**Quantum Tunneling Mediated Low-Temperature Synthesis of Interstellar Hemiacetals**

Jia Wang,1,2+ Anatoliy A. Nikolayev,3+ Joshua H. Marks,1,2 Mason Mcanally,1,2 Valeriy N. Azyazov,4 André K. Eckhardt,5\* Alexander M. Mebel,6\* Ralf I. Kaiser1,2\*

*1 W. M. Keck Research Laboratory in Astrochemistry, University of Hawaii at Manoa, Honolulu, HI 96822, USA*

*2 Department of Chemistry, University of Hawaii at Manoa, Honolulu, HI 96822, USA*

*3 Samara National Research University, Samara 443086, Russia*

*4 Lebedev Physical Institute, Samara 443011, Russia*

*5 Lehrstuhl für Organische Chemie II, Ruhr-Universität Bochum, Bochum 44801, Germany*

*6 Department of Chemistry and Biochemistry, Florida International University, Miami, Florida 33199, USA*

\*Corresponding Authors: [Andre.Eckhardt@ruhr-uni-bochum.de](mailto:Andre.Eckhardt@ruhr-uni-bochum.de), [mebela@fiu.edu](mailto:mebela@fiu.edu), [ralfk@hawaii.edu](mailto:ralfk@hawaii.edu)

+ Contributed Equally

**ABSTRACT**

Sugars and sugar-related molecules are ubiquitous in carbonaceous meteorites and in star-forming regions, but the underlying mechanisms of their formation have remained largely elusive. Herein, we report an unconventional synthesis of the hemiacetal, (*R/S*)-1-methoxyethanol (CH3OCH(OH)CH3), through quantum tunneling mediated reactions in low-temperature interstellar model ices composed of acetaldehyde (CH3CHO) and methanol (CH3OH). The detection of racemic 1-methoxyethanol through a bottom-up synthesis from simple, abundant precursor molecules within interstellar ices represents a vital starting point to the formation of complex interstellar hemiacetals. Once synthesized, hemiacetals may act as possible precursors to interstellar sugars and sugar-related molecules in deep space.

**TOC GRAPHIC**



Since Milas recognized the vital role of hemiacetals (ROCH(OH)R’) – short-lived organic molecules with a hydroxyl (OH) and alkoxy (OR) group bonded to the same carbon atom - as key transients in the formation of esters (RCOOR’) with R and R’ being organic groups nearly a century ago (1928),[1](#_ENREF_1) hemiacetals have emerged as fundamental reaction intermediates in organic synthe­sis (nucleophilic addition) and in molecular mass growth processes to sugars.[2-5](#_ENREF_2) Sugars such as D-ribose (C5H10O5), a pentose and molecular building block of ribonucleotides in ribonucleic acid (RNA), along with glucose (C6H12O6), a hexose and vital source of energy in living organisms, undergo an internalnucleophilic addition and exist primarily in a cyclic hemiacetal form.[4](#_ENREF_4) Considering the asymmetric nature of the central carbon atom, chiral hemiacetals have been recognized as enantioselective reagents in the production of esters catalyzed by proteins such as the alcohol dehydrogenase proteins.[6](#_ENREF_6) The existence of hemi­acetals is also essential for the formose (Butlerov) reaction under aqueous conditions and in the presence of methanol.[7](#_ENREF_7) A complex reaction sequence leads to the formation of sugars and sugar alcohols under abiotic conditions via polyconden­sation of formaldehyde (H2CO) under prebiotic conditions.[8](#_ENREF_8) However, the short lifetime of hemiacetals in the order of minutes[9](#_ENREF_9) under aqueous prebiotic conditions classifies hemiacetals as one of the most elusive classes of organic transient molecules that mainly exist in equilibrium with the alcohols (ROH) and aldehydes (RCHO).[10](#_ENREF_10) Therefore, untang­ling the formation mechanisms of short-lived hemiacetals[3](#_ENREF_3),[11](#_ENREF_11)of astrobiological relevance along with their chemical bonding is essential in not only constraining the chemical and physical conditions of molecular mass growth processes under prebiotic conditions, but also in defining the level of molecular com­plex­ity that can be achieved abiotically in deep space.

     Terrestrial scenarios for an abiotic formation of sugars rely on very specific reaction conditions such as surface-water catalyzed pathways[11](#_ENREF_11) to produce labile hemiacetals; these conditions might not have been prevalent under prebiotic conditions on the early Earth.[12](#_ENREF_12) Therefore, the chemical processing of complex ice mixtures on low-temperature interstellar nanoparticles (10 K) by energetic galactic cosmic rays (GCRs) and through vacuum ultraviolet photons (VUV) has been recommended as plausible alternatives for abiotic synthesis of complex organics such as amino acids and sugars of astrobiological relevance. Holtom et al.,[13](#_ENREF_13" \o "Holtom, 2005 #2679) Meinert et al.,[14](#_ENREF_14" \o "Meinert, 2016 #1406) and Zhu et al.[15](#_ENREF_15) provided compelling evidence on the forma­tion of amino acids, sugars, and (glycerol)phosphates which supports the scenario that vital biorelevant molecules, together with their precursors, might form in deep space. At least a fraction of these abiotically synthesized organics[16](#_ENREF_16) might be

D:\Dropbox\Astrochemistry\4 Hemiacetal\Figures\Hemiactal\hemiacetal conformers-new.tif

**Figure 1.** Formation of 1-methoxyethanol (**1**) and structures of six conformers.(**a**)Thermal reaction of acetaldehyde (CH3CHO) with methanol (CH3OH) forming 1-methoxyethanol (**1**) hemiacetal. (**b**) Ranges of computed adiabatic ionization energies (IEs) corrected for the electric field effect and relative energies (ΔE) calculated at the CCSD(T)/CBS//B3LYP/cc-pVTZ level of theory in eV and kJ mol−1, respectively. Point groups and electronic ground states of the conformers are *C*1 and 1A, respectively.

incorporated into meteoritic parent bodies and could have survived comet or meteorite impact on the Earth thus bolstering the concept of an exogenous source of key prebiotic molecules together with their precursors on proto-Earth.

Here, exploiting the hemiacetal, (*R/S*)-1-methoxyethanol (**1**, CH3OCH(OH)CH3; Figure 1) as a benchmark for the formation of hemiacetals in the interstellar medium via quantum tunneling, we provide the very first identification of **1** via thermal processing of interstellar model ices of acetaldehyde (CH3CHO) and methanol (CH3OH). Binary ice mixtures were processed thermally from 5 K on via temperature-programmed desorption (TPD). **1** was identified first infrared spectroscopically (FTIR) at 150 K after sublimation of the reactants and also *isomer-selectively* upon sublimation of **1** into the gas phase after vacuum ultraviolet (VUV) soft photoionization coupled with reflectron time-of-flight mass spectrometry (PI-ReToF-MS). Isotopic substitution experiments utilizing (par­ti­­ally) deutera­ted reactants permit sophisticated insights into the formation mechanisms of **1** and propose astronomical searches of the **1** with radio teles­copes such as the Atacama Large Millimeter/ submillimeter Array (ALMA) toward star-forming regions such as Sgr B2. Since acetaldehyde and methanol are contemplated to exist on icy interstellar grains. With abundances of acetaldehyde reaching up to a few percent[17](#_ENREF_17) and of methanol up to 30 % toward high-mass protostars such as RAFGL7009S,[18](#_ENREF_18) the preparation of racemic **1** in thermally processed interstellar model ices via quantum tunneling significantly advances the knowledge of the fundamental formation of key organics such as hemiacetals in deep space. Once prepared in interstellar ices and enduring star-forming regions and solar system formation, they can be incorporated into planetesimals and could have been delivered to planets like proto-Earth.[16](#_ENREF_16)

Fourier transform infrared (FTIR) spectroscopy was exploited to trace the thermal chemistry within acetaldehyde−methanol ices during the TPD phase to 320 K. At 5 K, the infrared absorptions are exclusively attributed to the normal modes of acetaldehyde and methanol (Figure S1). The ratio of acetaldehyde to methanol in the ice mixture was determined to be (1.1 ± 0.3):1. The spectra revealed prominent absorptions of acetaldehyde such as the overtone (2869 cm–1, 2*v*6) and the carbonyl stretching (1716 cm–1, *v*4);[19](#_ENREF_19) intense absorptions of methanol such as the broad O–H stretching (3020 – 3600 cm–1, *v*1) and the C–O stretching (1031 cm–1, *v*8)[20](#_ENREF_20) are also conspicuous (Table S1). During the TPD phase, prominent absorptions of **1** emerged (Figure S2); characteristic FTIR spectra collected at 150 K for 1-methoxyethanol and 1-methoxyethanol-d8 are presented in Figure 2 with assignments listed in Table S2. As revealed in Figure 2a, the absorptions are linked to the OH stretching (3310 cm–1), CH stretching (2988 cm–1, 2932 cm–1; 2832 cm–1), CH bending (1511 cm–1, 1456 cm–1, 1384 cm–1), and CH3 rocking (909 cm–1) modes. Upon deuteration, these absorptions were red-shifted in CD3CDO–CD3OD ices (Figure 2b) such as OD

Diagram

Description automatically generated

**Figure 2.** FTIR spectra of hemiacetals along with the temperature-dependent infrared signal of the hemiacetal. (**a**) and (**b**) are collected FTIR spectra in CH3CHO–CH3OH (**a**) and CD3CDO–CD3OD (**b**) after the sublimation of acetaldehyde and methanol. Temperature-dependent integrated signal of the absorption peaks (blue arrows) at 909 cm-1 in the CH3CHO–CH3OH ice (**c**) and 1274 cm-1 in CD3CDO–CD3OD ice (**d**), with the onsets of the signal (red arrows) of 113 ± 3 K and 118 ± 4 K, respectively. The blue dashed line indicates the end temperature of the sublimation of acetaldehyde (105–148 K) and methanol (125–148 K).

stretching (2461 cm–1), CD stretching (2244 cm–1, 2215 cm–1, 2069 cm–1), CD bending (1274 cm–1, 1256 cm–1), and CD3 rocking (978 cm–1) modes. Since the C–O stretching does not reflect the motions of hydrogen atoms, the C–O fundamentals do not shift significantly upon deuteration. These absorptions correlate exceptionally well with the computed gas-phase infrared spectra of 1-methoxyethanol and 1-methoxyethanol-d8 (Figure 3) with scaled harmonic frequencies and intensities of gas phase hemiacetal conformers **1a–1e** calculated at the B3LYP/cc-pVTZ level of theory. Note that the calculated gas-phase absorptions of OH and OD stretching modes are redshifted to 3310 cm–1 and 2461 cm–1, respectively, and broaden significantly due to hydrogen bonding under real ice conditions. Previously, Meadows et al.[10](#_ENREF_10) collected the infrared absorption



**Figure 3.** Experimental and calculated FTIR spectra of distinct conformers of **1** (left) and **1**-d8 (right).The scaled (0.967) harmonic frequencies and intensities of gas phase hemiacetal conformers **1a**–**1e** werecalculatedat theB3LYP/cc-pVTZ level of theory. Dashed lines indicate the peaks observed in the experiments.

spectrum of **1** in methanol solution from 800 cm–1 to 1300 cm–1 and reported absorptions at 1210 cm–1, 1140 cm–1, and 920 cm–1, which agree well with our data (Table S2). Further, we explored the temperature dependent evolution of key FTIR absorptions of **1** such as the 909 cm-1 fundamental (CH3 rocking) in the CH3CHO–CH3OH ice (Figure 2c) and the 1274 cm-1 mode (CD bending) in CD3CDO–CD3OD ice (Figure 2d). Onsets are clearly evident at 113 ± 3 K and 118 ± 4 K, respectively, suggesting that the onset of formation of 1-methoxyethanol and 1-methoxyethanol-d8 are within error limits identical. Both 1-methoxyethanol and 1-methoxyethanol-d8 started to decrease at about 148 K (Figures 2c-2d). Considering the range of sublimation temperatures of acetaldehyde (105 – 148 K) and methanol (125 – 148 K), the formation of 1-methoxyethanol and 1-methoxyethanol-d8 are likely linked to the sublimation of the reactants. Overall, our data present the first FTIR spectra of 1-methoxyethanol and 1-methoxyethanol-d8 ices, and hence provide compelling evidence for the synthesis and detection of **1**.

To further strengthen the identification of 1-methoxyethanol and 1-methoxyethanol-d8, the PI-ReToF-MS technique was exploited to detect **1** *isomer-specific* upon sublimation into the gas phase.[21](#_ENREF_21) Based on the adiabatic ionization energies of **1** (Figure 1, Table S3), photon energies of 10.49 eV, 9.70 eV, and 9.20 eV were chosen. At 10.49 eV, all conformers (**1a–1f**) can be ionized if formed; at 9.70 eV, only conformer **1f** can be ionized; at 9.20 eV, none of the conformers can be ionized. The mass spectra of the subliming molecules were collected as a function of temperature at the aforementioned photon energies (Figures S3 and 4). For CH3CHO−CH3OH ice, data recorded at 10.49 eV reveal prominent signal at a mass-to-charge ratio (*m/z*) of 61 along with the acetaldehyde (IE = 10.229 ± 0.0007 eV)[22](#_ENREF_22) at *m/z* = 44. Note that methanol (IE = 10.8393 ± 0.0005 eV)[23](#_ENREF_23) cannot be detected since its ionization energy is higher than 10.49 eV. It is important to stress that no signal for 1-methoxyethanol parent radical cation (**1∙+**, CH3OCH(OH)CH3**∙**+) at *m/z* = 76 was detected due to dissociative photoionization. Photoionization of **1** with photons with excess energy compared to the threshold ionization energy is followed by intramolecular vibrational energy redistribution. In the radical cation, the donation of electron density from oxygen to the disubstituted carbon destabilizes the carbon-carbon single bond while allowing delocalization of the charge. Therefore, the radical cation formed upon photoionization of the neutral dissociates to fragments to the methyl radical (ĊH3) plus the resonance-stabilized fragment ion, hydroxymethoxymethylium (**2+**, CH3OCH(OH)+), detected at *m/z* = 61. Though these fragmentation pathways rationalize the formation of fragment ion (**2+**) and are widely accepted, detailed energetics of this pathway have been absent in the literature. Therefore, we performed quantum-chemical calculations at the CBS-QB3 level of theory to document the dissociation channels (Figure S4, Table S4). The predicted pathways revealed that the 1-methoxyethanol radical cation (**1∙+**,*m/z* = 76) could pass a small barrier of only 2.0 kJ mol−1 forming a van-der-Waals complex (**3**), resulting in the methyl radical and fragment ion (**2+**, *m/z* = 61). This reaction represents an overall exoergic process of 12.0 kJ mol−1. The ionizing photon energy (10.49 eV) is higher by 48 kJ mol−1 (0.5 eV) than the ionization energy of **1** (IE = 9.54 – 9.98 eV); also, the internal energy of **1** at its sublimation temperature (151 K) is about 1.9 kJ mol−1; therefore, the gas phase 1-methoxyethanol radical cation (**1∙+**) can fragment readily once formed upon photoionization, which is in very good agreement with our experimental findings. Therefore, the TPD profiles of the target ion signal at *m/z* = 61 are of particular interest.

D:\Dropbox\Astrochemistry\4 Hemiacetal\Figures\TPD-profiles.tif

**Figure 4.** PI-ReToF-MS data collected in isotopic experiments. (**a**), (**b**), and (**c**) are the temperature program desorption (TPD) profiles obtained in CH3CHO−CH3OH ice at *m/z* = 61 (**a**), CD3CHO−CH3OH ice at *m/z* = 61 (**b**), and CD3CDO−CD3OH ice at *m/z* = 65 (**c**) photoionized with photon energies of 10.49 eV (blue), 9.70 eV (green), and 9.20 eV (gray). The dashed vertical line indicates the sublimation peak of **1**.

At 10.49 eV, the TPD profile of *m/z* = 61 exhibits a maximum at 151 K for the CH3CHO−CH3OH system (Figure 4a). Signal at *m/z* = 61 can only be associated with CHO3, C5H, and C2H5O2. To confirm the molecular formula of the ion at *m/z* = 61, isotopic substitution experiments were conducted with CD3CHO–CH3OH and CD3CDO–CD3OH ice mixtures. In the CD3CDO–CD3OH ice, 1-methoxyethanol-d7 (*m/z* = 83) is supposed to form, leading to methoxymethylideneoxidanium-d4 (*m/z* = 65) after photoionization (Figure S5, reaction [6]). The TPD profile collected at *m/z* = 65 in the CD3CDO–CD3OH ice (Figure 4c) is in excellent agreement with the data recorded for *m/z* = 61 in the CH3CHO–CH3OH ice, suggesting the presence of at least four hydrogen atoms. Therefore, the molecular formulae CHO3 and C5H can be ruled out; the molecular formula of the ion at *m/z* = 61 must be C2H5O2. This was also confirmed by the good agreement between the TPD profiles at *m/z* = 61 in both CH3CHO–CH3OH and CD3CHO–CH3OH ices (Figures 4a-4b), in which the same fragment ion, **2+**, at *m/z* = 61 was supposed to be detected upon photoionization of the neutral molecules (Figure S5, reactions [2] and [4]). Recall that the TPD profile of *m/z* = 61 (C2H5O2+) at 10.49 eV in the CH3CHO−CH3OH system reveals a sublimation peak at 151 K (Figure 4). This sublimation event could be linked to all conformers (**1a–1f**) being photoionized. Tuning down the photon energy to 9.70 eV, the sublimation event at *m/z* = 61 vanishes (Figure 4a); this is also confirmed in both the CD3CHO–CH3OH (*m/z* = 61) and CD3CDO–CD3OH (*m/z* = 65) systems (Figures 4b-4c). Since only conformer **1f** can be ionized at 9.70 eV, the sublimation peak at 151 K at 10.49 eV can only be associated with conformers **1a–1e**. An additional cross check at a photon energy of 9.20 eV reveals no ions, too, at *m/z* = 61 (Figure 4a). Considering the distance of 2.0 ± 0.2 mm between the photoionization region and the ice surface along with the average velocity of 204 m s−1 for **1** subliming at the temperature of 151 K, the lifetime of **1** in the gas phase has to exceed 10 ± 1 μs. Interestingly, the total counts for 1-methoxyethanol (19,800 ± 800), 1-methoxyethanol-d3 (7800 ± 300),and 1-methoxyethanol-d7 (2100 ± 500 ) at 10.49 eV reveal a decreasing intensity and hence yield upon an increasing level of deuteration. We then compared the dissociation pathways of 1-methoxyethanol, 1-methoxyethanol-d3, and1-methoxyethanol-d7 cations (Table S4). Since the barriers for the dissociation pathways of 1-methoxyethanol-d3 (3.6 kJ mol−1) and 1-methoxyethanol-d7 (2.5 kJ mol−1) cations are close to that of 1-methoxyethanol (2.0 kJ mol−1), it is not caused by the change of barrier in the decomposition of the radical cation. Instead, this result may be caused by the kinetic isotope effect in the formation of **1**.

Having provided compelling evidence on the preparation and detection of 1-methoxyethanol (**1**) in interstellar model ice mixtures of acetaldehyde and methanol via FTIR spectroscopy and PI-ReToF-MS, we shift our attention now to the formation mechanisms. **1** can be formed through a nucleophilic addition; the carbon of the carbonyl group (C=O) of acetaldehyde is electrophilic, whereas the hydroxy (OH) group of methanol is nucleophilic. The oxygen of methanol initiates a nucleophilic attack on the carbonyl carbon of acetaldehyde involving a proton transfer resulting in the formation of **1** in a single reaction step. Based on our PI-ReToF data, the proposed formation mechanism of **1** and its resonantly stabilized photoionization fragment ion (**2+**) are shown in Figure S5. To unravel the formation pathways, CD3CHO−CH3OH and CD3CDO−CD3OH systems were studied. In the CD3CHO−CH3OH system, 1-methoxyethanol-d3 (*m/z* = 79) was formed resulting in a non-deuterated fragment ion (**2+**, CH3OCH(OH)+) at *m/z* = 61 via reaction [4] (Figure S5). This result shows that the methyl-d3 is not incorporated into the cation. Similarly, 1-methoxyethanol-d7 (*m/z* = 83) was produced in the CD3CDO−CD3OH ice; this results in the observation of *m/z* = 65 (CD3OCD(OH)+) since the methyl-d3 from acetaldehyde is eliminated in reaction [6] (Figure S5), the remaining deuterium atoms are conserved (Figure 4c). Note that the fragmentation of **1** could be easily caused by the energetic Galactic Cosmic Rays (GCRs) or VUV photons, leading to the formation of fragment ion (**2+**) (Figures S4 and S5), which can survive for long periods of time relevant to astrophysical environments. Since fragment ion (**2+**) has a relatively large dipole moment (2.50 D), it could also be a suitable candidate for detection in the molecular cloud and star-forming environments via radio telescopes. Besides, the fragment ion (**2+**) may also contribute to the formation of methyl formate (CH3OCHO) and the recently detected methoxymethanol (CH3OCH2OH) via proton (H+) loss and hydride (H-) addition, respectively.

Prior theoretical work has been devoted to exploring the anomeric effect and *gas-phase* formation of **1**.[3](#_ENREF_3),[5](#_ENREF_5),[24](#_ENREF_24),[25](#_ENREF_25) Using **1** as a model, Jeffrey et al. performed *ab initio* electronic structure calculations on the anomeric effect in sugar molecules.[24](#_ENREF_24) Derricotteinvestigated the substituent effects on the *gas-phase* formation of **1** from acetaldehyde and methanol using symmetry-adapted perturbation theory,[25](#_ENREF_25) predicting the reaction energy to be thermodynamically favorable, but with a notable barrier of 142 kJ mol−1, which agrees well with our calculated results (Figure 5a). Robiette et al. suggested that protic donors may enhance the rate of the tertiary amine catalysed Morita-Baylis-Hillman reaction by allowing the proton-transfer step to occur via a concerted lower-energy pathway.[26](#_ENREF_26) Computational investigations found that solvent effects have a large influence on the relative stability of transition states, and polar solvation can decrease the activation barriers considerably.[27](#_ENREF_27) Given that acetaldehyde and methanol are polar molecules, solvent effects in the studied ices may lower the reaction barrier for the formation of **1**, allowing it to proceed at temperatures readily achievable during star formation in molecular clouds.

     To gain fundamental insight into the formation pathways of **1** in the condensed phase, we performed electronic structure calculations at the SCRF/SMD//ωB97X-D/6-311G(d,p) level of theory for the reactions of acetaldehyde (CH3CHO) and methanol (CH3OH). Incorporating solvating acetaldehyde and methanol molecules results in the formation of **1** and vinyl alcohol; the reaction barrier decreases by about 24 kJ mol−1 (Figure S6). However, the barriers for the formation of 1-methoxyethanol (**1**) in CH3CHO−(CH3OH)n (n = 1-5) systems decrease from 148 ± 10 kJ mol−1 to 60 ± 10 kJ mol−1 (Figures 5a-5e), providing evidence of the reduction in the Chart, scatter chart

Description automatically generated

**Figure 5.** Potential energy surfaces of reactions between acetaldehyde (CH3CHO) and methanol (CH3OH) molecules leading to the formation of **1**. Panels **a**−**e** illustrate the reaction pathways of the systems CH3CHO−(CH3OH)n (n = 1-5), respectively. Energies computed at the SCRF/SMD//ωB97X-D/6-311G(d,p) + ZPVE level of theory are shown in kJ mol−1 and are relative to the energy of the reactants. Panel **f** demonstrates the reduction and levelling of the reaction barrier as more methanol molecules are involved in hydrogen transfer. The error of the computed reaction barrier is 10 kJ mol−1.

reaction barrier through hydrogen transfer as the number of methanol molecules increases (Figure 5f). The transition state for the production of **1** in the CH3CHO−CH3OH system (Figure 5a) features a concerted character where the hydrogen atom transfer from the OH group of methanol to the carbonyl oxygen atom of acetaldehyde is accompanied by a new C-O bond formation. When additional methanol molecules are involved, they directly participate in the hydrogen atom transfer process such that the first hydrogen atom shifts from the reactant methanol molecule to the first intermediary methanol, which in turn passes its hydrogen atom from the hydroxyl (OH) group to the next intermediary, and so on; the last intermediary transfers the hydrogen atom of the hydroxyl (OH) group to acetaldehyde (Figures 5b-5e). The nature of all transition states TS1-TS5 has been verified by intrinsic reaction coordinate (IRC) calculations, which confirmed that the transition states connect the reactant complexes of acetaldehyde with one to five methanol molecules (R1-R5) with the **1** product (P1) or with the product complexes of 1-methoxyethanol with one to four methanol molecules (P2-P5). Interestingly, as more intermediary methanol molecules participate in the reaction, the character of the transition state becomes later with respect to the C-O bond formation; the length of the forming bond decreases from 172 pm in TS1 and TS2 to 166 pm in TS3 and 155 pm in TS4 and TS5. The barrier height in the CH3CHO−(CH3OH)n systems practically stabilizes at n = 3. It is also noteworthy that taking into account the implicit solvent through self-consistent reaction field (SCRF) calculations has a very small effect on the barrier height and the reaction energetics with the changes in relative energies of the transition states and products not exceeding 4 kJ mol-1. Thus, the barrier reduction in the ices owes to the direct involvement of solvent molecules (methanol) in the reaction rather than to the interaction with the dipole field of the polar solvent.

Our electronic structure calculations reveal that for thermal reactants, the formation of **1** should not take place at 113 K due to the presence of a significant barrier to reaction of at least 60 kJ mol−1 (0.62 eV) (Figures 5 and S6). However, the isomer selective identification of **1** contradicts this conclusion and indicates that quantum mechanical tunneling (QMT) must play a critical role in the formation of **1**. QMT is of fundamental importance in key chemical and biological reactions at low-temperatures involving hydrogen.[28-30](#_ENREF_28) In the interstellar medium (ISM), reactions of hydrogen on low-temperature grain surfaces likely take place via tunneling since the available energy is often too low for thermal reactivity. For example, QMT is essential for explaining the observed abundances of interstellar water (H2O), formaldehyde (H2CO), and methanol (CH3OH) via hydrogenation.[31](#_ENREF_31) However, a quantification of the tunneling dynamics remains a significant challenge, and various approaches have been proposed to decipher the role of tunneling and kinetic isotope effects.[32](#_ENREF_32)

To evaluate the importance of tunneling in the formation of **1**, we focus first on the instanton theory[33](#_ENREF_33) which provides the most probable tunneling path and probability that connects the reactant and product valleys of the potential energy surface through a potential energy barrier.[33-35](#_ENREF_33) Within this framework, the crossover temperature *T*c indicates whether a reaction is predominantly governed by tunneling (*T* < *Tc*) or thermal activation (*T* > *Tc*). *T*c is defined via *T*c = h*ν*/(2π*k*B) with the Planck constant h, the absolute value of imaginary frequency of the transition state *ν*, and the Boltzmann constant *k*B.[34](#_ENREF_34),[35](#_ENREF_35) Exploiting the computed imaginary frequencies at the transition states, the crossover temperatures for reactions of acetaldehyde and methanol reach up to 400 K. For instance, for the CH3CHO−(CH3OH)4 system, which has the lowest reaction barrier of only 60 kJ mol−1 and an imaginary frequency at the transition state of 678*i* cm−1, the crossover temperature corresponds to 155 K. This temperature exceeds the onset temperature (113 ± 3 K) of the formation of **1**. Second, we qualitatively estimated the tunneling transmission coefficient κ(T) defined as the ratio of the thermally averaged quantum tunneling probability to the quasiclassical transmission probability.[36](#_ENREF_36) Based on the computed barriers, reaction energies, and imaginary frequencies at the transition states, tunneling transmission coefficients greatly exceed unity thus corroborating the conclusion that the reactions to **1** are dominated by tunneling. This conclusion is reinforced by the large isotope effect determined experimentally with yields of 1-methoxyethanol-d7 decreased by a factor of ten compared to **1**. These isotope effects in hydrogen and proton transfer reactions are often associated with QMT.[37](#_ENREF_37) Hidaka et al. determined the ratio of the reaction rate constants, *k*D/*k*H, of 0.08 in the reactions of D and H atoms with carbon monoxide (CO) adsorbed on an amorphous water ice surface at 15 K.[38](#_ENREF_38) In our systems, the total ion counts of **1** decrease upon increasing levels of deuteration, with the ratio of 1-methoxyethanol, methoxyethanol-d3, and 1-methoxyethanol-d7 determined to be 1: 0.39: 0.11. This strong kinetic isotope effect provides further evidence of quantum tunneling in the formation of **1**.[37](#_ENREF_37)

The detection of the hemiacetal, 1-methoxyethanol (**1**), formed in a bottom-up synthesis from readily available acetaldehyde and methanol interstellar ices via quantum tunneling, represents a starting point to fully understand the formation of interstellar hemiacetals.Our results suggest the class of hemiacetals could be formed from ubiquitous interstellar aldehydes (RCHO) and alcohols (ROH) precursors, such as propynal (HC2CHO), propenal (C2H3CHO), propanal (C2H5CHO), cyanoformaldehyde (CHOCN), 3-hydroxypropenal (HOCHCHCHO) and glycolaldehyde (HCOCH2OH) for aldehydes; while ethanol (C2H5OH), vinyl alcohol (C2H3OH), ethylene glycol (OHCH2CH2OH), methoxymethanol (CH3OCH2OH), hydroxylamine (NH2OH), glycolonitrile (OHCH2CN), ethanolamine (OHCH2CH2NH2), 1-propanol (n-CH3CH2CH2OH) and isopropanol (CH3CH(OH)CH3) for alcohols.[39](#_ENREF_39) Recall that our FTIR results show the starting temperature of the thermal reaction in CH3CHO−CH3OH ice was 113 ± 3 K (Figure 2c); this temperature is within the temperature range of star-forming regions and hot molecular cores (100 – 300 K).[40](#_ENREF_40) Since the synthesis of the hemiacetal via an aldehyde and an alcohol is thermodynamically favored,[2](#_ENREF_2) those aldehydes and alcohols may already have formed their corresponding hemiacetals. For instance, the formation of glycolaldehyde hemiacetal (1-methoxy-1,2-ethanediol, CH3OCH(OH)CH2OH) can take place through the reaction between methanol and glycolaldehyde in ices prior to their sublimation, which may help probe the molecular origin of life on planets like Earth.[41](#_ENREF_41) Molecules that incorporate a hemiacetal may act as precursors for interstellar synthesis of sugar and sugar-related molecules upon exposure to ionizing radiation such as GCRs and ultraviolet (UV) photons in the molecular cloud. For instance, 1-methoxyethanol (**1**) could serve as a precursor to 5- and 6-deoxy sugars such as L-fucose.

To conclude, we prepared the hemiacetal, (*R/S*)-1-methoxyethanol (**1**), in interstellar model ices composed of acetaldehyde and methanol via quantum tunneling assisted thermal reaction and detected this molecule spectroscopically (FTIR) and during the sublimation phase utilizing tunable photoionization reflectron time-of-flight mass spectrometry (PI-ReToF-MS) along with isotopic substitution experiments. The infrared spectra (FTIR) of pure 1-methoxyethanol ice and 1-methoxyethanol-d8 ice were measured at 150 K after the sublimation of the reactants. This study reveals key formation pathways for **1** and **2+**, presenting the very first step toward a systematic elucidation of hemiacetal synthesis in deep space governed by quantum tunneling. Following the reaction mechanisms elucidated here, a complex inventory of interstellar hemiacetals could also be formed from the ubiquitous aldehydes and alcohols during the heating of interstellar ices in star-forming regions. Their fragment ions could also be produced after exposure to ionizing sources such as GCRs. Therefore, hemiacetals and their fragment ions are suitable candidates for detection in star-forming regions and hot molecular cores via radio telescopes. These hemiacetals may act as possible precursors to interstellar sugars and sugar-related molecules upon exposure to ionizing radiation such as GCRs, thus leading to a better understanding of the fundamental processes of abiotic syntheses of sugars in deep space. During star formation, complex molecules formed in ices are incorporated into planetoids, asteroids, and comets. Detailed analyses of meteorites revealed that biorelevant molecules, such as ribose or other biologically essential sugars, have survived harsh conditions in space as well as the impact on the Earth.[42](#_ENREF_42) Therefore, part of these complex molecules may have been delivered to the early Earth and acted as an exogenous source of biomolecules, providing a plausible additional pathway to the formation of biorelevant molecules on the prebiotic Earth.[43](#_ENREF_43) Future work is needed to provide more details on the syntheses of interstellar hemiacetals such as investigating the substituent effects[5](#_ENREF_5),[25](#_ENREF_25) involved in the quantum tunneling assisted thermal reactions between the identified aldehydes and alcohols in the ISM and the role of water on interstellar grain thus eventually deciphering the fundamental molecular processes of key molecules pertaining to the origin of life.

**ACKNOWLEDGMENTS**

The experiments at the University of Hawaii were supported by US National Science Foundation, Division of Astronomical Sciences under grant AST-2103269 awarded to the University of Hawaii at Manoa (R. I. K.). The W. M. Keck Foundation and the University of Hawaii at Manoa financed the construction of the experimental setup. A.K.E. thanks the Fonds der Chemischen Industrie (Liebig Fellowship) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy – EXC-2033 – 390677874 - RESOLV for funding. The calculations of the reaction potential energy surfaces in ices were supported by the Ministry of Higher Education and Science of the Russian Federation under grant No. 075-15-2021-597.

**ASSOCIATED CONTENT**

**Supporting Information Available:** Methods (experimental and computational), calculations of the tunneling transmission coefficient, FTIR spectra, PI-ReToF-MS mass spectra, calculated dissociation pathways, formation mechanisms of 1-methoxyethanol, potential energy surfaces of the reactions between various combinations of acetaldehyde and methanol, error analysis of adiabatic ionization energies, VUV generation, and cartesian coordinates and harmonic frequencies for structures

**Notes**

The authors declare no competing financial interests.

**REFERENCES**

(1) Milas, N. A. Catalytic oxidations in aqueous solutions. II. The oxidation of primary alcohols. *J. Am. Chem. Soc.* **1928**, *50*, 493-499.

(2) Wiberg, K. B.; Morgan, K. M.; Maltz, H. Thermochemistry of carbonyl reactions. 6. A study of hydration equilibria. *J. Am. Chem. Soc.* **1994**, *116*, 11067-11077.

(3) Dutta, P.; Dutta, M. A theoretical study of spectroscopic properties of a hemiacetal by TDDFT method. *Orient. J. Chem.* **2011**, *27*, 87-94.

(4) Benner, S. A.; Kim, H.-J.; Carrigan, M. A. Asphalt, water, and the prebiotic synthesis of ribose, ribonucleosides, and RNA. *Acc. Chem. Res.* **2012**, *45*, 2025-2034.

(5) Azofra, L. M.; Alkorta, I.; Elguero, J. A theoretical study of hemiacetal formation from the reaction of methanol with derivatives of CX3CHO (X = H, F, Cl, Br and I). *J. Phys. Org. Chem.* **2012**, *25*, 1286-1292.

(6) Kusano, M.; Sakai, Y.; Kato, N.; Yoshimoto, H.; Sone, H.; Tamai, Y. Hemiacetal dehydrogenation activity of alcohol dehydrogenases in *Saccharomyces Cerevisiae*. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1956-1961.

(7) Shigemasa, Y.; Taji, T.; Sakazawa, C.; Nakashima, R.; Matsuura, T. Formose reactions: VIII. Solvent effects in the formose reaction. *J. Catal.* **1979**, *58*, 296-302.

(8) Cheng, L.; Doubleday, C.; Breslow, R. Evidence for tunneling in base-catalyzed isomerization of glyceraldehyde to dihydroxyacetone by hydride shift under formose conditions. *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112*, 4218-4220.

(9) Hooley, R. J.; Rebek, J. Chemistry and catalysis in functional cavitands. *Chem. Biol.* **2009**, *16*, 255-264.

(10) Meadows, G. W.; Darwent, B. D. The reactions of acetaldehyde with methanol. *Can. J. Chem.* **1952**, *30*, 501-506.

(11) Eckhardt, A. K.; Wende, R. C.; Schreiner, P. R. 1,3-Dioxolane-4-ol hemiacetal stores formaldehyde and glycolaldehyde in the gas-phase. *J. Am. Chem. Soc.* **2018**, *140*, 12333-12336.

(12) Kaiser, R. I.; Maity, S.; Jones, B. M. Synthesis of prebiotic glycerol in interstellar ices. *Angew. Chem. Int. Ed.* **2015**, *54*, 195-200.

(13) Holtom, P. D.; Bennett, C. J.; Osamura, Y.; Mason, N. J.; Kaiser, R. I. A combined experimental and theoretical study on the formation of the amino acid glycine (NH2CH2COOH) and its isomer (CH3NHCOOH) in extraterrestrial ices. *Astrophys. J.* **2005**, *626*, 940-952.

(14) Meinert, C.; Myrgorodska, I.; de Marcellus, P.; Buhse, T.; Nahon, L.; Hoffmann, S. V.; d’Hendecourt, L. L. S.; Meierhenrich, U. J. Ribose and related sugars from ultraviolet irradiation of interstellar ice analogs. *Science* **2016**, *352*, 208-212.

(15) Zhu, C.; Turner, A. M.; Abplanalp, M. J.; Kaiser, R. I.; Webb, B.; Siuzdak, G.; Fortenberry, R. C. An interstellar synthesis of glycerol phosphates. *Astrophys. J.* **2020**, *899*, L3.

(16) Arumainayagam, C. R.; Garrod, R. T.; Boyer, M. C.; Hay, A. K.; Bao, S. T.; Campbell, J. S.; Wang, J.; Nowak, C. M.; Arumainayagam, M. R.; Hodge, P. J. Extraterrestrial prebiotic molecules: Photochemistry vs. radiation chemistry of interstellar ices. *Chem. Soc. Rev.* **2019**, *48*, 2293-2314.

(17) Gibb, E. L.; Whittet, D. C. B.; Boogert, A. C. A.; Tielens, A. G. G. M. Interstellar ice: The infrared space observatory legacy. *Astrophys. J., Suppl. Ser.* **2004**, *151*, 35-73.

(18) Dartois, E.; Schutte, W. A.; Geballe, T. R.; Demyk, K.; Ehrenfreund, P.; d'Hendecourt, L. B. Methanol: The second most abundant ice species towards the high-mass protostars RAFGL7009S and W 33A. *Astron. Astrophys.* **1999**, *342*, L32.

(19) Kleimeier, N. F.; Kaiser, R. I. Interstellar enolization-acetaldehyde (CH3CHO) and vinyl alcohol (H2CCH(OH)) as a case study. *ChemPhysChem* **2021**, *22*, 1229-1236.

(20) Maity, S.; Kaiser, R. I.; Jones, B. M. Formation of complex organic molecules in methanol and methanol–carbon monoxide ices exposed to ionizing radiation – A combined FTIR and reflectron time-of-flight mass spectrometry study. *Phys. Chem. Chem. Phys.* **2015**, *17*, 3081-3114.

(21) Turner, A. M.; Kaiser, R. I. Exploiting photoionization reflectron time-of-flight mass spectrometry to explore molecular mass growth processes to complex organic molecules in interstellar and solar system ice analogs. *Acc. Chem. Res.* **2020**, *53*, 2791-2805.

(22) P. J. Linstrom, W. G. M. NIST chemistry webBook, NIST standard reference database, NIST standard reference database number 69. *Natl. Inst. Stand. Technol.* **2013** (accessed 20 February, 2023); http://webbook.nist.gov/.

(23) Dai, Z.; Gao, S.; Wang, J.; Mo, Y. Torsional energy levels of CH3OH+/CH3OD+/CD3OD+ studied by zero-kinetic energy photoelectron spectroscopy and theoretical calculations. *J. Chem. Phys.* **2014**, *141*, 144306.

(24) Jeffrey, G. A.; Yates, J. H. Application of ab Initio molecular-orbital calculations to the structural moieties of carbohydrates. *Carbohydr. Res.* **1981**, *96*, 205-213.

(25) Derricotte, W. D. Symmetry-adapted perturbation theory decomposition of the reaction force: Insights into substituent effects involved in hemiacetal formation mechanisms. *J. Phys. Chem. A* **2019**, *123*, 7881-7891.

(26) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. Mechanism of the Morita−Baylis−Hillman reaction:  A computational investigation. *J. Am. Chem. Soc.* **2007**, *129*, 15513-15525.

(27) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. Solvent effects. 1. The mediation of electrostatic effects by solvents. *J. Am. Chem. Soc.* **1991**, *113*, 4776-4782.

(28) Trakhtenberg, L. I.; Fokeyev, A. A.; Zyubin, A. S.; Mebel, A. M.; Lin, S. H. Matrix reorganization with intramolecular tunneling of H atom: Formic acid in Ar matrix. *J. Chem. Phys.* **2009**, *130*, 144502.

(29) Schreiner, P. R. Tunneling control of chemical reactions: The third reactivity paradigm. *J. Am. Chem. Soc.* **2017**, *139*, 15276-15283.

(30) Bernhardt, B.; Ruth, M.; Eckhardt, A. K.; Schreiner, P. R. Ethynylhydroxycarbene (H–C≡C–C̈–OH). *J. Am. Chem. Soc.* **2021**, *143*, 3741-3746.

(31) Watanabe, N.; Shiraki, T.; Kouchi, A. The dependence of H2CO and CH3OH formation on the temperature and thickness of H2O-CO ice during the successive hydrogenation of CO. *Astrophys. J.* **2003**, *588*, L121.

(32) Liu, Y.; Yan, Y.; Xing, T.; Shi, Q. Understanding the large kinetic isotope effect of hydrogen tunneling in condensed phases by using double-well model systems. *J. Phys. Chem. B* **2021**, *125*, 5959-5970.

(33) Meisner, J.; Kästner, J. Reaction rates and kinetic isotope effects of H2 + OH → H2O + H. *J. Chem. Phys.* **2016**, *144*, 174303.

(34) Gillan, M. J. Quantum-classical crossover of the transition rate in the damped double well. *J. Phys. C: Solid State Phys.* **1987**, *20*, 3621.

(35) Álvarez-Barcia, S.; Flores, J. R.; Kästner, J. Tunneling above the crossover temperature. *J. Phys. Chem. A* **2014**, *118*, 78-82.

(36) Bao, J. L.; Truhlar, D. G. Variational transition state theory: Theoretical framework and recent developments. *Chem. Soc. Rev.* **2017**, *46*, 7548-7596.

(37) Wu, A.; Mader, E. A.; Datta, A.; Hrovat, D. A.; Borden, W. T.; Mayer, J. M. Nitroxyl radical plus hydroxylamine pseudo self-exchange reactions: Tunneling in hydrogen atom transfer. *J. Am. Chem. Soc.* **2009**, *131*, 11985-11997.

(38) Hidaka, H.; Kouchi, A.; Watanabe, N. Temperature, composition, and hydrogen isotope effect in the hydrogenation of CO on amorphous ice surface at 10–20K. *J. Chem. Phys.* **2007**, *126*, 204707.

(39) McGuire, B. A. 2021 Census of interstellar, circumstellar, extragalactic, protoplanetary disk, and exoplanetary molecules. *Astrophys. J., Suppl. Ser.* **2022**, *259*, 30.

(40) Kaiser, R. I. Experimental investigation on the formation of carbon-bearing molecules in the interstellar medium via neutral−neutral reactions. *Chem. Rev.* **2002**, *102*, 1309-1358.

(41) Li, Y.; Shi, Y.; Song, X.; Zhao, Z.; Zhang, N.; Hao, C. Insights into the existing form of glycolaldehyde in methanol solution: An experimental and theoretical investigation. *New J. Chem.* **2021**, *45*, 8149-8154.

(42) Furukawa, Y.; Chikaraishi, Y.; Ohkouchi, N.; Ogawa, N. O.; Glavin, D. P.; Dworkin, J. P.; Abe, C.; Nakamura, T. Extraterrestrial ribose and other sugars in primitive meteorites. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 24440-24445.

(43) Kleimeier, N. F.; Eckhardt, A. K.; Schreiner, P. R.; Kaiser, R. I. Interstellar formation of biorelevant pyruvic acid (CH3COCOOH). *Chem* **2020**, *6*, 3385-3395.