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Chemistry of Sugar Formation in the Gas Phase: Following the Activated Aldehyde

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Abstract

Sugars are produced by living organisms, and are required building blocks for life as we know it, which raises the foundational question of how sugars formed in a prebiotic environment. The abiotic formose reaction produces sugars from formaldehyde, but our understanding of its initiation step remains murky, with chemists invoking the concept of an “activated aldehyde” to seed this reaction. Singlet hydroxycarbenes, high-energy isomers of aldehydes, were recently reported to facilitate sugar formation under cold, non-aqueous conditions relevant to interstellar environments. We generate singlet methylhydroxycarbene ($^1\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$) from the photodissociation of pyruvic acid and experimentally measure its gas-phase reaction with d_4 -acetaldehyde using multiplexed photoionization mass spectrometry. The $\text{C}_4\text{H}_4\text{D}_4\text{O}_2$ isomer d_4 -acetoin is the sole product, which we kinetically link to the reactant $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$, and attribute to a carbonyl-ene formation mechanism. We see no evidence of 3-hydroxybutanal, the

C-H insertion product expected in carbene chemistry. Using automated exploration we calculate stationary points on the potential energy surface and report master equation rate coefficients from $T = 20\text{--}600$ K, providing quantitative kinetics of this fast reaction for use in chemical models. The pre-reactive complex in this reaction is stabilized by both hydrogen bonding and electrophilic carbene C=O interactions. These effects create a short-range dynamical bottleneck for the reaction besides the long- and mid-range barrierless bottlenecks. Combined with recent reports of $^1\text{H}\ddot{\text{C}}\text{OH}$ production from methanol photodissociation and pyruvic acid production in cold irradiated ices, this work provides evidence that singlet hydroxycarbene + aldehyde chemistry is a feasible path to prebiotic sugar formation.

Introduction

Sugars, a subset of carbohydrates, are one of the four types of large molecules necessary for life, the others being nucleic acids, proteins, and lipids.¹⁻⁵ Although some sugars (saccharides) such as lactose are produced by animals, most are produced in plants via photosynthesis. However, these plants require sugars to form structural elements, such as cellulose, a polymer of the monosaccharide glucose that is a component of cell walls. The fact that plants produce most sugars, yet need these sugars to exist, raises the existential question: how were sugars synthesized before the emergence of living organisms?⁶

Monosaccharides such as glucose, fructose, ribose, and galactose are polymers of formaldehyde, with empirical formula $(\text{CH}_2\text{O})_n$. In their acyclic forms they contain a single carbonyl group (either aldehyde or ketone) with all other carbon atoms bearing an -OH group. The simplest sugar is therefore glycolaldehyde (HOCH_2CHO). The abiotic formation of sugars has been known since at least 1861, when Alexander Butlerov,⁷ who discovered formaldehyde, found that an aqueous solution of formaldehyde in the presence of a base produces glycolaldehyde and larger sugars. The kinetics of this “formose” reaction are described by a long induction period of very slow reaction to produce the first glycolaldehyde molecules, followed

by much faster kinetics in which glycolaldehyde autocatalyzes the formation of additional glycolaldehyde, leading further to trioses, tetroses, and larger sugars.⁸ The mechanism of this second rapid step was proposed by Breslow⁹ as an autocatalytic cycle that, once glycolaldehyde is present, enables the overall reaction $\text{CH}_2\text{O} + \text{CH}_2\text{O} \longrightarrow \text{HOCH}_2\text{CHO}$. Breslow noted that the initial formation of glycolaldehyde from the reaction of two formaldehyde molecules is “of course very unlikely,” and that attempts at that time to explain this first slow step invoked an “active formaldehyde or some other ill-defined species.” Although the formose reaction has some problematic aspects^{6,10} as a prebiotic source of sugars needed for the origin of life, several works provide evidence that silicate mineral substrates make the formose reaction a more feasible source of abiotic sugar formation on Earth.^{11,12}

Another hypothesis for the origin of chemicals necessary for life is that they were delivered to Earth from space.¹ In 2000, Hollis et al.¹³ observed gas-phase glycolaldehyde in interstellar space via millimeter-wave rotational spectroscopy. They proposed that glycolaldehyde could be formed by polymerization of formaldehyde either in the gas phase or on surfaces. In 2001, Cooper et al.¹⁴ identified the triose dihydroxyacetone and related compounds in the seven-billion-year-old Murchison meteorite, providing further evidence that simple sugars can form in space and were delivered to Earth via meteorite impact. In later work Halfen et al.¹⁵ made astronomical observations of both formaldehyde and glycolaldehyde via millimeter-wave spectroscopy in the molecular cloud Sagittarius B2(N), suggesting that “ H_2CO may function as the precursor to glycolaldehyde in a gas-phase ‘formose’ reaction.” More recently, glycolaldehyde was detected in the nucleus of comet 67P/Churyumov-Gerasimenko¹⁶ and in other comets,¹⁷ substantiating the existence of sugars in other stellar and interstellar objects that could have impacted the early Earth.

Building on earlier reports,^{18–20} a key advance in elucidating abiotic sugar synthesis came in 2018 when Eckhardt et al.²¹ provided evidence from both gas-phase flow pyrolysis and condensed phase cryogenic experiments that singlet hydroxycarbenes—the two smallest being $^1\text{H}\ddot{\text{C}}\text{OH}$ (hydroxycarbene) and $^1\text{CH}_3\text{—}\ddot{\text{C}}\text{—OH}$ (methylhydroxycarbene, MHC)—react

with carbonyl molecules to form simple sugars, polyols, and other sugar derivatives. They proposed that hydroxycarbenes—high-energy isomers of aldehydes—could be the nebulous “activated aldehyde” previously invoked by Breslow⁹ and others.²² Notably, Eckhardt’s experiments at $T = 28$ K provided clear evidence for the production of $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{OH}$ (hydroxyacetone) when MHC is formed in the presence of H_2CO in the solid phase. The formation of hydroxyacetone at cryogenic temperatures implied the absence of a reaction barrier on the potential energy surface (PES), which they corroborated using electronic structure calculations showing a deeply submerged-barrier. They denoted this pathway a carbonyl-ene addition mechanism. Eckhardt et al.²¹ provided evidence that singlet hydroxycarbenes could enable sugar and sugar derivative formation in both the gas phase and in cold environments without liquid water. Rinaldi et al.²³ used quantum chemical simulations to argue that the reaction of glycolaldehyde with $^1\text{H}\ddot{\text{C}}\text{OH}$ is a feasible path to the triose glyceraldehyde both in the gas phase and on silica surfaces.

Recently Samanta et al.²⁴ showed that gas-phase pyruvic acid (PA, $\text{CH}_3\text{C}(\text{O})\text{C}(\text{O})\text{OH}$) excited with a 351-nm photon produces MHC as a primary photodissociation product, opening the door to detailed gas-phase studies of hydroxycarbene chemistry. In the present work we provide kinetic insight on the formation of sugars via reactions of hydroxycarbenes with aldehydes. We produce MHC via photodissociation of PA and react it with d_4 -acetaldehyde (CD_3CDO), with independent control of reactant concentrations. Using time-resolved Multiplexed Photoionization Mass Spectrometry (MPIMS) we follow the time history of both reactants and products with isomeric specificity, and identify the isomer d_4 -acetoin ($\text{CH}_3\text{C}(\text{O})\text{CD}(\text{OH})\text{CD}_3$) as the sole $\text{C}_4\text{H}_4\text{D}_4\text{O}_2$ reaction product. The experimental data kinetically link the acetoin product to the $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH} + \text{CD}_3\text{CDO}$ reactants. To provide further insight to the reaction mechanism, we use the KinBot code^{25–27} for automated exploration of this system’s PES, together with master equation calculations to predict the reaction kinetics from $T = 20 - 600$ K. The results of our microcanonical two-transition state model are consistent with our experiments and those of Eckhardt et al.,²¹ and provide the

reaction rate coefficient as a function of temperature for use in chemical reaction models. Although we note that acetoin is a sugar derivative, not a sugar *per se*, this experimentally tractable system provides strong evidence that the reactions of hydroxycarbenes with aldehydes are a generally plausible route to sugar formation even in cold, dry environments.

Methods

Experimental

We used the MPIMS at the Chemical Dynamics Beamline of the Advanced Light Source Synchrotron to perform the experiments. This instrument has been described in detail,^{28–30} and is a powerful method enabling universal, sensitive, and isomer-resolved studies of chemical reaction mechanisms. The 3-dimensional datasets the MPIMS produces are ion counts as a function of m/z ratio, kinetic time relative to a sudden chemical event, and photon energy of the ionizing radiation that converts neutrals into cations. The cation intensities, suitably calibrated, represent neutral species concentrations as a function of time, with isomeric identification enabled by photoionization spectroscopy.

A controlled mixture of PA, CD₃CDO, and helium flowed at a speed of 4 m s⁻¹ through a halocarbon-wax-coated (Halocarbon Products Corporation, series 2300) tubular quartz reactor of 1.05 cm inner diameter. The reactor pressure was maintained at 4 Torr (number density 1.28×10^{17} cm⁻³) by active control of a valve throttling the vacuum pump that evacuated the reactor tube at its end. A portion of the gas in the reactor tube expanded through a 650 μ m diameter pinhole in the tube sidewall, forming a molecular beam that passed through a 1.5 mm diameter skimmer and entered the ionization region ($P = 8 \times 10^{-6}$ Torr). This neutral molecular beam was crossed with tunable, quasi-continuous, vacuum ultraviolet (VUV) monochromatized undulator radiation for single-photon ionization. The ions produced were injected into an orthogonal-acceleration time-of-flight mass spectrometer (50 kHz extraction frequency, mass resolution ~ 900) and were detected by a microchannel

plate detector. For time-resolved experiments, an unfocused excimer laser pulse ($\lambda = 351$ nm, 15 ns pulsewidth, 7.0×10^{16} photons cm^{-2} pulse $^{-1}$) propagated down the reactor tube to photodissociate PA, forming $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH} + \text{CO}_2$.

Pyruvic Acid (Sigma-Aldrich; 98%) is typically a yellow liquid upon receipt, and was twice distilled as described earlier,²⁴ yielding a clear liquid sample. Helium was bubbled at 4 sccm via a porous frit through the liquid PA sample held in a thermostatted bath at 21 °C and a total pressure of 37 Torr. At this temperature the vapor pressure of PA is ~ 1 Torr, yielding a 0.027 mole fraction of PA exiting the bubbler. CD_3CDO (Sigma-Aldrich, > 99 atom% D, > 98% chemical purity) was degassed by pumping on the liquid. A 6.67% mixture of CD_3CDO in balance helium was prepared manometrically in a stainless steel cylinder and delivered at mass flow rates of 0 – 20 sccm. Pure helium was added to achieve a total flow of 100 sccm. The resulting number densities in the reactor tube were: $[\text{PA}] = 0$ or 1.4×10^{14} cm^{-3} , $[\text{CD}_3\text{CDO}] = 0 - 1.7 \times 10^{15}$ cm^{-3} . The time response of the MPIMS instrument was evaluated and optimized using the 351-nm photodissociation $\text{NO}_2 \longrightarrow \text{O}(^3\text{P}) + \text{NO}$, where the 10–90% rise time of the NO photoproduct was 500 μs , a value limited not by the photochemistry of NO_2 but only by the instrument response function.

Theory

To explore and characterize the PES of the $\text{C}_4\text{H}_8\text{O}_2$ system, we used our automatic kinetics workflow software KinBot.^{25–27} The standard features of the software are described in previous publications;^{25,26} here we provide only a brief summary. Starting from a user-defined well and using a relatively cheap L1 level of theory (here B3LYP/6-31G), KinBot identified low-energy reactive first-order saddle points that were verified using intrinsic reaction coordinate (IRC) calculations. The rovibrational properties of the lowest conformer of each stationary point at L1 were further refined at L2 = $\omega\text{B97X-D/6-311++G(d,p)}$, and finally, single-point energies were further refined at the L3 = CCSD(T)-F12a/cc-pVTZ-F12// $\omega\text{B97X-D/6-311++G(d,p)}$ level. The L1 and L2 results were obtained using the Gaus-

sian 16³¹ (Rev. B.01) quantum chemistry package, whereas the L3 calculations used Molpro 2023.2.³²

Two new features were implemented in KinBot for this work. First, weakly bound species such as van der Waals (vdW) or hydrogen-bonded complexes are now identified, characterized, and retained by the code. Second, we implemented algorithms to perform variable reaction coordinate transition state theory (VRC-TST) calculations for barrierless reactions.^{33,34} KinBot was interfaced with the rotDpy code,³⁵ which samples the interfragment potential on dividing surfaces along the reaction coordinate to calculate the microcanonical flux. The sampled dividing surfaces in VRC-TST are defined by a set of pivot points assigned to each fragment. These pivots are automatically placed on the structures in our workflow based on the chemical nature of the forming/breaking bond(s). For the formation of the pre-reaction complex between $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH}$ and CH_3CHO , one pivot point was placed on each fragment. Details regarding the inter-pivotal sampling are provided in Section S2 of the Supporting Information (SI). The geometries of the separated fragments were optimized at the $\omega\text{B97X-D/6-311++G(d,p)}$ level of theory using Gaussian 16, and these rigid structures were used during the Monte Carlo sampling, where the position-dependent energies were evaluated using Molpro2023.2 at the $\omega\text{B97X-D/cc-pVDZ}$ level of theory. We employed a 1-D correction potential (see Figure S7) to account for geometry and basis set effects, effectively yielding a CCSD(T)-F12a/aug-cc-pVTZ// $\omega\text{B97X-D/cc-pVDZ}$ level interfragment potential. The single-reference wavefunction approach is adapted for the formation of this complex because the fragments are both closed-shell single-reference molecules. Similar interactions have been previously studied successfully with single-reference approach.³⁶⁻³⁸ An additional indication of the single-reference nature of this system is the constant low T1 diagnostic along the 1-D correction, reaching a maximum of 0.0151 at the shortest distance of 1.9 Å.

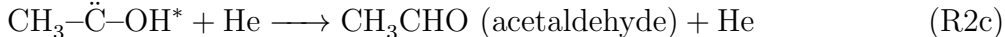
High-pressure-limit rate coefficients were calculated using the MESS master equation solver³⁹ with the input containing the molecular properties automatically assembled by KinBot. Partition functions were calculated using a rigid-rotor-harmonic-oscillator approach

using unscaled L2 frequencies, amended with hindered rotors for rotatable bonds, where the frequency corresponding to the rotor was projected out from the harmonic frequencies. For reactions through barriers a simple 1-D Eckart barrier⁴⁰ was used to account for tunneling. The combined effect of barrierless and submerged-barrier pathways were represented using an effective two-transition-state model at the microcanonical level.^{41–44}

Results

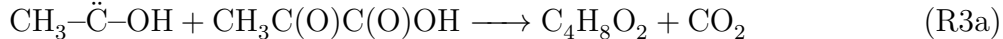
Experiment

A prerequisite for the study of the $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH} + \text{CD}_3\text{CDO}$ reaction is the ability to create the MHC reactant. Samanta et al.²⁴ studied the 351-nm photodissociation of PA and assigned the following processes:

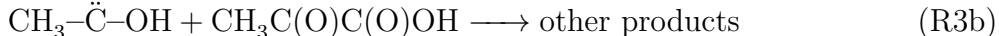


where $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH}^*$ denotes MHC formed with excess internal energy from the photodissociation dynamics (R1). They concluded that at a total pressure of 4 Torr, $\sim 50\%$ of the $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH}^*$ photoproducts were formed with sufficient vibrational energy to isomerize to the more stable isomers vinyl alcohol (R2b) and acetaldehyde (R2c), whereas the remaining $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH}^*$ were collisionally stabilized to $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH}$ (R2a) in its ground electronic sin-

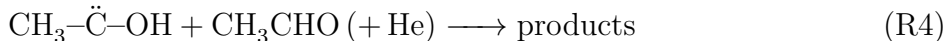
glet state. MHC is consumed rapidly in the presence of PA, and Samanta et al. showed that it undergoes the following chemical reaction:



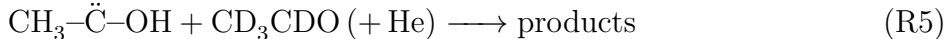
They could not clarify the isomer of $\text{C}_4\text{H}_8\text{O}_2$ formed in (R3a), but verified it was not acetoin. As described in SI Section S5, our exploration of the PES for the MHC + PA reaction revealed more about the nature of (R3). We find a plausible pathway that connects the reactants in (R3a) to CO_2 and the isomer $\text{CH}_3\text{C(OH)=C(OH)CH}_3$, which we denote as species “P”. In addition, the calculations find two other pathways that we do not detect experimentally. We denote the combination of these two pathways as:



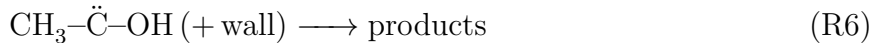
In summary, Samanta et al. showed that $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH}$ can be produced promptly via photodissociation, collisionally thermalized, and its bimolecular reactions interrogated. This advance enables exploration of other chemical reactions of MHC including the reaction



of MHC reacting with an aldehyde, as suggested by Eckhardt et al.²¹ with relevance to prebiotic sugar formation chemistry. In order to shift any products of (R4) away from the $m/z = 88$ region, where signals from PA and species “P” overlap, we choose fully deuterated acetaldehyde as the reactant:



Finally, we note that highly reactive species such as MHC may also be consumed by collisions with the walls of the reactor tube:



When we flow pyruvic acid in helium through the reactor tube the only signals observed with 10.242 eV ionizing radiation are $m/z = 88.02$ and 43.02 amu. Both signals represent neutral PA, where the former is the parent ion of PA (IE ~ 10.1 eV)⁴⁵ and the latter is $\text{C}_2\text{H}_3\text{O}^+$, a fragment ion of PA. Separately, when CD_3CDO in excess helium flows into the reactor tube, the only signal we observe at 10.242 eV is $m/z = 48.05$ amu, confirming the isotopic purity of the d_4 -acetaldehyde sample. In this case, admitting the 351 nm photodissociation laser to the reactor tube does not produce time-resolved photofragments, consistent with the very small absorption cross section of CD_3CDO at 351 nm (6.95×10^{-23} cm² molecule⁻¹, base e)⁴⁶ and the fact that the thermochemical threshold for $\dot{\text{C}}\text{D}_3 + \dot{\text{D}}\text{CO}$ formation is $\lambda = 346$ nm.

By contrast, Figure 1 shows time-resolved and time-integrated mass spectra when PA is photodissociated at 351 nm in the presence of CD_3CDO . Note that the VUV photon energy range is chosen to avoid ionizing PA and CD_3CDO , which are present at much higher densities than all other molecules, and would dominate the mass spectra if ionized. In the upper panel of Figure 1 the most prominent time-resolved signals represent neutral molecules detected at $m/z = 44.03$, 88.05 , and 92.09 amu. From this information we assign these peaks to empirical formulas $\text{C}_2\text{H}_4\text{O}$, $\text{C}_4\text{H}_8\text{O}_2$, and $\text{C}_4\text{H}_4\text{D}_4\text{O}_2$, respectively. (See SI Section S1 for additional mass spectra).

Figure 2 shows the experimental time profiles of these three species. As we confirm below based on photoionization spectroscopy, these signals represent vinyl alcohol from R2b, the $\text{C}_4\text{H}_8\text{O}_2$ product (species “P”) from (R3a), and the product d_4 -acetoin from (R5). All three species show instrument-limited risetimes (see SI Figure S2 for the same data magnified along the kinetic time axis) followed by a gradual increase over the next 90 ms. The gradual increase in signal is an artifact of a small gradient in laser fluence along the reactor tube in the MPIMS apparatus. The photodissociation of NO_2 , in which the long-time concentration

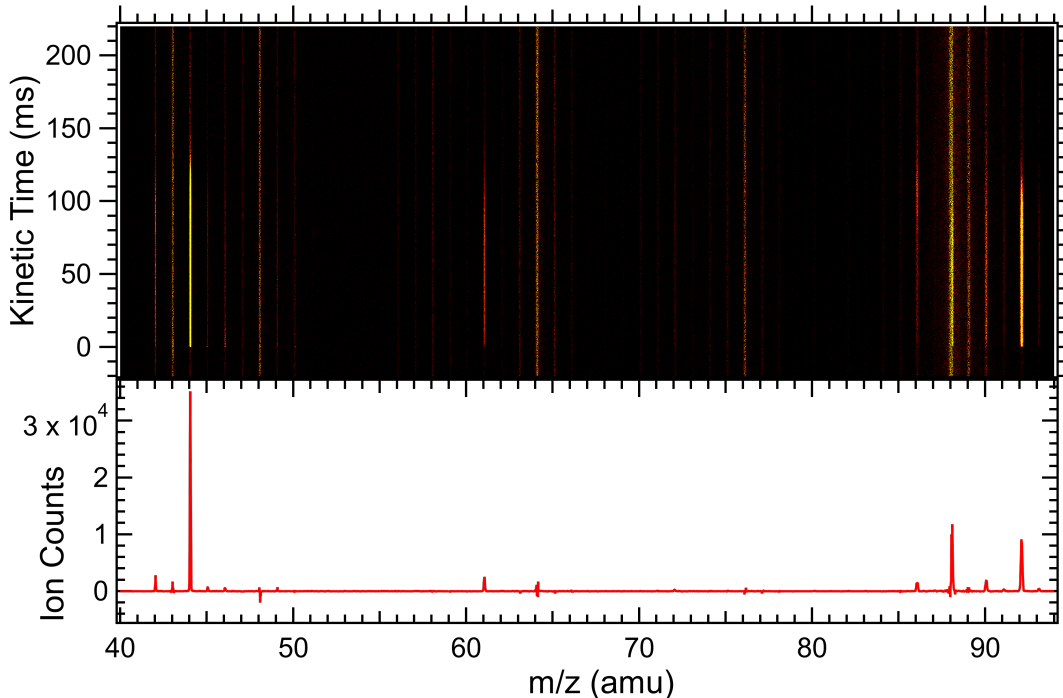


Figure 1: Mass spectra of PA ($1.4 \times 10^{14} \text{ cm}^{-3}$) and CD_3CDO ($2.6 \times 10^{14} \text{ cm}^{-3}$) in helium at $P = 4$ Torr, summed over VUV photon energies $8.941 - 10.141 \text{ eV}$. The upper panel shows time-resolved mass spectra, where the 351 nm photodissociation laser fires at kinetic time $= 0$. The average pre-laser mass spectrum is subtracted from each time-dependent mass spectrum. The lower panel shows the time-integrated mass spectrum.

of NO is known to be constant, shows the same gradual increase in signal. Therefore the kinetic profiles in Figure 2 for $t > 2 \text{ ms}$ indicate stable concentrations of the neutral species as a function of time until gas that was not photolyzed reaches the reactor pinhole at $t \sim 90 \text{ ms}$.

The 351-nm absorption cross section of PA is $4.28 \times 10^{-20} \text{ cm}^2 \text{ molecule}^{-1}$ base e .⁴⁷ At our laser fluence we expect to photodissociate 0.30% of PA,²⁴ yielding the initial number density from (R2a) of $[\text{MHC}]_{t=0} = 2.1 \times 10^{11} \text{ cm}^{-3}$, taking into account the fraction of MHC stabilized by collisions. Our expectation is that MHC will react rapidly with PA and with CD_3CDO as parallel pseudo-first-order reactions because PA and CD_3CDO are present at concentrations more than two orders of magnitude greater than $[\text{MHC}]$. Ideally one would choose $[\text{CD}_3\text{CDO}] \gg [\text{PA}]$ in order to make the reaction of MHC with acetaldehyde dominant, but given the

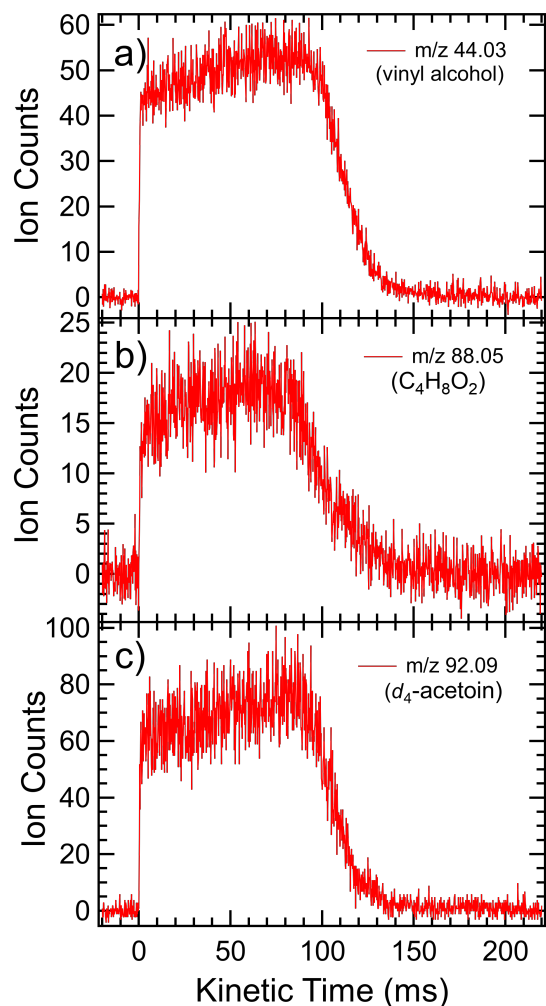


Figure 2: Kinetic time profiles with 0.2 ms point spacing of a) vinyl alcohol, b) C₄H₈O₂, and c) d₄-acetoin. Data in panels a) and c) are summed over VUV energies 8.941 – 10.141 eV, whereas data in panel b) is summed over 8.941 – 9.841 eV to avoid minor contributions from pyruvic acid.

small photodissociation fraction of PA, which is the source of MHC, we are constrained to use rather large concentrations of PA, and hence the competing reaction is unavoidable.

The signal of acetoin in Figure 2c is only present when [CD₃CDO] > 0, providing some evidence that acetoin is a product of (R5). However, if we choose a VUV photon energy of 9.00 eV, which is below the 9.17 eV ionization energy of *anti*-vinyl alcohol,⁴⁸ we avoid ionizing both vinyl alcohol and acetaldehyde (IE = 10.227 eV).⁴⁹ The signal observed at $m/z = 44.03$ in this case is shown as black circles in Figure 3. Note that this signal forms

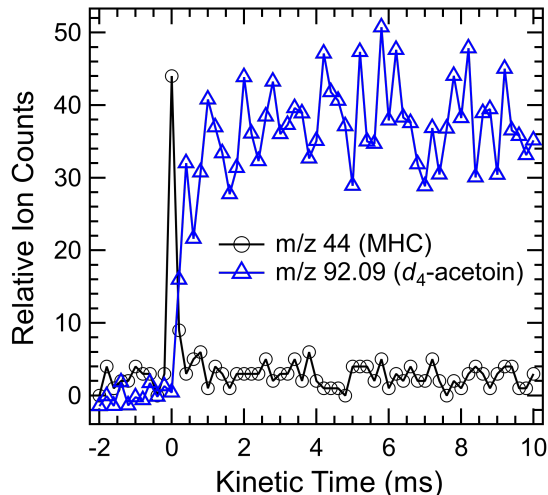


Figure 3: Kinetic time profiles with 0.2 ms point spacing of MHC (black circles) at $E = 9.00$ eV, and d_4 -acetoin (blue triangles) summed over $E = 8.941 - 10.141$ eV.

promptly at $t = 0$ and decays in < 1 ms. We attribute this signal to the direct ionization of MHC, and its time profile is consistent with a highly reactive species.²⁴ For comparison, the time profile of acetoin is also shown as blue triangles in Figure 3. Within our signal-to-noise, the risetime of acetoin matches the decay time of MHC, kinetically linking the product acetoin to the reactant MHC via reaction (R5). Because the rise- and fall-times of these data are similar to our instrument-limited response time, and because (R3a) and (R5) both consume MHC, it is not possible to extract the bimolecular rate coefficient k_5 directly from the species’ time profiles. Hence, we calculated k_4 (to approximate k_5 , as we do not expect any significant isotope effects) using an effective two-transition-state model, as detailed in the Methods:Theory Section.

However, we can test the validity of our calculated value of k_4 and provide additional evidence that acetoin is a primary product of (R5) through a relative rate study. To do so, we held $[PA]$ constant at $1.4 \times 10^{14} \text{ cm}^{-3}$, and hence $[MHC]_{t=0} = 2.1 \times 10^{11} \text{ cm}^{-3}$, while varying $[CD_3CDO]$ from $0 - 1.7 \times 10^{15} \text{ cm}^{-3}$. In this case the pseudo-first-order rate constant $k'_{3a} = k_{3a}[PA]$ is fixed, while the corresponding rate constant $k'_5 = k_5[CD_3CDO]$ increases. Symbols in Figure 4 plot the relative signals of species “P” (red) from (R3a) and d_4 -acetoin

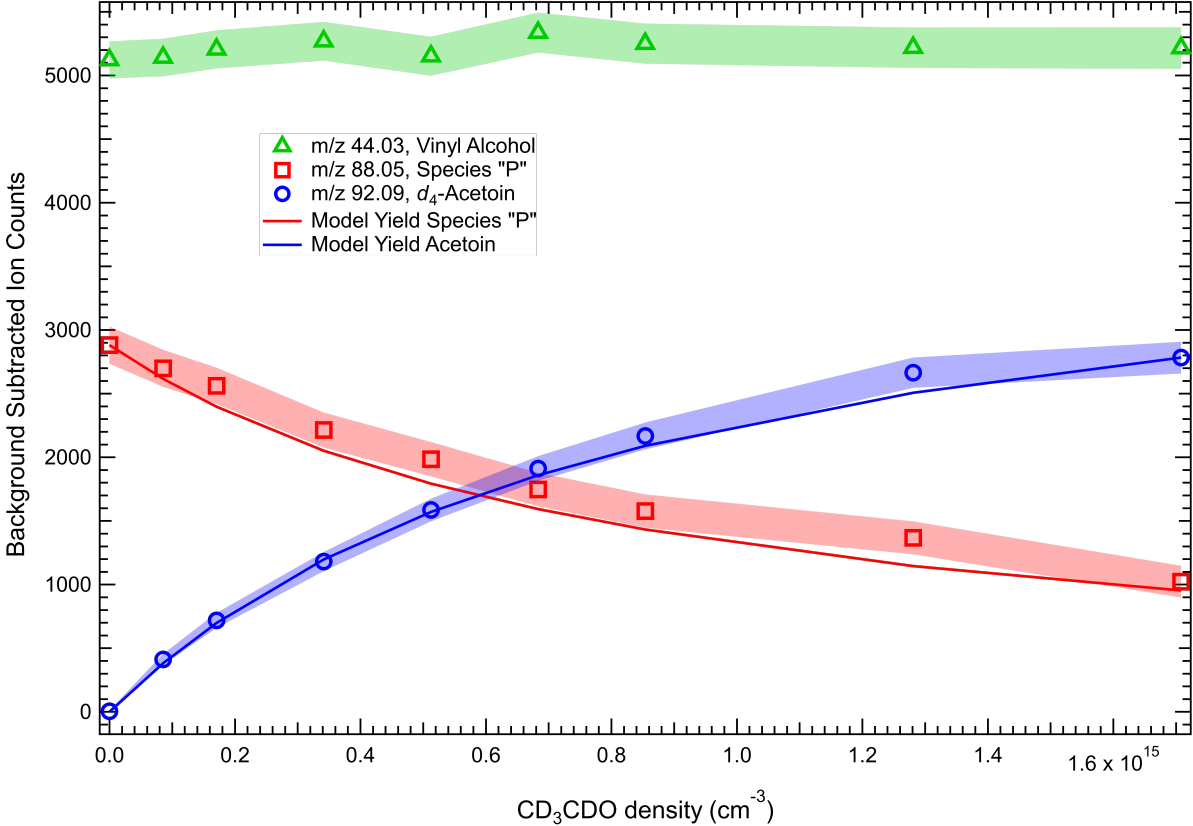


Figure 4: Open symbols show experimental signals of three key species vs CD₃CDO number density, with shaded 2- σ Poisson error bars. The photon energy is 9.75 eV. Solid lines show simulated yields from the parallel reactions kinetic model. See text for details.

(blue) from (R5). The decrease of “P” with a concomitant rise in d_4 -acetoin is consistent with the channels’ competition as parallel reactions that consume MHC. The vinyl alcohol signal (green) from (R2b) remains constant across the range of [CD₃CDO], providing evidence that no systematic drift in the apparatus occurred during this experiment and thus $[\text{MHC}]_{t=0}$ remained essentially constant. The solid lines show a kinetic yield simulation that is fit to the experimental data and will be described in the Discussion section.

There are many possible isomers potentially consistent with the time profile of C₄H₄D₄O₂ ($m/z = 92.09$) in Figures 2c and 3. The MPIMS apparatus can distinguish different neutral isomers detected at the same m/z ratio via their photoionization (PI) spectra, that is, ion signal as a function of VUV photon energy. Both the onset energy and shape of PI spectra are valuable fingerprints to assign isomers and quantify their contributions. The open sym-

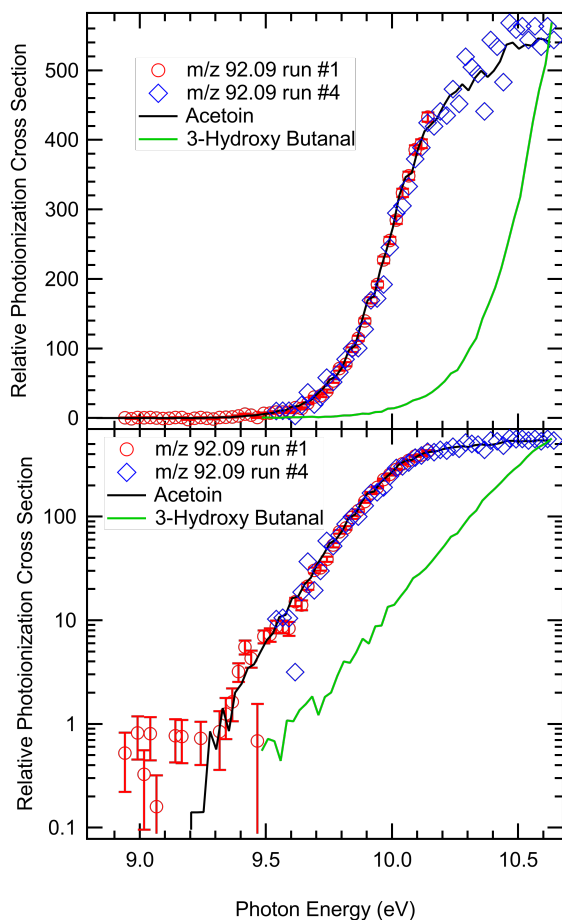


Figure 5: Photoionization spectra of $m/z = 92.09$ summed over all kinetic time are plotted on a linear (upper) or logarithmic (lower) ordinate. Red circles with Poisson error bars are from the dataset in Figure 1, whereas blue diamonds are data taken on a different day. Reference spectra of acetoin (black line) and 3-hydroxy-butanal (green line) are shown for comparison.

Figure 5 show time-integrated PI spectra of $C_4H_4D_4O_2$ from the PA + CD_3CDO + 351 nm system, plotted on linear and logarithmic ordinates. Data from two different runs on different days are plotted, where the latter dataset extends to higher photon energy. For comparison we also plot reference spectra from commercial samples (Sigma-Aldrich) of acetoin ($CH_3C(O)CH(OH)CH_3$, > 95% purity) and 3-hydroxy-butanal ($CH_3CH(OH)CH_2CHO$, purity not stated by manufacturer, freeze-pump-thawed three times before use), where the latter is another mechanistically plausible product that will be discussed in more detail below. Our reactive PI spectra show excellent agreement with the acetoin isomer and no

indication that 3-hydroxy-butanal is formed in (R5).

Theory

To gain additional insight into the title reaction and its mechanism, we present our electronic structure and kinetics results. Figure 6 depicts stationary points—including zero point energy (ZPE)—on the $C_4H_8O_2$ PES (for the d_4 -PES see Figure S8 in the SI), where the zero of potential energy is assigned to the reactants shown in the center. On the left, the red pathway shows a pre-reactive complex leading to a saddle point for insertion of the carbene carbon of MHC into a methyl group C-H bond of acetaldehyde. This plausible insertion pathway leads to the isomer 3-hydroxybutanal, which was our reason for experimentally measuring the PI spectrum of this compound. On the right side, a deeper pre-reactive complex leads to the upper, cyan pathway, reaching a saddle point for the analogous carbene insertion into the formyl C-H bond of acetaldehyde. Insertion is a common mechanism invoked for singlet carbenes,⁵⁰ yet both of these pathways have high barriers, requiring thermal activation or quantum mechanical tunneling to proceed. By contrast, the lowest energy pathway is the blue carbonyl-ene²¹ pathway, in which the submerged saddle point at $-8.4 \text{ kcal mol}^{-1}$ corresponds to a five-member -C-O-H-O-C- ring structure that proceeds to acetoin. The lowest energy forward reaction from acetoin identified by Kinbot with a first-order saddle point at $-17.9 \text{ kcal mol}^{-1}$ leads to the isomer 2,2-hydroxymethylpropanal, which is only slightly less stable than acetoin.

Given the topography of the PES in Figure 6, we expect that the lower energy blue addition pathway will dominate at low to moderate temperatures. We employ an effective microcanonical two-transition state model in which the barrierless entry to the pre-reactive complex comprises the outer, barrierless transition state (TS), whereas the tight, inner transition state is located at the saddle point leading to acetoin at $-8.4 \text{ kcal mol}^{-1}$.

The magenta line in Figure 7 shows our calculated effective high-pressure rate coefficient vs temperature and its components: the rate coefficient due to the outer TS (black) and

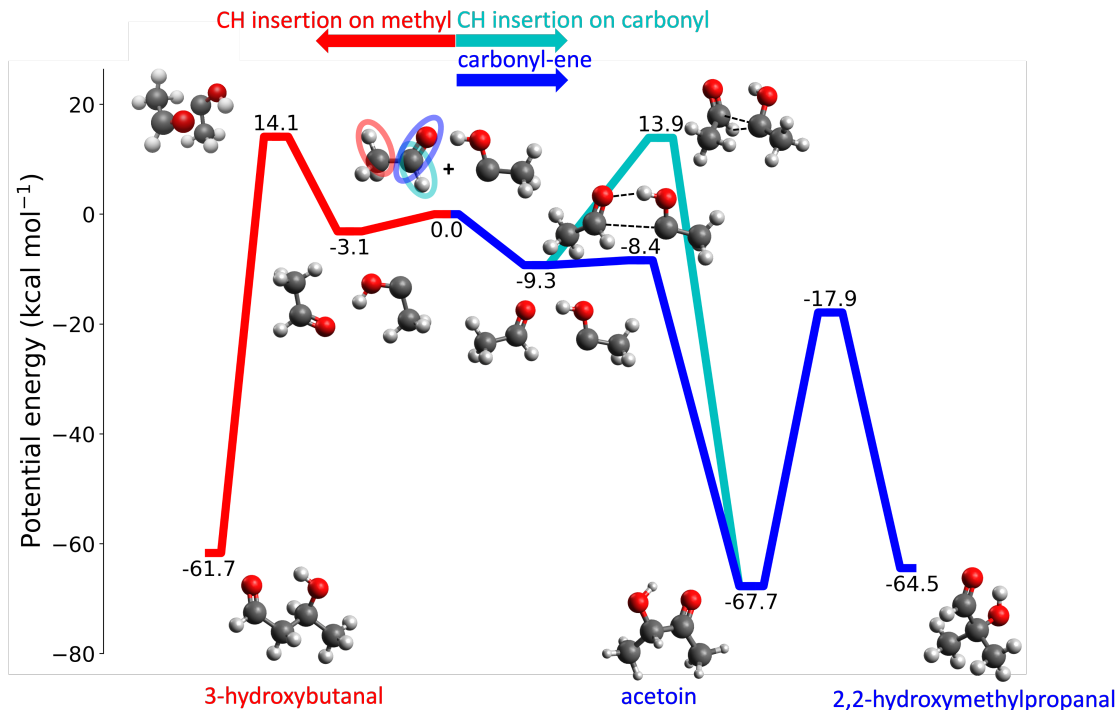


Figure 6: The ZPE-inclusive PES connecting wells and first-order saddle points of $C_4H_8O_2$, calculated at the CCSD(T)-F12a/cc-pVTZ-F12// ω B97X-D/6-311++G(d,p) level of theory. Acetaldehyde and MHC are shown in the center at $E = 0.0$.

due to the inner TS (yellow). We estimate the uncertainty in the calculated effective rate coefficient by combining our estimate for the uncertainty (50%) in the rate coefficient corresponding to the outer TS with the effect of the estimated 1 kcal mol^{-1} uncertainty in the inner saddle point energy.

As expected, the outer TS rate coefficient is only a weak function of temperature, whereas the inner rate coefficient controlled by a tight TS is strongly dependent on temperature – inversely in this case, because the corresponding barrier is submerged. The individual components are equal near $T = 450 \text{ K}$. The overall, effective rate coefficient is smaller than either of its individual components. Our best estimate of the room temperature rate coefficient is $k_4(T = 300 \text{ K}, P = \infty) = 1.37 \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ with a factor of two uncertainty, whereas $k_4(T = 28 \text{ K}, P = \infty)$ approaches $9.3 \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. We do not expect any significant isotope effect, and hence assume $k_5 \cong k_4$. In the $130 - 600 \text{ K}$ range we can express the rate coefficient of reaction (R4) with the following, non-Arrhenius

form:

$$k_4 = 3.21 \times 10^{-12} + 9.99 \times 10^{-10} e^{-0.0067397T} + 1.41 \times 10^{-9} e^{-0.024514T} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}.$$

Although reaction (R3) is not our focus here, and a full treatment of it is beyond the scope of this work, we have used KinBot to explore the PES for this reaction because of the competition between (R3) and (R4) or (R5). See SI Section S5 for details. The reaction of MHC with PA is in many ways a more complex version of the MHC + acetaldehyde reaction, because PA has a keto carbonyl, an acid carbonyl, and an acidic hydrogen, all of which interact with the approaching MHC.

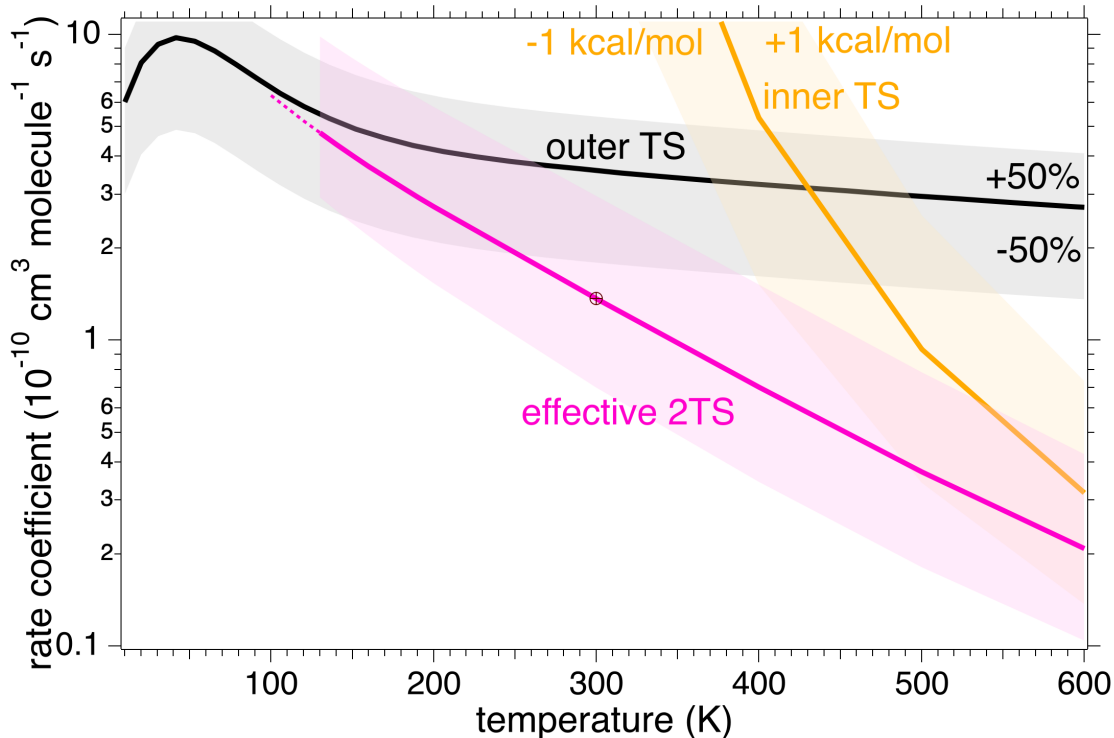


Figure 7: Calculated temperature-dependent rate coefficients for (R4). The black line shows the results for the outer, loose TS, the yellow line for the inner, submerged TS, and the magenta line is the effective rate coefficient from the two-TS model. The shaded areas are the uncertainty bounds. The dashed section of the magenta line is extrapolated in a regime where the numerical results from the master equation could not be converged.

Discussion

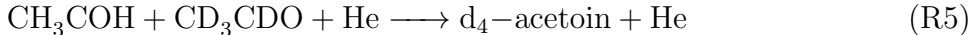
We now consider whether the relative rate measurements in Figure 4 are consistent with our calculated rate coefficient. Our kinetic simulation of the final product yields of species “P” and d_4 -acetoin also includes reaction (R6) representing loss of MHC on the walls of the reactor (see SI Section S4). The first two reactions are always pseudo-first order under our conditions, whereas the third reaction is first order. This kinetic model may be solved analytically, with the equations and a full analysis given in the SI Section S4. Unfortunately, we do not have enough information on this system for an absolute yield model because we do not know the photoionization cross section of species “P”, which would be needed to convert the signals in Figure 4 into product number densities. However, the relative signals in Figure 4 are valuable because the (unknown) multiplicative factor that converts signal to number density for a particular species must be fixed across all points along the abscissa of Figure 4, and hence is a constraint in fitting the data.

If we scale the simulated yield of species “P” (red line) when $[\text{CD}_3\text{CDO}] = 0$ to the experimental signal of species “P” (red squares), and scale the simulated yield of d_4 -acetoin to match its signal at the highest $[\text{CD}_3\text{CDO}]$, then the simulation is controlled by only two independent parameters: the ratio k_{3a}/k_5 , and the wall loss rate coefficient k_6 . We obtain the most reasonable fit to the data, shown in Figure 4, when we use the lower error limit of our calculated value for $k_5 = 6.85 \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ and wall loss of $k_6 = 20,000 \text{ s}^{-1}$, resulting in $k_3 = k_{3a} + k_{3b} = 2.7 \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. As shown in the SI, the fit is insensitive to the branching fraction k_{3a}/k_3 , and we choose a plausible value of 0.5 based on our calculations of the PES for reaction (R3) (see SI Section S4). In summary, although the relative signal measurements in Figure 4 cannot provide a definitive experimental value for k_5 , simulations using the lower error bound of our calculated k_5 are consistent with the curvature of the data, and show that the $\text{MHC} + \text{CD}_3\text{CDO}$ reaction has a large rate coefficient at 300 K, although smaller than the rate coefficient for the $\text{MHC} + \text{PA}$ reaction. Our exploration of the PES for $\text{MHC} + \text{PA}$ provides some evidence supporting the conclusion

that k_3 should be larger than k_5 .

Although the simplest carbene $^3\ddot{\text{C}}\text{H}_2$ is a ground state triplet, where the two non-bonding electrons adopt a $\sigma^1\pi^1$ configuration, the smallest hydroxycarbenes— $^1\text{H}\ddot{\text{C}}\text{OH}$ and $^1\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$ —are ground state closed-shell singlets with $\sigma^2\pi^0$ configuration and significant singlet-triplet splittings of 24.7 and 29.3 kcal mol $^{-1}$, respectively.⁵¹ The lone pairs on the oxygen of the -OH substituent donate electron density to the empty carbene π^0 orbital, thereby stabilizing the closed-shell singlet configuration. A review of carbene chemistry⁵⁰ categorizes singlet carbenes reaction types as (1) 1,2-shift isomerizations, (2) cycloaddition to C=C bonds, (3) dimerization, (4) addition to oxygen atoms in carbonyl groups to form carbonyl ylides, and (5) insertion into C-H bonds. Of these reaction types, the 1,2-shift isomerization is simply the isomerization to acetaldehyde (cf. R2c). Cycloaddition to C=C bonds and carbene dimerization are not relevant in the present case where PA and CD₃CDO are present in great excess, intercepting essentially all MHC molecules that are not consumed on the reactor walls. The electrophilic addition of the empty carbene π -orbital of CH₃– $\ddot{\text{C}}$ –OH to an oxygen lone pair in CD₃CDO would form a carbonyl ylide, in this case CH₃C(OH)–O–C(D)CD₃ that would be expected to rearrange to a hydroxy-substituted oxirane. Finally, insertion into a methyl group C-D bond of *d*₄-acetaldehyde would yield the isomer 3-hydroxybutanal, whereas insertion into the aldehyde C-D bond would yield acetoin. These canonical reaction types⁵⁰ do not include the carbonyl-ene mechanism proposed by Eckhardt et al.²¹

The experimental data presented in Figures 1–5 provide strong evidence that reaction (R5) may be more precisely written as



with *d*₄-acetoin as the only product. The calculations of Eckhardt et al.²¹ and our own calculations summarized in Figure 6 show substantial barriers to insertion, consistent with our lack of experimental evidence for the 3-hydroxybutanal product. Note that both cyan and blue pathways in Figure 6, insertion and the carbonyl-ene mechanism, form acetoin.

In the insertion mechanism the carbonyl group of CD_3CDO remains intact, whereas in the carbonyl-ene mechanism it becomes a C-OH group via H transfer from MHC. For this reason our experiments cannot decisively eliminate the insertion mechanism forming acetoin, but if it were active we would also expect to see 3-hydroxybutanal due to the similar barrier height for that competing insertion. However, the low-energy submerged barrier we calculate for the carbonyl-ene addition pathway in Figure 6 should lead to the complete dominance of this mechanism over insertion.

In a flow-pyrolysis experiment, Eckhardt et al.²¹ pyrolyzed PA in the presence of acetaldehyde, where they assumed that PA pyrolysis produces CH_3COH . End-product analysis by NMR and GC-MS showed signals of acetoin, acetaldehyde, and acetic acid. They concluded that the acetoin “in all likelihood is the product of the bimolecular reaction of $\text{CH}_3\text{COH} + \text{acetaldehyde}$.” Our experiments provide definitive evidence that this statement is correct, kinetically linking the acetoin product to these two reactants.

In a separate experiment, Eckhardt et al.²¹ used high vacuum flash pyrolysis of an appropriate precursor to form either $\text{H}\ddot{\text{C}}\text{OH}$ or $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$ and deposited the resultant gases in an argon matrix at $T = 3$ K. They confirmed the creation of these hydroxycarbenes using infrared spectroscopy. They co-doped the matrix with either H_2CO or CH_3CHO , but due to spectroscopic interference were only able to examine co-deposition of $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$ with H_2CO . Upon annealing the matrix for five minutes at $T = 28$ K, enabling species diffusion, they observed the infrared spectrum of hydroxyacetone $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{OH}$. This observation provides evidence that the $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH} + \text{H}_2\text{CO}$ reaction analogous to (R4) occurs and is rapid even at very low temperatures. Our master equation calculations for the temperature-dependent kinetics of (R4) shows that it is also rapid at low temperatures, consistent with the instrument-limited experimental kinetics of Figure 3. We expect the reactions of other hydroxycarbenes with other aldehydes to be similarly fast. We estimate our rate coefficients are accurate within a factor of two and will be useful in models of interstellar chemistry.

It is important to remember that our reported rate coefficient is the capture rate co-

efficient, i.e., the limit when all reactive collisions leading to acetoin result in stabilized acetoin. Although this limit is certainly true at 4 Torr and 300 K, it would not be true at the very low number densities of the interstellar medium, where three-body collisions are exceedingly rare within the lifetime of acetoin formed with $67.7 \text{ kcal mol}^{-1}$ excess energy. Instead, at very low pressure the adduct in the gas phase could isomerize through energetically accessible channels until it dissociates to some bimolecular products. Our more extensive KinBot calculations of this PES indicate that one such exit channel is methylcyclopropanone + H_2O . However, reactivity on dust grains in the interstellar medium⁵² would provide an environment in which the solid surface could efficiently remove excess energy after the bimolecular collision, stabilizing acetoin formation and more generally sugar formation from hydroxycarbene + aldehyde reactants.

Prior to the work of Eckhardt et al.,²¹ there were previous implications of formaldehyde photochemistry-induced formation of sugars,^{10,18} including one study that hypothesized the involvement of $\text{H}\ddot{\text{C}}\text{OH}$.⁵³ In related work, Kaiser and co-workers^{54,55} observed glycolaldehyde formation from irradiation of methanol and methanol-CO ices. They concluded that CH_3OH photolysis leads to $\text{CH}_3\dot{\text{O}}$, $\dot{\text{C}}\text{H}_2\text{OH}$, and $\text{H}\dot{\text{C}}\text{O}$ radicals, after which the $\text{H}\dot{\text{C}}\text{O} + \dot{\text{C}}\text{H}_2\text{OH}$ reaction forms glycolaldehyde. These authors do not mention the possibility of carbene chemistry. However, Feng et al. showed that photolysis of $\dot{\text{C}}\text{H}_2\text{OH}$ gives rise to both $\text{H}\ddot{\text{C}}\text{OH}$ and H_2CO .⁵⁶ More recently, Hockey et al.⁵⁷ observed the formation of both $\text{H}\ddot{\text{C}}\text{OH}$ and H_2CO in the 193-nm photodissociation of gas-phase methanol. This production of $\text{H}\ddot{\text{C}}\text{OH}$ from methanol irradiation offers another likely contribution to glycolaldehyde formation in methanol ices, which are believed to be abundant in interstellar environments. Of direct relevance to the present work, Kleimeier et al.⁵⁸ observed the formation of PA in laboratory experiments irradiating acetaldehyde and carbon dioxide ices. They assign the $\text{HO}\dot{\text{C}}\text{O} + \text{CH}_3\dot{\text{C}}\text{O}$ radical recombination reaction as the source of PA. Similar work provides evidence for formation of glyoxylic acid (a precursor to $\text{H}\ddot{\text{C}}\text{OH}$) from cosmic ray irradiation of $\text{CO}/\text{H}_2\text{O}$ ices.⁵⁹ These findings, coupled with the known presence of small aldehydes in space⁶⁰ and

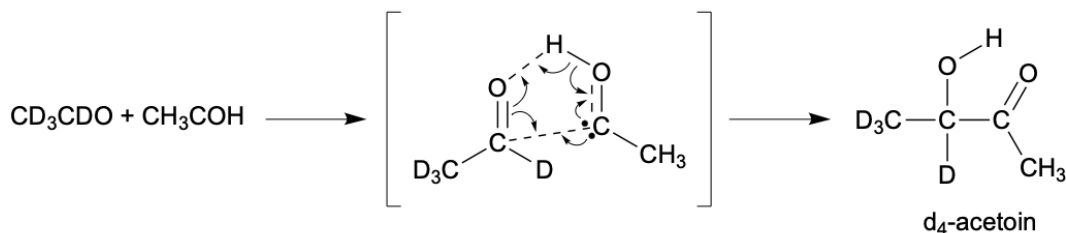
the availability of UV photons, provides all the necessary building blocks for the relevance of hydroxycarbene + aldehyde reactions in cold interstellar environments. We note, however, that hydroxycarbenes can isomerize to their more stable aldehyde isomers via quantum mechanical tunneling, with lifetimes of 2.1 hours ($\text{H}\ddot{\text{C}}\text{OH}$)⁶¹ and 1.1 hours ($\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$)⁶² at cryogenic temperatures and shorter calculated lifetimes of ≈ 30 minutes at 300 K.²⁰

In their analysis of the Murchison and Murray meteorites, Cooper et al.¹⁴ suggested that the aqueous formose reaction could have contributed to the sugars they observed based on other evidence of liquid water presence on the meteorites’ precursors. However, our work and that of Eckhardt et al. shows that aqueous environments are not a requirement for the synthesis of sugars and sugar derivatives, and Krisnamurthy⁶ points out a number of problematic aspects in the hypothesis that the formose reaction could have created the first sugars utilized in living organisms.

The chemistry of hydroxycarbenes has been frequently implied, but rarely directly examined, due to the twin difficulties of creating a sufficient concentration of hydroxycarbenes and proving that this sample is not one of the more stable, closed-shell isomers. As examples of their broader relevance, there is evidence⁶³ that $\text{H}\ddot{\text{C}}\text{OH}$ is a key chemical intermediate in the industrially important Fischer-Tropsch synthesis of liquid hydrocarbons from $\text{CO} + \text{H}_2$ feedstock. The presence of PA in Earth’s atmosphere, and the fact that its main decay channel is photolysis⁶⁴ rather than reaction with OH, provides a significant source of $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$ in the troposphere. The fate and consequences of $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH}$ in atmospheric chemistry has been the source of recent debate, with Mondal et al.⁶⁵ concluding, based on CCSD(T)/6-311++G(3df,3pd)//M06-2X/6-311++G(3df,3pd) electronic structure and kinetics calculations, that MHC decays dominantly via the $\text{CH}_3\text{--}\ddot{\text{C}}\text{--OH} + \text{H}_2\text{O} \longrightarrow \text{CH}_3\text{CHO} + \text{H}_2\text{O}$ reaction, that is, effectively the 1,2-shift isomerization of MHC to acetaldehyde. However, the mechanism is actually water-catalyzed, where water provides an H-atom shuttle, thereby lowering the energy barrier compared to a traditional 1,2-shift isomerization, yielding a 300 K rate coefficient of $2.7 \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. They argue that this process plays a sig-

nificant role in the acetaldehyde budget in Earth’s atmosphere. Our preliminary exploration of the PES for the MHC + PA reaction (SI Figure S10) revealed a similar PA-catalyzed H-shuttle reaction pathway, although when PA is the catalyst, this pathway is barrierless at the ω B97X-D/6-311++G(d,p) level, in contrast to the at least 7.5 kcal mol⁻¹ barrier leading out from a pre-reactive complex found by Mondal et al. when H₂O is the catalyst.

On a fundamental level, we note that the pre-reactive complex of the carbonyl-ene mechanism is unusually stable, lying -9.3 kcal mol⁻¹ below reactants (Figure 6). This significant interaction energy is larger than can be rationalized by the O—HO hydrogen bond, and is indicative of additional stabilization⁵⁰ from the interaction of the electrophilic empty carbene π orbital with the π electron density of the C=O bond in acetaldehyde. Indeed, as shown in Scheme 1, the carbonyl-ene mechanism can be understood as a 6-electron pericyclic rearrangement. Note that in insertion mechanisms commonly invoked for reactivity of singlet carbenes, the spin-paired electrons of the carbene lone pair form two new σ bonds with two atoms of the *other* reactant, as in the C-H insertions shown in Figure 6. By contrast, we emphasize that the carbonyl-ene mechanism is qualitatively different: one of the carbene lone-pair electrons incorporates into a new σ bond with the carbonyl carbon of the other reactant (CD₃CDO), whereas the remaining carbene lone-pair electron is part of a new π bond between the C-O atoms of the carbene reactant, forming the nascent carbonyl group of acetoin. The low-strain geometry depicted within brackets in Scheme 1 is consistent with the small (~ 1 kcal mol⁻¹) energetic cost of rearrangement from the pre-reactive complex to the saddle point leading to acetoin. The reactions of hydroxycarbenes with larger aldehydes should have similarly favorable energetics leading to very fast kinetics even at low temperatures.



Scheme 1: The 6-electron pericyclic rearrangement of the carbonyl-ene mechanism forming acetoin

Conclusion

In this work we report time-resolved measurements of the gas-phase methylhydroxycarbene ($\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH}$) + d_4 -acetaldehyde (CD_3CDO) reaction, with isomeric characterization of reactants and products using Multiplexed Photoionization Mass Spectrometry. By producing the highly reactive carbene via pulsed 351-nm photodissociation of pyruvic acid, we have independent control of the concentrations of both reactants. The only product we observe is the isomer acetoin ($\text{CH}_3\text{C}(\text{O})\text{CD}(\text{OH})\text{CD}_3$), with no evidence for the potential insertion product 3-hydroxybutanal.

We construct a potential energy surface using automated exploration to reduce the likelihood that an important pathway is overlooked. These calculations support the previously proposed carbonyl-ene mechanism,²¹ in which an unusually deep pre-reactive complex well is stabilized both by hydrogen bonding and donation of π electron density from acetaldehyde’s carbonyl group into the empty π orbital of the carbene. This pre-reactive complex has nearly the same geometry as the submerged saddle point that enables a facile six-electron pericyclic rearrangement leading to acetoin. We employ an effective microcanonical two-transition state model in our master equation kinetics calculations that treats both the barrierless long-range attraction and the submerged saddle point as bottlenecks to the reaction. Our predicted rate coefficients over the 20 – 600 K temperature range indicate a very fast reaction, with the largest rate coefficient for $T < 100$ K. These conclusions are consis-

tent with our relative rate experimental data, and with earlier studies²¹ of the isoelectronic $\text{CH}_3\text{-}\ddot{\text{C}}\text{-OH} + \text{H}_2\text{CO} \longrightarrow \text{CH}_3\text{C(O)CH}_2\text{OH}$ reaction that proceeded even at $T = 28$ K.

Although acetoin and hydroxyacetone are sugar derivatives, rather than sugars *per se*, we argue that the key interactions between the carbonyl group of the aldehyde and the hydroxycarbene will render analogous reactions that produce sugars, such as $\text{H}\ddot{\text{C}}\text{OH} + \text{H}_2\text{CO} \longrightarrow \text{HOCH}_2\text{CHO}$, to be equally facile at low temperatures. These fast kinetics imply that hydroxycarbene + aldehyde reactions are plausible prebiotic sources of sugars in cold, non-aqueous environments. Considering that recent laboratory experiments irradiating acetaldehyde ices produced pyruvic acid under simulated interstellar conditions,⁵⁸ each individual component necessary for this pathway to prebiotic sugar formation seems feasible.

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Supporting Information Available

The Supporting Information is available free of charge at (DOI inserted by production staff).

S1: Additional experimental mass spectra, species time traces, and photoionization spectra.

S2: Computation details regarding the MHC + CD₃CDO rate coefficient. S3: PES of C₄H₄D₄O₂. S4: Details of the Kinetic Yield Model. S5: PES of the MHC + PA reaction.

The file structures.txt contains the relevant optimized geometries.

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TOC Graphic

