Potential for Release of Pulmonary Toxic Ketene from Vaping Pyrolysis of Vitamin E Acetate

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A combined analytical, theoretical and experimental study has shown that the vaping of vitamin E acetate has the potential to produce exceptionally toxic ketene gas, which may be a contributing factor to the upsurge in pulmonary injuries associated with using e-cigarette/vaping products. Additionally, the pyrolysis of vitamin E acetate also produces carcinogen alkenes and benzene for which the negative long-term medical effects are well recognized. As temperatures reached in vaping devices can be equivalent to a laboratory pyrolysis apparatus, the potential for unexpected chemistries to take place on individual components within a vape mixture is high. Educational programs to inform of the danger are now required, as public perception has grown that vaping is not harmful.

Significance Statement

The CDC has recently reported an increasing number of clinically cases of lung injury following use of vaping products. The cause(s) of this growing epidemic of vaping associated pulmonary injury remain unidentified, though vitamin E acetate has been identified as one possible causative agent (see Nature 574, 303 (2019). In this research, a combined analytical, theoretical and experimental study has shown that the vaping of vitamin-E-acetate has the potential to produce exceptionally toxic ketene gas, which may be a contributing factor to the upsurge in lung injuries associated with vaping products. It is important that our results be urgently published to inform medical practitioners, research scientists and the public as this may assist in bringing this medical crisis under control.

Keywords

Vitamin E acetate; ketene; vaping; pyrolysis; lung injury

Author contributions

DOS conceived and designed the research and wrote the manuscript with support from DW. DW designed and conducted the experiments, did the DFT calculations, collected and analyzed the MS and NMR data and contributed to writing the manuscript.

Competing interests

The authors declare no competing interests.
Footnotes

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Graphical Abstract
The Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) have recently reported an increasing number of clinically reported cases of pulmonary injury following use of e-cigarette/vaping products (1). The cause(s) of this growing epidemic of vaping associated pulmonary injury remain unidentified, though studies in mice have shown that chronic exposure to e-cigarette vapor abnormally alters the physiology of lung epithelial cells with changes in lipid homeostasis being independent of nicotine (2). Vitamin E acetate 1 is used as an additive in some vaping products and was recently reported as one possible causative agent (Fig. 1). Results from a multi-centered study have identified it in bronchoalveolar lavage fluid specimens from all 29 patients examined (3). As the synthetic O-acetylated analog of vitamin E 2, it is widely used in cosmetic skin care products and as a dietary supplement. The acetylated version of the vitamin is preferred due to its more facile purification during production, its increased formulation stability and as ester hydrolysis in vivo generates vitamin E (4). As it is a viscous lipid oil, 1 is added to some vape mixtures, especially to those containing tetrahydrocannabinol (THC) and cannabidiol (CBD) oils. These mixtures are growing in use for non-medical recreational purposes, which appears to be closely linked to the current medical crisis (1).

In the first preliminary reports, lipid accumulation in the lungs as a result of vaping was proposed to play a role in causing exogenous lipid pneumonia (5, 6). In a subsequent report of six patients suffering from vaping-associated lung injury, CT scans did not show known features consistent with exogenous lipid pneumonia (7). Most recently, pathology of seventeen patients with vaping-associated lung injury revealed patterns more consistent with airway-centered chemical pneumonitis from inhaled toxic substance(s) rather than exogenous lipid pneumonia (8). To date, the causative agent(s) remain unidentified and with so many parameters and variables involved, it appears unlikely that vitamin E acetate alone would have such acute and severe toxicity.

However, the chemical stability and reactivity of 1, under high temperature pyrolysis conditions, has not been investigated. Critically, the temperature of heating coils within vaping devices is highly variable and has been measured to range between 110 and 1008 °C. Several factors can contribute to the actual temperature(s) applied to the complex vape mixture, such as the heating coil resistance, voltage applied, composition of the mixture being vaporized, and the mode of user usage (9, 10). In reality, a vaping device should be considered as a crude uncontrollable mini-pyrolysis apparatus capable of causing changes to the chemical composition of a vaping mixture in an unpredictable manner. Specifically, the aryl acetate functional group present within 1 attracted our attention as a functional group sensitive to pyrolysis. The same functional group is present in phenyl acetate 3, the simplest aryl acetate, which is known to liberate the highly toxic gas ketene 4 under pyrolysis (Fig. 1). In this communication, we describe our initial efforts to illustrate and highlight the potential of vitamin E acetate to release ketene under pyrolysis conditions, and that such conditions are achievable using a vaping device.

Pyrolysis of phenyl acetate 3 undergoes a thermal unimolecular elimination reaction to form phenol and ketene 4 at temperature of 625 °C, with ketene obtained in an 84% yield (Fig. 1) (11). This pyrolysis has been studied using electron ionization (EI) mass spectrometry to generate conditions to promote the elimination of ketene (12). Ketene is manufactured by pyrolysis of acetic acid at 700-800 °C and is used for synthetic acetylation reactions and for the production of bulk reagents (13). It is a colorless gas (b.p. -56 °C) with a penetrating odor above 12 ppm. Due to its extreme reactivity, the public extremely rarely encounters ketene, as when industrially produced it is not isolated but reacted in situ.
However, it has very high pulmonary toxicity, and is lethal at high concentrations. At lower concentrations in animal studies, minor irritation during exposure and central nervous system impairment were observed (14, 15). It can acetylate nucleophilic components of proteins in aqueous solution and the pulmonary effects of inhalation exposure to 4 may be manifested in the absence of direct irritation by ketene. Severe damage to the lungs at the alveolar level may manifest as long as 24 h post exposure. Thus, it is unknown whether odor detection and minor irritation would provide adequate warning of ketene exposure, especially given the potential for delayed pulmonary toxicity. The toxicity of ketene has been assessed in various animal species and these studies indicate that it has similar clinical effect and mode of action as phosgene (COCl₂) (16). In toxicity studies with primates, the minimum lethal in-air concentration was determined to be 200 ppm, causing death after a single 10-minute exposure (17).

**Fig. 1.** Chemical structures of vitamin E acetate 1, vitamin E 2, phenyl acetate 3 and ketene 4.

As vitamin E acetate contains a similar acetate functional found in phenyl acetate, it appeared plausible to us that it too may produce ketene upon pyrolysis (Fig. 1). To investigate this possibility, a three-fold investigation was adopted utilizing mass spectrometry, DFT calculations and analysis of isolated products from vaped vitamin E acetate.

**Mass Spectrometry Study.** Phenyl acetate 3 was analyzed using atmospheric pressure chemical ionization (APCI) mass spectrometry at a series of increasing source cone voltages (CV) from 5 to 30 eV. At 15 eV the parent ion [M+H]⁺ was identifiable as the mass to charge ratio (m/z) of 137.1 (10%) with fragmentation ion at 95.2 (100%) (Fig. 2A, SI Appendix, Fig. S1). This corresponds with a mass loss of 42 from the parent ion, which is equivalent to ketene 4 and consistent with previous studies that used EI MS instrumentation (Fig. 3A) (12). An identical analysis of vitamin E acetate 1 also showed the elimination of ketene (m/z = 42) from the parent ion (as seen for 3) and from a fragment with m/z of 207.2 (Fig. 2B, SI Appendix, Fig. S2). A representative spectrum taken with CV of 20 eV shown in Fig. 2B reveals the parent ion m/z of 473.6 (100%) with fragmentation ions at 431.5 (15%), 207.2 (65%) and 165.2 being the most prominent features. Increasing the cone voltage to 25 eV decreased the abundance of the parent ion and increased the fragmentation such that (m/z) abundances were 473.6 (10%), 431.5 (10%), 207.2 (100%), and 165.2 (10%) (SI Appendix, Fig. S2). Clearly two fragmentation patterns can occur for 1 with fragmentation pattern A due to elimination of ketene 4 from the molecular ion producing vitamin E 2 ([Ar⁻OH₂]⁺, m/z 431.5) whereas fragmentation pattern B has loss of prist-1-ene 7 producing 6 ([Ar⁻OH₂]⁺, m/z 207.2) from which elimination of 4 generates [Ar²OH₂]⁺ (m/z 165.2) (Fig. 3B). As a control, vitamin E 2 was also included in the MS study showing, as expected,
no m/z loss of 42 and showing the same \([\text{Ar}^3\text{OH}_2]^+\) (m/z 165.2) species observed as the lowest molecular weight fragment from 1 and attributable to structure 8 (Fig. 2C, SI Appendix, Fig. S3).

**Fig. 2.** Positive mode APCI-MS of (A) phenyl acetate 3 with source voltage of 15 eV showing loss of ketene; (B) vitamin E acetate 1 with source voltage of 20 eV showing loss of ketene from both the parent ion and a fragmentation species of m/z 207.2; (C) vitamin E 2 with source voltage of 20 eV with sole fragmentation to \([\text{Ar}^3\text{OH}_2]^+\).

**Fig. 3.** APCI-MS fragmentation patterns of A phenyl acetate 3 and B vitamin E acetate 1 each of which are observed as +H\(^+\) masses in the mass spectra.

As the APCI-MS for 1 and 3 both showed loss of ketene from the molecular ion but 1 also showed a loss from an intermediate fragment, we sought to further explore this possibility using DFT
calculations. The energy profiles and transition states (TS) for the elimination of ketene from 1, 3 and 6 were calculated in the gas phase at the M06-2X/6-311G (d,p) level using the Gaussian 09 package (18).

**DFT Theoretical Study.** The elimination of ketene from 3 has been reported to proceed via four membered TS with a concerted [1,3] hydrogen shift from methyl to oxygen as shown in Fig. 4 (19, 20).

![Fig. 4](image)

**Fig. 4.** Calculated energy profiles for the pyrolysis of the three aryl acetate substrates 1, 3, and 6 via concerted [1,3] hydrogen shift mechanism. Relative free energies (kcal mol⁻¹) for starting materials, transition states and products formed for the pyrolysis of phenyl acetate, vitamin E acetate and 6 leading to the elimination of ketene 4. For details of calculation data see SI Appendix, Fig. S4, S5, S6. Simplified structures used for calculation of 1 and 2 without C₁₅H₃₂ alkyl group.

Gas phase M06-2X/6-311G (d,p) calculations from 3 gave an activation energy of 65.4 kcal/mol via this pathway, confirming that it would be energetically feasible under pyrolysis conditions (Fig. 4, black energy profile). At this level of theory, the barrier for ketene elimination from 1 was only 4.1 kcal/mol higher than 3 at 69.5 kcal/mol (Fig. 4, blue energy profile). As the MS fragmentation data for 1 indicated ketene elimination from fragment 6 can also occur, its energy barrier to release ketene was calculated and found to be 65.9 kcal/mol, which is lower than 1 and comparable with 3 (Fig. 4, green energy profile). The optimized geometry of the four-membered cyclic transition states for the unimolecular decomposition of 1, 3 and 6 showed similarity for each and that ortho-methyl substituents of 1 and 6 acetate did not impede ketene elimination (Fig. 5, SI Appendix, Fig. S4, S5, S6). Additionally, intrinsic reaction coordinate (IRC) calculations confirmed that the TS structures associated with the products and reactants along the minimum energy pathway.

![Fig. 5](image)

**Fig. 5.** Optimized geometries (M06-2X/6-311G(d,p) level) for the transition states corresponding to the pyrolysis of phenyl acetate 3 (left) and vitamin E acetate 1 (middle) and 6 (right), leading to the elimination of ketene. Simplified structures used for calculation of 1 and 2 without C₁₅H₃₂ alkyl group. For details of calculation data see SI Appendix, Fig. S4, S5, S6.
As two pathways are operable for the elimination of ketene from 1, DFT calculations were carried out to determine if either one was more favorable. The competitive first steps of the two pathways are either loss of ketene from 1 forming 2 or loss of prist-1-ene 7 from 1 forming 6, from which subsequent elimination of ketene would occur (Fig. 3B). Conversion of 1 into 6 + 7 is akin to the pyrolysis of a chroman ring. Chroman pyrolysis occurs through a retro Diels-Alder reaction to produce ortho-quinone methide and ethane by C-C and C-O bond cleavage in the dihydropyran ring (21). Employing gas phase M06-2X/6-311G (d,p) calculations, the TS energy barrier for the formation of 6 from 1 was determined to be 58.8 kcal/mol (SI Appendix, Fig. S7). This value is lower than conversion of 1 into 4 + 2 by 10.7 kcal/mol. As such, it seems probable that both ketene-producing pathways may be in operation i.e. 1 → 4 + 2 and 1 → 6 → 4 + 8 but that the latter is more favorable.

**Experimental Analysis of Vaped 1.** With experimentation and theoretical evidence for the elimination of ketene from 1, we felt compelled to directly investigate the effect, if any, on vaping vitamin E acetate. However, it should be noted that these experiments were not designed to exactly replicate a user’s experience; rather the goal was to determine the vaping pyrolysis effect on 1 as a single pure substance at the chemistry molecular level. Extrapolation of the exact relevance of these results to the direct cause of lung injury is beyond the scope of this preliminary report due to the diversity in vaping devices, mixtures and their modes of use. As described in the methods section, the isolated mixture of vaped 1 was collected and analyzed as either the total vaped mixture or following separation into its volatile (VC) and non-volatile components (NVC). APCI-MS analysis was inconclusive, as spectra closely resembled that of pure 1, though it was suspected that changes may be masked by the fragmentation pattern of remaining 1 and the formation of hydrocarbon fragments that are not APCI-MS responsive (SI Appendix, Fig. S8). As such, NMR data was collected for the total vaped material and individually for the volatile and non-volatile components of the vaped mixture. Comparison of the 1H NMR spectrum of the entire vaped material with that of pure 1 was revealing as it showed that significant chemical transformations had occurred. Numerous peaks with complex splitting patterns, not observed for vitamin E acetate, between 4.6 and 7.4 ppm were recorded in the vaped material and the spectral region between 0.8 and 2.1 ppm showed increased complexity (Fig. 6, SI Appendix, Fig. S9).

![Fig. 6. Top: 1H NMR spectrum of pure 1. Bottom: 1H NMR spectrum of entire isolated vaped mixture from 1. For clarity the peak at 7.36 ppm is not shown in cropped view, see SI Appendix, Fig. S9 for full spectra. Inset box (i) indicates volatile components (VC); box (ii) indicates mixture of volatile and non-volatile components; box (iii) primarily non-volatile components (NVC).](image-url)
Separate $^1$H NMR spectra were obtained for both non-volatile and volatile components. Close examination of the non-volatile components spectrum and comparison with 1 and 2 provided important insights (Fig. 7, SI Appendix, Fig. S10). This showed that non-volatile component comprised of vitamin E acetate 1, (key singlet peaks at 2.09, 2.03, 1.98 ppm), 2,3,5,6-tetramethylcyclohexa-2,5-diene-1,4-dione, (duroquinone) 8 (key singlet peak at 2.01 ppm) and prist-1-ene 7 (key doublet peak at 4.68 ppm). The assignments of 7 and 8 were further confirmed by $^{13}$C spectra, proton-carbon correlations using heteronuclear single quantum coherence spectroscopy (HSQC) and heteronuclear multiple bond correlations (HMBC) (SI Appendix, Fig. S11). Comparison with a spectrum of pure 2 showed that, perhaps surprisingly, no vitamin E was contained in the mixture (key singlet peaks at 2.18, 2.13 ppm, two overlapping singlets) (Fig. 7). Integration of a methyl singlet of 1 versus that for duroquinone 8 gave an estimate of vape induced pyrolysis between 15-20%. This amount of pyrolytic conversion was consistent across six independent experiments.

NMR analysis identified the volatile components in the mixture as benzene (key singlet peak at 7.36 ppm), butadiene (key multiplet peak at 6.36 ppm), propene (key d,d,q peaks at 5.83 ppm), ethene (key singlet peak at 5.41 ppm), 2-methylprop-1-ene (key singlet peak at 4.66 ppm) and lower molecular weight 1-methyl-1-alkyl-alkenes (key doublet peak at 4.67 ppm) (Fig. 8). Trace amounts of THF, formaldehyde and short chain aliphatic aldehydes were also observed (SI Appendix, Fig. S12). Propene was the most abundant volatile material with a three to four fold stoichiometric ratio greater than that of duroquinone 8. This indicates that upon release of prist-1-ene 7 from 1, it fragments into numerous propene units and the other identified alkenes. Trace aldehydes would be oxidation products of these alkenes and benzene a downstream by-product from them.
Fig. 8. Portion of the $^1$H NMR spectrum of the isolated volatile component (VC) following vaping vitamin E acetate 1. See SI Appendix, Fig. S12 for full spectrum including benzene peak at 7.36 ppm. Red asterisk 1-methyl-1-alkyl alkenes; blue asterisk propene; black asterisk butadiene.

The routes to forming the spectrum of compounds generated by the vape pyrolysis of 1 are illustrated in Fig. 9. In pathway A, ketene is released from 1 to produce vitamin E which undergoes C-C and C-O bond breaking of the dihydropyran ring to produce 8 and 7. Pathway B generates the same mixture of end products but by a different sequence such that first the dihydropyran ring cleaves followed subsequently by loss of ketene from 6. Long aliphatic-chained alkene 7 undergoes further decomposition to produce the lower molecular weight alkenes ethene, propene, butadiene and aromatic benzene. Importantly, many of these alkenes and benzene are known carncinogenic constituents within tobacco smoke (22, 23) and elevated amounts of their oxidative metabolites have been found in a study of adolescent e-cigarette users (24). Both pathways produced duroquinone 8, which is an organic oxidant though insufficient data is currently available of its inhalation hazards (25). The high ketene reactivity prevented its NMR detection within the isolated complex volatile mixture. Cumulatively, theoretical DFT calculations, analytical APCI-MS and experimental results point towards pathway B being the predominate route of pyrolysis under vaping conditions.

Fig. 9. Rationale of experimental and theoretical results from vape pyrolysis reactions of vitamin E acetate 1.

As direct isolation of ketene under low temperature conditions proved challenging, chemical trapping experiments were next carried out to verify its formation. Benzylamine 9 was chosen as a
representative amine nucleophile as the chemical shift of its methylene group (s, 3.85 ppm) appears in a spectral region devoid of peaks in the vape mixture (between 4.6 and 3.8 ppm). Experimentally, the vaped mixture of 1 was passed through a trap containing a solution of benzylamine in CDCl$_3$ at room temperature. Subsequent NMR analysis clearly showed an additional doublet at 4.36 ppm (not present in the vape mixture alone) which was consistent with an authentic sample of the acetylation benzylamide product 10 (Fig. 10, SI Appendix, Fig. S13, S14). Integration of the benzylamide methylene peak, from three independent experiments, with that of the methyl signal for 8 approximated that 30% of ketene produced had reacted with 9.

![Diagram of chemical trapping of vaped produced ketene with benzylamine 9 forming benzylamide 10.](image)

**Fig. 10.** Chemical trapping of vaped produced ketene with benzylamine 9 forming benzylamide 10. Portion of the $^1$H NMR spectra showing vape mixture from 1 isolated in CDCl$_3$ containing 9 and an authentic sample of benzylamide 10. Black asterisk methylene peak of 9, red asterisk methylene peak of 10. See SI Appendix, Fig. S13 and S14 for full spectra.

The current worrying trend of increasing vaping associated lung injuries is due to complex and multifaceted issues encompassing social, physical, biological and medical sciences. When viewed from a physical science standpoint, medical complications from vaping a diverse set of substrates is perhaps not unexpected as the pyrolytic chemistry of single pure compounds is complex, so what occurs within ill-defined mixtures is a risky venture into the unknown. The temperatures obtainable within vaping devices places them in the category of a small-scale laboratory pyrolysis apparatus which if not used with precision and care can have unforeseen outcomes. In this report, we have highlighted the chemical basis for concern over vitamin E acetate, just one known component of vape mixtures. Our primary concern initially lay with the ability of the aryl acetate functional group to eliminate as ketene, though other reactive and known carcinogen (alkenes, benzene) are also produced for which the negative long-term effects are well recognized. Thermal activation of aryl acetates above their decomposition temperatures leads to the formation of highly toxic ketene, which if inhaled into the lungs, even in small quantities, can cause severe pulmonary injury. Evidence for ketene formation from vitamin E acetate, was obtained from APCI-MS, DFT calculations and trapping experiments. In closing, it is important to note that it is most likely that other aryl O-acetates would eliminate ketene in a similar manner to the two substrates investigated in this report. Additionally, published data on
the pyrolysis of flavor ingredients and additives used in vape products verified the generation of a spectrum of known carcinogens (26). Considering the continuing evolving and large number of natural and synthetic substances used in recreational vaping and the unknown chemistries that may occur under vaping pyrolysis conditions, urgent research into this topic is now required. The most efficient approach would appear to be the development of pyrolysis prediction software, cross-referenced with toxicity data, allowing the rapid identification of individual compounds and compound mixtures that pose the most serious risks.

**Methods:**

DL-α-Tocopherol acetate (vitamin E acetate), (±)-α-tocopherol (vitamin E), phenyl acetate, duroquinone, benzylamine and chloroform d₅ were purchased from Sigma Aldrich. Benzylamide was synthesized following a literature procedure (27). Vaping device (NEXUS P-1) was purchased in a retail outlet in Dublin, Ireland. Vaping device (30 - 50 W, 129 A, 0.25 Ω Kanthal coil) was used fully charged and at 50 W power setting. Mass spectra of each sample were recorded using an Advion Expression mass spectrometer, with each sample analyzed at a series of source voltages of 5, 10, 20 and 30 eV. Other instrument parameters including capillary temperature: 250 °C; capillary voltage 180 eV; source voltage span 30 eV; source gas temperature 350 °C; APCI corona discharge 5 were used consistently for all samples. MS solvent system of MeOH/IPA/H₂O/CHO₂H in a ratio of 80:10:10:0.1. Positive mode was superior to negative mode and was selected for use throughout the study. Positive mode ESI mass spectra of vitamin E acetate were complicated by the appearance of significant amounts of sodium adducts which were not prevalent in the APCI spectra, as such APCI was selected as the preferred mode for analysis. NMR spectra were obtained on a 400 MHz instrument in CDCl₃. HPLC analysis used an Atlantis dC18 reverse phase column (5µM, 4.6 x 250 mm with UV-Vis detector at 254 and 220 nm, mobile phase ACN/H₂O 70:30, flow rate 1 mL/min).

**Apparatus for vape pyrolysis trapping experiments**

Glass traps were purchased from Rettberg GmbH, catalogue number 137082015. Rubber tubing was used to connect vaping device to the glass trap 1, the glass traps together and glass trap to the vacuum source. Low form Dewar flasks (Sigma Aldrich catalogue number Z150398) were used for liquid nitrogen baths. Schematics of the apparatus configurations are shown in Fig. 11 and photographs showing the apparatus used are shown in Fig. S15. The average weight of isolated vaped material was measured from three independent experiments at 2.4 mg/puff.
Fig. 11. Apparatus set up for trapping vaped products of vitamin E acetate 1. Setup A: Apparatus for low temperature trapping of all vaped material. Setup B: Apparatus for low temperature trapping of all vaped material followed by separation of volatile from nonvolatile components. Setup C: Apparatus for trapping of vape produced ketene by benzylamine in CDCl₃.

Procedure for vape pyrolysis with low temperature trapping.
Vaping experiments were conducted in a fumehood using the apparatus set up as shown in Fig. 11A. The vaping device containing 1 was connected via rubber tubing to the stopcock which in turn was connected to the glass trap, the outlet of which was connected by rubber tubing to the vacuum source. Once assembled the glass trap was placed into a liquid N₂ bath for 2 min and vaping then commenced. The vaping device was turned on for 5 sec with an airflow (65 mL/min) applied, generated by a vacuum, to draw the vapor (puff volume 35 mL) into the trap. This was repeated 8 times at 30 sec intervals and the airflow was stopped by closing the vacuum. To analyze the vaped material, the trap was isolated from the vaping device by closing the stopcock, CDCl₃ (1.0 mL) was added to the trap, the trap removed from the liquid N₂ bath and allowed warm to room temperature. The CDCl₃ was removed from the trap and immediately analyzed by NMR.
Procedure for vape pyrolysis with low temperature trapping and separation of volatile from non-volatile components.

All vaping experiments were conducted in a fumehood using the apparatus set up as shown in Fig. 11B. The vaping device containing 1 was connected via rubber tubing to stopcock 1 which was connected to glass trap 1. The outlet of glass trap 1 was connected to stopcock 2, which was connected to trap 2 which was connected by rubber tubing to the vacuum source. Once assembled glass trap 1 and 2 were placed into individual liquid N$_2$ baths for 2 min and vaping then commenced. The vaping device was turned on for 5 sec with an airflow (65 mL/min) applied, generated by a vacuum, to draw the vapor (puff volume 35 mL) into trap 1. This was repeated 8 times at 30 sec intervals, the airflow stopped by closing the vacuum and stopcock 1 closed to isolate the traps from the vaping device. Trap 1 was removed from its liquid N$_2$ bath and allowed warm to room temperature. Once trap 1 reached room temperature, it was isolated from trap 2 by closing stopcock 2. Following isolation of traps 1 and 2 from each other, CDCl$_3$ (1.0 mL) was added to each trap. Trap 2 was removed from its liquid N$_2$ bath and allowed warm to room temperature. The CDCl$_3$ was removed from both traps and immediately analyzed by NMR. Spiking vape samples with pure benzene and duroquinone confirmed their assignments.

Procedure for trapping vape pyrolysis produced ketene 4 with benzylamine 9.

All vaping experiments were conducted in a fumehood using the apparatus set up as shown in Fig. 11C. The vaping device containing 1 was connected via rubber tubing to the stopcock which in turn was connected to the glass trap, the outlet of which was connected by rubber tubing to the vacuum source. Benzylamine 9 (0.02 mL, 0.183 mmol) in CDCl$_3$ (2.0 mL) was added into the glass trap. The vaping device was turned on for 5 sec with an airflow (65 mL/min) applied, generated by a vacuum, to draw the vapor (puff volume 35 mL) into the trap. This was repeated 30 times at 30 sec intervals and the airflow was stopped by closing the vacuum. The CDCl$_3$ was removed from the trap and immediately analyzed by NMR and reverse phase HPLC (Atlantis dC18 reverse phase column, mobile phase ACN/H$_2$O 70:30, flow rate 1 mL/min). Benzylamide 10 was identified in vape mixture NMR by a doublet peak at 4.36 ppm and confirmed by spiking the vape sample with pure 10. HPLC retention time for benzylamide in the vape mixture was 4.2 min, which was confirmed by spiking the vape mixture with an authentic sample of 10. A control experiment showed no formation of benzylamide 10 following mixing 1 and 9 in CDCl$_3$ for 24 h.

Data and Materials Availability

All data are available in the main text or SI Appendix. Raw data files are available from the corresponding author upon request.

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Supporting Information

Potential for Release of Pulmonary Toxic Ketene from Vaping Pyrolysis of Vitamin E Acetate

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General Methods.
Atmospheric-pressure chemical ionization (APCI) and electrospray ionization (ESI) mass spectra were acquired using Advion Expression Mass Spectrometer in positive and negative modes as required. $^1$H NMR and $^{13}$C NMR spectra were recorded at room temperature at 400 MHz and 100 MHz respectively, and calibrated using residual non-deuterated solvent as an internal reference. HPLC analysis used an Atlantis dC18 reverse phase column (5µM, 4.6 x 250 mm with UV-Vis detector at 254 and 220 nm). All vaping experiments were carried out in a ventilated fumehood.

Computational Details.
All of the calculations reported in this work were carried out using the Gaussian 09e01 package from Irish Centre for High-End Computing (ICHEC). The M06-2X density-functional method in conjunction with the 6-311G(d,p) basis set was selected for all the geometry optimizations and frequency analysis. All geometries were optimized in gas phase. Frequency calculations at 298.15 K and 1 atm pressure on all the stationary points were carried out at the same level of theory as the geometry optimizations to ascertain the nature of the stationary points. All of the presented relative energies are free energies at 298.15 K with respect to the reactants, unless otherwise stated. Each TS was confirmed by IRC calculations and vibrational analysis showing a single imaginary frequency. A six-membered TS in which proton transfer to an ortho-aryl ring position followed by enolization to phenol has also been proposed for the loss of ketene from phenyl acetate (1). As the ortho aryl positions of 1 are methyl substituted loss of ketene is unlike to proceed through six-membered proton transfer to the aryl ring so the four membered TS was selected for comparative calculations.

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**Figure S1.** APCI-MS cone-voltage study for phenyl acetate 3.

Fig. S1a: 10 eV, APCI-MS (positive mode).

Fig. S1c: 20 eV, APCI-MS (positive mode).

Fig. S1d: 25 eV, APCI-MS (positive mode).

Fig. S1e: 30 eV, APCI-MS (positive mode).
Figure S2. APCI-MS cone-voltage studies for vitamin E acetate 1

**Fig. S2a:** 5 eV, APCI-MS (positive mode).

**Fig. S2b:** 10 eV, APCI-MS (positive mode).

**Fig. S2c:** 15 eV, APCI-MS (positive mode).

**Fig. S2d:** 20 eV, APCI-MS (positive mode).
Fig. S2f: 30 eV, APCI-MS (positive mode).
Figure S3. APCI-MS cone-voltage studies for vitamin E

Fig. S3a: 5 eV, APCI-MS (positive mode).

Fig. S3b: 10 eV, APCI-MS (positive mode).

Fig. S3c: 20 eV, APCI-MS (positive mode).

Fig. S3d: 30 eV, APCI-MS (positive mode).
Figure S4. DFT calculation data for 3 and transition state

Ground state structure of phenyl acetate 3

E(RM062X) = -460.052680107
Zero-point correction = 0.143297 (Hartree/Particle)
Thermal correction to Energy = 0.152147
Thermal correction to Enthalpy = 0.153091
Thermal correction to Gibbs Free Energy = 0.108399
Sum of electronic and zero-point Energies = -459.909383
Sum of electronic and thermal Energies = -459.900533
Sum of electronic and thermal Enthalpies = -459.899589
Sum of electronic and thermal Free Energies = -459.944281
Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
|               | 1             | 6           | 0.000000 -2.461087 -1.071596 0.274742 |
|               | 2             | 6           | 0.000000 -2.960549 0.213076 0.092541 |
|               | 3             | 6           | 0.000000 -2.093537 1.249227 -0.236957 |
|               | 4             | 6           | 0.000000 -0.731044 1.017001 -0.385217 |
|               | 5             | 6           | 0.000000 -0.249634 -0.271794 -0.194087 |
|               | 6             | 6           | 0.000000 -1.101048 0.213076 0.092541 |
|               | 7             | 1           | 0.000000 3.128229 -1.866254 0.528666 |
|               | 8             | 1           | 0.000000 4.020091 0.406237 0.205620 |
|               | 9             | 1           | 0.000000 0.000000 2.252805 -0.379570 |
|               | 10            | 1           | 0.000000 0.000000 1.821804 -0.630791 |
|               | 11            | 1           | 0.000000 0.000000 2.307996 -0.265838 |
|               | 12            | 8           | 0.000000 1.884015 -0.610537 -0.389011 |
|               | 13            | 6           | 0.000000 2.077816 0.157872 0.139254 |
|               | 14            | 6           | 0.000000 3.412590 -0.446371 -0.192692 |
|               | 15            | 1           | 0.000000 3.500814 -0.567763 -1.272771 |
|               | 16            | 1           | 0.000000 4.200639 0.198517 0.185922 |
|               | 17            | 1           | 0.000000 3.484469 -1.436762 0.258890 |
|               | 18            | 8           | 0.000000 1.893018 1.152982 0.770553 |

Ground state structure of ketene 4

E(RM062X) = -152.578714584
Zero-point correction = 0.032023 (Hartree/Particle)
Thermal correction to Energy = 0.035501
Thermal correction to Enthalpy = 0.036445
Thermal correction to Gibbs Free Energy = 0.009110
Sum of electronic and zero-point Energies = -152.546692
Sum of electronic and thermal Energies = -152.543214
Sum of electronic and thermal Enthalpies = -152.542270
Sum of electronic and thermal Free Energies = -152.569605
Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
|               | 1             | 6           | 0.000000 -0.000000 -0.000000 -0.103973 |
|               | 2             | 8           | 0.000000 -0.000000 -0.000000 1.258820 |
|               | 3             | 6           | 0.000000 0.000000 0.000000 -1.284928 |
|               | 4             | 1           | 0.000000 -0.000000 0.940447 -1.732415 |
|               | 5             | 1           | 0.000000 0.000000 -0.940447 -1.732415 |
Ground state structure of phenol 5

$E(RM062X) = -307.417355370$

Zero-point correction = 0.105600 (Hartree/Particle)
Thermal correction to Energy = 0.111050
Thermal correction to Enthalpy = 0.111994
Thermal correction to Gibbs Free Energy = 0.076670
Sum of electronic and zero-point Energies = -307.311755
Sum of electronic and thermal Energies = -307.306305
Sum of electronic and thermal Enthalpies = -307.305361
Sum of electronic and thermal Free Energies = -307.340685

Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
| 1             | 6             | 0           | X: -1.127194 Y: 1.214015 Z: -0.000000 |
| 2             | 6             | 0           | X: 0.263486 Y: 1.194447 Z: 0.000000 |
| 3             | 6             | 0           | X: 0.937438 Y: -0.023909 Z: 0.000000 |
| 4             | 6             | 0           | X: 0.220142 Y: -1.218571 Z: 0.000000 |
| 5             | 6             | 0           | X: -1.166337 Y: -1.185985 Z: -0.000000 |
| 6             | 6             | 0           | X: -1.849530 Y: 0.027643 Z: -0.000000 |
| 7             | 1             | 0           | X: -1.644688 Y: 2.165939 Z: -0.000000 |
| 8             | 1             | 0           | X: 0.825228 Y: 2.123497 Z: 0.000000 |
| 9             | 1             | 0           | X: 0.769113 Y: -2.151795 Z: 0.000000 |
| 10            | 1             | 0           | X: -1.718883 Y: -2.118096 Z: -0.000000 |
| 11            | 1             | 0           | X: -2.931768 Y: 0.046321 Z: -0.000000 |
| 12            | 8             | 0           | X: 2.295374 Y: -0.118676 Z: 0.000000 |
| 13            | 1             | 0           | X: 2.669969 Y: 0.773706 Z: 0.000001 |

Transition state image of $3 \rightarrow 4 + 5$

Transition state structure for $3 \rightarrow 4 + 5$

Imaginary Frequency: -1637.0775.
$E(RM062X) = -459.939805174$

Zero-point correction = 0.135319 (Hartree/Particle)
Thermal correction to Energy = 0.144461
Thermal correction to Enthalpy = 0.145405
Thermal correction to Gibbs Free Energy = 0.099782
Sum of electronic and zero-point Energies = -459.804486
Sum of electronic and thermal Energies = -459.795344
Sum of electronic and thermal Enthalpies = -459.794400
Sum of electronic and thermal Free Energies = -459.840023

Standard orientation:
| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|------------------------|
|               |               |             | X          | Y          | Z          |
| 1             | 6             | 0           | 2.337300  | -1.084505 | -0.206101 |
| 2             | 6             | 0           | 1.049393  | -1.220256 | 0.300383  |
| 3             | 6             | 0           | 0.267495  | -0.085306 | 0.550677  |
| 4             | 6             | 0           | 0.804453  | 1.182431  | 0.287040  |
| 5             | 6             | 0           | 2.090228  | 1.303622  | -0.219286 |
| 6             | 6             | 0           | 1.049393  | -1.220256 | 0.300383  |
| 7             | 1             | 0           | 2.932915  | -1.971434 | -0.390245 |
| 8             | 1             | 0           | 0.642878  | -2.198695 | 0.532814  |
| 9             | 1             | 0           | 0.197416  | 2.054695  | 0.501023  |
| 10            | 1             | 0           | 2.494613  | 2.290495  | -0.414895 |
| 11            | 1             | 0           | 3.868617  | 0.275123  | -0.865369 |
| 12            | 8             | 0           | -0.988722 | -0.201784 | 1.009236  |
| 13            | 1             | 0           | -1.719082 | -1.211474 | 0.552670  |
| 14            | 6             | 0           | -2.467855 | 0.177694  | -0.321309 |
| 15            | 8             | 0           | -2.834906 | 1.252840  | -0.264673 |
| 16            | 6             | 0           | -2.424359 | -1.207636 | -0.553457 |
| 17            | 1             | 0           | -3.375963 | -1.628899 | -0.864352 |
| 18            | 1             | 0           | -1.580240 | -1.456043 | -1.199423 |
Figure S5. DFT calculation data for 1† and its transition state

Ground state structure of 1†

E(RMP2X) = -848.51836312
Zero-point correction = 0.351643 (Hartree/Particle)
Thermal correction to Energy = 0.371700
Thermal correction to Enthalpy = 0.372644
Thermal correction to Gibbs Free Energy = 0.303642
Sum of electronic and zero-point Energies = -848.167293
Sum of electronic and thermal Energies = -848.147237
Sum of electronic and thermal Enthalpies = -848.146292
Sum of electronic and thermal Free Energies = -848.215295

Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
|               |               |             | X           | Y           | Z           |
| 1             | 6             | 0           | 1.060561    | 0.492672    | 0.067751    |
| 2             | 6             | 0           | 0.631667    | -0.829997   | -0.874317   |
| 3             | 6             | 0           | -0.717081   | -1.083801   | -0.356313   |
| 4             | 6             | 0           | -1.591167   | -0.008158   | -0.456422   |
| 5             | 6             | 0           | -1.173743   | 1.316091    | -0.312559   |
| 6             | 6             | 0           | 0.178290    | 1.578826    | -0.837893   |
| 7             | 6             | 0           | -3.841196   | -0.431864   | 0.237451    |
| 8             | 8             | 0           | -2.926565   | -0.259312   | -0.763344   |
| 9             | 8             | 0           | -4.977089   | -0.639519   | 0.057574    |
| 10            | 6             | 0           | -1.212676   | -2.496005   | -0.529877   |
| 11            | 1             | 0           | -1.276123   | -3.015600   | 0.432525    |
| 12            | 1             | 0           | -2.199160   | -2.509559   | -0.989559   |
| 13            | 1             | 0           | -0.534251   | -3.072886   | -1.161404   |
| 14            | 6             | 0           | 0.667799    | 2.983101    | 0.126890    |
| 15            | 1             | 0           | 0.734610    | 3.487120    | -0.842678   |
| 16            | 1             | 0           | -0.011723   | 3.567133    | 0.750820    |
| 17            | 1             | 0           | 1.655685    | 2.994653    | 0.580022    |
| 18            | 6             | 0           | 1.608893    | -1.971593   | 0.682420    |
| 19            | 1             | 0           | 1.161610    | -2.758595   | 0.695360    |
| 20            | 1             | 0           | 1.808247    | 2.425671    | -0.895727   |
| 21            | 6             | 0           | 2.999801    | -1.494865   | 0.719213    |
| 22            | 1             | 0           | 2.756089    | -1.318641   | 1.788263    |
| 23            | 1             | 0           | 3.694425    | -2.248287   | 0.614721    |
| 24            | 8             | 0           | 2.361133    | 0.817908    | 0.334262    |
| 25            | 6             | 0           | 3.370095    | -0.178788   | 0.894750    |
| 26            | 6             | 0           | 3.596956    | -0.298166   | -1.411208   |
| 27            | 1             | 0           | 2.669595    | -0.534189   | -1.936335   |
| 28            | 1             | 0           | 3.975541    | 0.648081    | -1.801796   |
| 29            | 1             | 0           | 4.327300    | -1.082793   | -1.624213   |
| 30            | 6             | 0           | 4.611956    | 0.352784    | 0.790182    |
| 31            | 1             | 0           | 5.453428    | -0.324650   | 0.638370    |
| 32            | 1             | 0           | 4.870593    | 1.355502    | 0.391766    |
| 33            | 1             | 0           | 4.431878    | 0.449023    | 1.862314    |
| 34            | 6             | 0           | -2.156619   | 2.449727    | -0.450995   |
| 35            | 1             | 0           | -3.098373   | 2.105780    | -0.874702   |
| 36            | 1             | 0           | -2.362903   | 2.914451    | 0.519055    |
| 37            | 1             | 0           | -1.754887   | 3.230472    | -1.899339   |
| 38            | 6             | 0           | -3.328548   | -0.343620   | 1.654308    |
| 39            | 1             | 0           | -4.168591   | -0.509485   | 2.322752    |
| 40            | 1             | 0           | -2.551533   | -1.897777   | 1.829909    |
| 41            | 1             | 0           | -2.883333   | 0.635239    | 1.841931    |

† Simplified structure used for calculation without C_{15}H_{32} alkyl group.
Ground state structure of $2^*$

E(RM062X) = -695.883672263

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
|               | 1             | 6           | X 0.283099 Y 0.458090 Z -0.145796 |
|               | 2             | 6           | X 0.027932 Y -0.914811 Z -0.137802 |
|               | 3             | 6           | X 1.296994 Y -1.358301 Z -0.019870 |
|               | 4             | 6           | X 2.328073 Y -0.422371 Z 0.021265 |
|               | 5             | 6           | X 2.075821 Y 0.951546 Z -0.010932 |
|               | 6             | 6           | X 0.755360 Y 1.395187 Z -0.072893 |
|               | 7             | 8           | X 3.641709 Y -0.815216 Z 0.118103 |
|               | 8             | 6           | X 1.637259 Y -2.827834 Z 0.065951 |
|               | 9             | 1           | X 0.771090 Y -3.429260 Z 0.333071 |
|               | 10            | 1           | X 2.022775 Y -3.216236 Z -0.841432 |
|               | 11            | 1           | X 2.394934 Y -3.003976 Z 0.834606 |
|               | 12            | 6           | X 0.445369 Y 2.869465 Z -0.076428 |
|               | 13            | 1           | X 1.058146 Y 3.403307 Z 0.641581 |
|               | 14            | 1           | X 0.655999 Y 3.302600 Z -1.076923 |
|               | 15            | 1           | X -0.604879 Y 3.044553 Z 0.136085 |
|               | 16            | 6           | X -1.171140 Y -1.899852 Z -0.255704 |
|               | 17            | 1           | X -0.915041 Y -2.679023 Z -0.978114 |
|               | 18            | 1           | X -1.327252 Y -2.407563 Z 0.703823 |
|               | 19            | 6           | X -2.456883 Y -1.204678 Z -0.692782 |
|               | 20            | 1           | X -2.465404 Y -0.966069 Z -1.759461 |
|               | 21            | 1           | X -3.321702 Y -1.854886 Z -0.537521 |
|               | 22            | 8           | X -1.551114 Y 0.974663 Z -0.249052 |
|               | 23            | 6           | X -2.650527 Y 0.188418 Z 0.062989 |
|               | 24            | 6           | X -2.712547 Y -0.096973 Z 1.576096 |
|               | 25            | 1           | X -1.769613 Y -0.489287 Z 1.961746 |
|               | 26            | 1           | X -2.908208 Y 0.857488 Z 2.062878 |
|               | 27            | 1           | X -3.513387 Y -0.795022 Z 1.833673 |
|               | 28            | 6           | X -3.881754 Y 0.847681 Z -0.434304 |
|               | 29            | 1           | X -4.784640 Y 0.276323 Z -0.207791 |
|               | 30            | 1           | X -3.952567 Y 1.823263 Z 0.050349 |
|               | 31            | 1           | X -3.818285 Y 1.000968 Z -1.513083 |
|               | 32            | 6           | X 3.218788 Y 1.931512 Z 0.834787 |
|               | 33            | 1           | X 4.165969 Y 1.426897 Z -0.140643 |
|               | 34            | 1           | X 3.091373 Y 2.713146 Z -0.717334 |
|               | 35            | 1           | X 3.274258 Y 2.423842 Z 1.010799 |
|               | 36            | 1           | X 3.717877 Y -1.735903 Z -0.140304 |

† Simplified structure used for calculation without C_{15}H_{32} alkyl group.
Transition state image of $1 \rightarrow 4 + 2$

Transition state structure of $1' \rightarrow 4 + 2'$

Imaginary Frequency: -1669.7490.
E(RM062X) = -848.401721573
Zero-point correction = 0.344957 (Hartree/Particle)
Thermal correction to Energy = 0.36819
Thermal correction to Enthalpy = 0.365763
Thermal correction to Gibbs Free Energy = 0.297155
Sum of electronic and zero-point Energies = -848.056765
Sum of electronic and thermal Energies = -848.036903
Sum of electronic and thermal Enthalpies = -848.035958
Sum of electronic and thermal Free Energies = -848.104567

Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
|               |               |             | X           | Y           | Z           |
| 1             | 6             | 0           | 0.311464    | 1.545022    | 0.080560    |
| 2             | 6             | 0           | -1.028275   | 1.409248    | -0.312785   |
| 3             | 6             | 0           | -1.571673   | 0.127753    | -0.495900   |
| 4             | 6             | 0           | -0.782920   | -1.029314   | -0.362773   |
| 5             | 6             | 0           | 0.540078    | -0.882043   | 0.043397    |
| 6             | 6             | 0           | 1.063625    | 0.398805    | 0.272670    |
| 7             | 8             | 0           | -2.889845   | -0.012276   | -0.813886   |
| 8             | 1             | 0           | -3.720235   | 0.824572    | -0.277777   |
| 9             | 6             | 0           | -4.081070   | -0.680882   | 0.564528    |
| 10            | 8             | 0           | -4.314516   | -1.796517   | 0.467180    |
| 11            | 6             | 0           | -4.288407   | 0.661315    | 0.926738    |
| 12            | 1             | 0           | -5.243116   | 0.854665    | 1.405848    |
| 13            | 1             | 0           | -3.418745   | 1.065087    | 1.446098    |
| 14            | 6             | 0           | -1.376921   | -2.383282   | -0.662730   |
| 15            | 6             | 0           | 1.530699    | -1.999922   | 0.228214    |
| 16            | 6             | 0           | -1.857670   | 2.643468    | -0.575608   |
| 17            | 6             | 0           | 0.930281    | 2.901113    | 0.298344    |
| 18            | 6             | 0           | 2.817194    | -1.592510   | -0.499638   |
| 19            | 8             | 0           | 2.345900    | 0.484498    | 0.753788    |
| 20            | 6             | 0           | 3.373221    | -0.267151   | 0.063798    |
| 21            | 1             | 0           | -1.257287   | 3.411118    | -1.966566   |
| 22            | 1             | 0           | -2.703409   | 2.420487    | -1.225910   |
| 23            | 1             | 0           | -2.247819   | 3.085583    | 0.347915    |
| 24            | 1             | 0           | 1.055206    | 3.431464    | -0.651164   |
| 25            | 1             | 0           | 0.302427    | 3.525743    | 0.938483    |
| 26            | 1             | 0           | 1.989108    | 2.798887    | 0.762022    |
| 27            | 1             | 0           | -0.710181   | -2.968524   | -1.299251   |
| 28            | 1             | 0           | -1.552927   | -2.961843   | 0.249002    |
| 29            | 1             | 0           | -2.329140   | -2.272406   | -1.178173   |
| 30            | 1             | 0           | 1.739272    | -2.135579   | 1.296165    |
| 31            | 1             | 0           | 1.153051    | -2.948149   | -0.153324   |
| 32            | 1             | 0           | 2.585878    | -1.478712   | -1.562607   |
|    |    |    |    |    |    |    |
|---|---|---|---|---|---|---|
| 33| 1 | 0 | 3.586055 | -2.364809 | -0.412374 |
| 34| 6 | 0 | 4.422055 | -0.530287 | 1.134092  |
| 35| 6 | 0 | 3.919916 | 0.616378  | -1.051342 |
| 36| 1 | 0 | 4.697634 | 0.407010  | 1.620471  |
| 37| 1 | 0 | 4.025768 | -1.209198 | 1.892595  |
| 38| 1 | 0 | 4.680334 | 0.084653  | -1.629319 |
| 39| 1 | 0 | 3.107781 | 0.900219  | -1.726240 |
| 40| 1 | 0 | 4.362887 | 1.523109  | -0.633805 |
| 41| 1 | 0 | 5.314759 | -0.977273 | 0.691203  |

† Simplified structure used for calculation without C<sub>13</sub>H<sub>32</sub> alkyl group.
Figure S6. DFT calculation data of 6 and its transition state

**Ground state structure of 6**

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
| 1             | 6             | 0           | X 1.638646 Y 1.290650 Z 0.009154 |
| 2             | 6             | 0           | X 2.311849 Y -0.056226 Z 0.100299 |
| 3             | 6             | 0           | X 1.464417 Y -1.259614 Z -0.054193 |
| 4             | 6             | 0           | X 0.140542 Y -1.119873 Z -0.290424 |
| 5             | 6             | 0           | X -0.472826 Y 0.218974 Z -0.360972 |
| 6             | 6             | 0           | X 0.196316 Y 1.367247 Z -0.228511 |
| 7             | 8             | 0           | X -1.838881 Y 0.244807 Z -0.638032 |
| 8             | 6             | 0           | X -2.687053 Y -0.047579 Z 0.389520 |
| 9             | 6             | 0           | X -4.190735 Y -0.001232 Z -0.866873 |
| 10            | 1             | 0           | X -4.259363 Y -0.775618 Z -0.841369 |
| 11            | 1             | 0           | X -4.776616 Y -0.164359 Z 0.755049 |
| 12            | 1             | 0           | X -4.311663 Y 0.961558 Z -0.557195 |
| 13            | 8             | 0           | X -2.312280 Y -0.304950 Z 1.491798 |
| 14            | 6             | 0           | X -0.762682 Y -2.304502 Z -0.495771 |
| 15            | 1             | 0           | X -1.339017 Y -2.496020 Z 0.414800 |
| 16            | 1             | 0           | X -1.470832 Y -2.112999 Z -1.303915 |
| 17            | 1             | 0           | X -0.193832 Y -3.198923 Z -0.738834 |
| 18            | 6             | 0           | X 2.157817 Y -2.589701 Z 0.052739 |
| 19            | 1             | 0           | X 1.622675 Y -3.264977 Z 0.722654 |
| 20            | 1             | 0           | X 2.235782 Y -3.075581 Z -0.924502 |
| 21            | 1             | 0           | X 3.164427 Y -2.440717 Z 0.432871 |
| 22            | 6             | 0           | X -0.472784 Y 2.707483 Z -0.306267 |
| 23            | 1             | 0           | X -1.529150 Y 2.604651 Z -0.542655 |
| 24            | 1             | 0           | X -0.376474 Y 3.238013 Z 0.644893 |
| 25            | 1             | 0           | X -0.006753 Y 3.324124 Z -1.079072 |
| 26            | 6             | 0           | X 2.410466 Y 2.373025 Z 0.170801 |
| 27            | 8             | 0           | X 3.580860 Y -0.140831 Z 0.288547 |
| 28            | 1             | 0           | X 2.012901 Y 3.379318 Z 0.128974 |
| 29            | 1             | 0           | X 3.470042 Y 2.241400 Z 0.353496 |

**Ground state structure of 8**

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
| 1             | 6             | 0           | X 1.638646 Y 1.290650 Z 0.009154 |
| 2             | 6             | 0           | X 2.311849 Y -0.056226 Z 0.100299 |
| 3             | 6             | 0           | X 1.464417 Y -1.259614 Z -0.054193 |
| 4             | 6             | 0           | X 0.140542 Y -1.119873 Z -0.290424 |
| 5             | 6             | 0           | X -0.472826 Y 0.218974 Z -0.360972 |
| 6             | 6             | 0           | X 0.196316 Y 1.367247 Z -0.228511 |
| 7             | 8             | 0           | X -1.838881 Y 0.244807 Z -0.638032 |
| 8             | 6             | 0           | X -2.687053 Y -0.047579 Z 0.389520 |
| 9             | 6             | 0           | X -4.190735 Y -0.001232 Z -0.866873 |
| 10            | 1             | 0           | X -4.259363 Y -0.775618 Z -0.841369 |
| 11            | 1             | 0           | X -4.776616 Y -0.164359 Z 0.755049 |
| 12            | 1             | 0           | X -4.311663 Y 0.961558 Z -0.557195 |
| 13            | 8             | 0           | X -2.312280 Y -0.304950 Z 1.491798 |
| 14            | 6             | 0           | X -0.762682 Y -2.304502 Z -0.495771 |
| 15            | 1             | 0           | X -1.339017 Y -2.496020 Z 0.414800 |
| 16            | 1             | 0           | X -1.470832 Y -2.112999 Z -1.303915 |
| 17            | 1             | 0           | X -0.193832 Y -3.198923 Z -0.738834 |
| 18            | 6             | 0           | X 2.157817 Y -2.589701 Z 0.052739 |
| 19            | 1             | 0           | X 1.622675 Y -3.264977 Z 0.722654 |
| 20            | 1             | 0           | X 2.235782 Y -3.075581 Z -0.924502 |
| 21            | 1             | 0           | X 3.164427 Y -2.440717 Z 0.432871 |
| 22            | 6             | 0           | X -0.472784 Y 2.707483 Z -0.306267 |
| 23            | 1             | 0           | X -1.529150 Y 2.604651 Z -0.542655 |
| 24            | 1             | 0           | X -0.376474 Y 3.238013 Z 0.644893 |
| 25            | 1             | 0           | X -0.006753 Y 3.324124 Z -1.079072 |
| 26            | 6             | 0           | X 2.410466 Y 2.373025 Z 0.170801 |
| 27            | 8             | 0           | X 3.580860 Y -0.140831 Z 0.288547 |
| 28            | 1             | 0           | X 2.012901 Y 3.379318 Z 0.128974 |
| 29            | 1             | 0           | X 3.470042 Y 2.241400 Z 0.353496 |
| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|------------------------|
| 1             | 6             | 0           | 1.030883 -1.112045 -0.003198 |
| 2             | 6             | 0           | 0.434815 -1.468541 0.004811 |
| 3             | 6             | 0           | -1.414396 -0.356234 0.001811 |
| 4             | 6             | 0           | -0.973973 0.919557 -0.001491 |
| 5             | 6             | 0           | 0.467555 1.231678 -0.001329 |
| 6             | 6             | 0           | 1.434185 0.291780 0.009974 |
| 7             | 8             | 0           | 0.694305 2.574115 -0.011066 |
| 8             | 6             | 0           | -1.899904 2.101948 -0.004249 |
| 9             | 1             | 0           | -1.706769 2.733565 0.865887 |
| 10            | 1             | 0           | -1.713534 2.723230 -0.883321 |
| 11            | 1             | 0           | -2.942863 1.795414 0.001688 |
| 12            | 6             | 0           | -2.869714 -0.738090 0.004128 |
| 13            | 1             | 0           | -3.380318 -0.348429 0.87953 |
| 14            | 1             | 0           | -3.382859 -0.347917 -0.877998 |
| 15            | 1             | 0           | -2.958021 -1.822317 0.004200 |
| 16            | 6             | 0           | 2.904772 0.606326 0.025230 |
| 17            | 1             | 0           | 3.128447 1.670079 0.121317 |
| 18            | 1             | 0           | 3.392136 0.109957 0.868468 |
| 19            | 1             | 0           | 3.389721 0.254386 -0.889869 |
| 20            | 6             | 0           | 1.898767 -2.133475 -0.029933 |
| 21            | 8             | 0           | -0.795567 -2.628221 0.011721 |
| 22            | 1             | 0           | 2.971170 -1.986515 -0.943418 |
| 23            | 1             | 0           | 1.518043 -3.146968 -0.041667 |
| 24            | 1             | 0           | 1.638581 2.740930 -0.053011 |

Transitions state image of $6 \rightarrow 4 + 8$

Transition state structure of $6 \rightarrow 4 + 8$

Imaginary Frequency: -886.8120.
E(RM062X) = -691.142913169
Zero-point correction = 0.228994 (Hartree/Particle)
Thermal correction to Energy = 0.245075
Thermal correction to Enthalpy = 0.246020
Thermal correction to Gibbs Free Energy = 0.184954
Sum of electronic and zero-point Energies = -690.913920
Sum of electronic and thermal Energies = -690.897838
Sum of electronic and thermal Enthalpies = -690.896894
Sum of electronic and thermal Free Energies = -690.957959

Standard orientation:
| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) |
|---------------|---------------|-------------|-------------------------|
|               |               |             | X           | Y           | Z           |
| 1             | 6             | 0           | 2.062301    | -0.740116  | -0.032863   |
| 2             | 6             | 0           | 0.859372    | -1.274797  | 0.264801    |
| 3             | 6             | 0           | -0.366336   | -0.443774  | 0.444835    |
| 4             | 6             | 0           | -0.288484   | 0.926184   | 0.383844    |
| 5             | 6             | 0           | 0.973130    | 1.575833   | 0.065969    |
| 6             | 6             | 0           | 2.284983    | 0.729829   | -0.153328   |
| 7             | 8             | 0           | -1.488696   | -1.092041  | 0.601360    |
| 8             | 1             | 0           | -2.038285   | -1.315044  | -0.871127   |
| 9             | 6             | 0           | -3.586101   | -0.176497  | -0.494674   |
| 10            | 8             | 0           | -4.302903   | 0.016581   | 0.271477    |
| 11            | 6             | 0           | -2.629112   | -0.536344  | -1.525041   |
| 12            | 1             | 0           | -3.160088   | -0.794197  | -2.439480   |
| 13            | 1             | 0           | -1.847951   | 0.230481   | -1.633316   |
| 14            | 6             | 0           | -1.494985   | 1.756501   | 0.718996    |
| 15            | 1             | 0           | -2.049687   | 2.116074   | -0.164681   |
| 16            | 1             | 0           | -2.175196   | 1.181244   | 1.348327    |
| 17            | 1             | 0           | -1.210968   | 2.650108   | 1.278814    |
| 18            | 6             | 0           | 1.130728    | 2.902027   | -0.084000   |
| 19            | 6             | 0           | 0.661687    | -2.755281  | 0.430000    |
| 20            | 1             | 0           | -0.072844   | -2.943424  | 1.212115    |
| 21            | 1             | 0           | 0.257794    | -3.191774  | -0.490514   |
| 22            | 1             | 0           | 1.595532    | -3.264044  | 0.663539    |
| 23            | 6             | 0           | 3.308563    | -1.557109  | -0.244080   |
| 24            | 1             | 0           | 3.682371    | -1.958423  | 0.702952    |
| 25            | 1             | 0           | 3.124325    | -2.400277  | -0.912712   |
| 26            | 1             | 0           | 4.087302    | -0.927995  | -0.670823   |
| 27            | 8             | 0           | 3.278201    | 1.236100   | -0.418512   |
| 28            | 1             | 0           | 0.311746    | 3.600869   | 0.030149    |
| 29            | 1             | 0           | 2.108581    | 3.292539   | -0.334587   |
Figure S7. DFT calculation data for chroman retro Diels-Alder transition state for 1†

Calculated (gas phase at the M06-2X/6-311G (d,p) level) energy profile for the retro Diels-Alder pyrolysis of vitamin E acetate (calculation version). Relative free energies (kcal mol\(^{-1}\)) for starting materials, transition state and products formed for the pyrolysis of 1† leading to the formation of 6 and 7††.

† Simplified structure used for calculation without C\(_{15}H_{32}\) alkyl group. ††2-Methylprop-1-ene representing 7.

Ground state structure of 2-methylprop-1-ene (representing 7).

\[
E(RM062X) = -157.179383224
\]

Zero-point correction= 0.108660 (Hartree/Particle)

Thermal correction to Energy = 0.113879

Thermal correction to Enthalpy = 0.114824

Thermal correction to Gibbs Free Energy = 0.081493

Sum of electronic and zero-point Energies = -157.070724

Sum of electronic and thermal Energies = -157.065504

Sum of electronic and thermal Enthalpies = -157.064560

Sum of electronic and thermal Free Energies = -157.097890

Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) | X     | Y     | Z     |
|---------------|---------------|-------------|-------------------------|-------|-------|-------|
| 1             | 6             | 0           | 0.001250                | -1.455560 | -0.000009 |
| 2             | 6             | 0           | 0.000028                | -0.126264 | -0.000013 |
| 3             | 6             | 0           | 1.270638                | 0.679225  | 0.000011 |
| 4             | 1             | 0           | 2.153773                | 0.040007  | -0.000100 |
| 5             | 1             | 0           | 1.311438                | 1.330002  | -0.879051 |
| 6             | 1             | 0           | 1.311589                | 1.329940  | 0.879096  |
| 7             | 6             | 0           | -1.271800               | 0.677270  | 0.000016  |
| 8             | 1             | 0           | -1.313397               | 1.328320  | 0.878849  |
| 9             | 1             | 0           | -1.313684               | 1.327697  | -0.879257 |
| 10            | 1             | 0           | -2.154080               | 0.036912  | 0.000323  |
| 11            | 1             | 0           | 0.927383                | -2.019514 | 0.000036  |
| 12            | 1             | 0           | -0.923721               | -2.021392 | 0.000071  |
Transitions state image representing $1 \rightarrow 6 + 7$

Transition state structure of $1^\dagger \rightarrow 6 + 7^{\dagger\dagger}$

Imaginary Frequency: -398.8034.
E(RM062X) = -848.418968657

Zero-point correction=                           0.346404 (Hartree/Particle)
Thermal correction to Energy                    = 0.367276
Thermal correction to Enthalpy                 = 0.368220
Thermal correction to Gibbs Free Energy        = 0.297471

Sum of electronic and zero-point Energies       = -848.072565
Sum of electronic and thermal Energies          = -848.051692
Sum of electronic and thermal Enthalpies        = -848.050748
Sum of electronic and thermal Free Energies     = -848.121498

Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) | X     | Y     | Z     |
|---------------|---------------|-------------|-------------------------|-------|-------|-------|
| 1             | 6             | 0           | -2.770997               | -1.863904 | 0.410401 |
| 2             | 6             | 0           | -1.774072               | -1.444261 | -1.344134 |
| 3             | 6             | 0           | -0.723766               | -0.559637 | -1.082001 |
| 4             | 6             | 0           | -1.150724               | 0.798246 | -0.782195 |
| 5             | 6             | 0           | -3.163314               | -0.648196 | 0.926375 |
| 6             | 6             | 0           | 0.641940                | -0.953758 | -0.946331 |
| 7             | 6             | 0           | -0.127152               | 1.780199 | -0.439513 |
| 8             | 6             | 0           | 1.182064                | 1.389294 | -0.387710 |
| 9             | 6             | 0           | 1.540050                | 0.014960 | -0.614014 |
| 10            | 8             | 0           | -2.370488               | 1.051556 | -0.732664 |
| 11            | 1             | 0           | -1.931147               | -2.376050 | 0.868544 |
| 12            | 1             | 0           | -3.514242               | -2.497048 | -0.062753 |
| 13            | 1             | 0           | -2.669044               | -1.018852 | -1.779611 |
| 14            | 1             | 0           | -1.557305               | -2.476747 | -1.596290 |
| 15            | 6             | 0           | -2.266920               | 0.040433 | 1.903486 |
| 16            | 1             | 0           | -2.509502               | 1.098247 | 2.001620 |
| 17            | 1             | 0           | -2.342216               | -0.438890 | 2.885773 |
| 18            | 1             | 0           | -1.221647               | -0.053643 | 1.579735 |
| 19            | 6             | 0           | -4.525795               | -0.093204 | 0.661680 |
| 20            | 1             | 0           | -5.184249               | -0.324416 | 1.507769 |
| 21            | 1             | 0           | -4.484006               | 0.987881 | -0.537994 |
| 22            | 1             | 0           | -4.961277               | -0.534481 | -0.236232 |
| 23            | 6             | 0           | 1.059393                | -2.378626 | -1.186417 |
| 24            | 1             | 0           | 0.599494                | -3.053117 | -0.456285 |
| 25            | 1             | 0           | 0.743825                | -2.709358 | -2.178835 |
| 26            | 1             | 0           | 2.140582                | -2.489116 | -1.125606 |
| 27            | 6             | 0           | -0.582845               | 3.188068 | -0.166489 |
| 28            | 1             | 0           | -1.670977               | 3.218171 | -0.172243 |
| 29            | 1             | 0           | -0.224931               | 3.547431 | 0.801490 |
|   |   |   |     |     |     |
|---|---|---|-----|-----|-----|
| 30 | 1 | 0 | -0.218737 | 3.880399 | -0.931000 |
| 31 | 6 | 0 | 2.302132  | 2.349150  | -0.082728  |
| 32 | 1 | 0 | 1.962648  | 3.381991  | -0.116886  |
| 33 | 1 | 0 | 2.725482  | 2.166945  | 0.911333   |
| 34 | 1 | 0 | 3.116193  | 2.217840  | -0.797375  |
| 35 | 8 | 0 | 2.896123  | -0.291536 | -0.528037  |
| 36 | 6 | 0 | 3.438048  | -0.662086 | 0.670843   |
| 37 | 8 | 0 | 4.611250  | -0.859986 | 0.732630   |
| 38 | 6 | 0 | 2.484595  | -0.815673 | 1.832797   |
| 39 | 1 | 0 | 1.920939  | 0.103202  | 2.005253   |
| 40 | 1 | 0 | 1.759926  | -1.605216 | 1.622884   |
| 41 | 1 | 0 | 3.070788  | -1.071470 | 2.711044   |

† Simplified structure used for calculation without C_{15}H_{32} alkyl group. ††2-Methylprop-1-ene representing 7.
Figure S8. APCI-MS cone-voltage study of vaped vitamin E acetate 1

Fig. S8a: 5 eV, APCI (positive mode).

Fig. S8b: 10 eV, APCI (positive mode).

Fig. S8c: 20 eV, APCI (positive mode).

Fig. S8d: 30 eV, APCI (positive mode).
Figure S9. $^1$H NMR spectrum of isolated mixture from vaped 1 and pure vitamin E acetate 1

Isolated mixture from vaped 1

Pure vitamin E acetate 1
Figure S10 ¹H NMR spectrum of the non-volatile component (NVC) of isolated mixture from vaped 1

¹H NMR (CDCl₃, 400 MHz)

¹³C NMR (CDCl₃, 100 MHz)
**Figure S11.** Identification of duroquione 8 and prist-1-ene 7 in non-volatile component (NVC) of isolated mixture from vaped 1.

$^1$H NMR (CDCl$_3$, 400 MHz)

![1H NMR spectrum](image)

$^{13}$C NMR (CDCl$_3$, 100 MHz)

![13C NMR spectrum](image)

*: Duroquinone 8. $^1$H NMR (400 MHz, CDCl$_3$) δ:2.01 (s, 12H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) δ:187.6, 140.5, 12.5 ppm.
Confirmatory spiking NMR spectra. Top spectrum: vape mixture containing duroquinone 8 (red asterisk). Bottom spectrum: vaped mixture containing duroquinone following spiking with pure duroquinone 8.

Vape mixture containing 8 (red asterisk)

Above vape mixture spiked with pure 8
Figure S12. Identification of benzene, ethene, propene, butadiene, THF, 2-methylprop-1-ene in volatile component (VC) of isolated mixture from vaped 1.

$^1$H NMR (CDCl$_3$, 400 MHz)
* Benzene: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.36 (s) ppm.

* Ethene: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 5.41 (s) ppm.

* Propene: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 5.93-5.72 (ddq =CH, 1H), 4.97 (dd, $J = 21.9$ Hz, $J = 9.8$ Hz, CH$_2$=, 2H), 2.01 (d, $J = 5.5$ Hz, CH$_3$, 3H) ppm.

* Butadiene: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 6.41-6.29 (m, 2H) ppm, 5.23 (d, $J = 16.2$ Hz, 2H), 5.12 (d, $J = 9.5$ Hz, 2H) ppm.

THF: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 3.76 (m, 4H), 1.85 (m, 4H) ppm.

2-Methylprop-1-ene: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 4.66 (s, CH$_2$=, 2H), 1.71 (s, CH$_3$, 6H) ppm.
Figure S13. $^1$H NMR spectra of isolated vaped 1 with benzylamine 9 as trap for ketene.

$^1$H NMR (CDCl$_3$, 400 MHz) of vape mixture containing benzylamide 10 (red asterisk)

Confirmatory spiking NMR spectra. Top spectrum: vape mixture containing benzylamide 10 (red asterisk). Bottom spectrum: vaped mixture containing benzylamide 10 following spiking with pure benzylamide.
**Figure S14.** $^1$H NMR spectrum of synthesized benzylamide 10.

$^1$H NMR (CDCl$_3$, 400 MHz)

**Figure S15.** Photographs of experimental setup for Fig. 11A-C

Apparatus set up as shown in Fig. 11A and C

Apparatus set up as shown Fig. 11B
Appendix NMR spectra of pure 1, 2, 8 and 9

Vitamin E acetate 1

$^1$H NMR (CDCl$_3$, 400 MHz)
Vitamin E 2

$^1$H NMR (CDCl$_3$, 400 MHz)
Duroquinone 8

$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 100 MHz)
Benzylamine 9

$^1$H NMR (CDCl$_3$, 400 MHz)