OH$ may be a general process that proceeds in atmospheric condensed phases that contain liquid water and H^+ .^{43,59}

CONCLUSION

Here, we report the results of a mass spectrometric investigation of the liquid-phase fates of C_{10} and C_{13} SOZs synthesized by the ozonolysis of C_{10} α -terpineol in water:acetone (1:1 = vol:vol) mixtures as a function of time. The C_{10} SOZ and C_{13} SOZs were generated by isomerization of α -Tp CIs and bimolecular reaction of α -Tp CIs with acetone, respectively, and were detected as their Na^+ adducts by positive-ion electrospray mass spectrometry. Our results suggested that the isomerization of CIs also produced C_{10} HP-THP/THF products. By using isotope solvents and kinetic analyses, we identified three types of C_{13} SOZ (aldehyde, ketone, and lactol). We found that these SOZs were remarkably stable in water:acetone (1:1) mixtures at $T = 298\ K$, some of which persisted for more than a week. Theoretical calculations revealed that the aldehyde-type SOZs underwent intramolecular rearrangement to the more stable lactol-type SOZs. The present results suggest that specific SOZs may cause endoperoxide moieties to remain in atmospheric condensed phases until they are inhaled and delivered to the epithelium lining fluid of pulmonary alveoli via particulate matter, where they may exert hitherto unrecognized adverse health effects.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jpca.2c04077>.

Additional experimental data including the schematic setup of the present experiment, positive-ion mass spectrum of (α -terpineol + NaCl) in water:acetone solution in the absence of ozone, negative-ion mass spectra of (α -terpineol + NaCl + O₃) in water:acetone solution, and Cartesian coordinates for structural geometry in the theoretical calculations (PDF)

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Author Contributions

S.E. designed the research; J.Q. and S.E. performed the experiments; M.F. performed the theoretical calculations; K.T. and S.E. contributed new reagents/analytic tools; S.E. wrote the first draft of the manuscript; all the authors analyzed the data and contributed to the revisions of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

S.E. is grateful for receiving a Japan Society for the Promotion of Science KAKENHI grant (No. 19H01154).

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