Zwitter Ionization of Glycine at Outer Space Conditions due to Microhydration by Six Water Molecules

Gerhard Schwaab,[1] Ricardo Pérez de Tudela,[2] Devendra Mani,[4] Nitish Pal,[1] Tarun Kumar Roy,[1] Fabio Gabas,[3]
Riccardo Conte,[3] Laura Durán Caballero,[2] Michele Ceotto,[3] Dominik Marx,[2] and Martina Havenith[1,*]
[1]*Lehrstuhl für Physikalische Chemie II, Ruhr-Universität Bochum, 44780 Bochum, Germany*
[2]*Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum, 44780 Bochum, Germany*
[3]*Dipartimento di Chimica, Università degli Studi di Milano, 20133 Milano, Italy*
[4]*Department of Chemistry, Indian Institute of Technology Kanpur, Uttar Pradesh 208016, India*

(Received 27 February 2021; revised 9 August 2021; accepted 4 December 2021; published 19 January 2022)

We investigate glycine microsolvation with water molecules, mimicking astrophysical conditions, in our laboratory by embedding these clusters in helium nanodroplets at 0.37 K. We recorded mass selective infrared spectra in the frequency range 1500–1800 cm^{-1} where two bands centered at 1630 and 1724 cm^{-1} were observed. By comparison with the extensive accompanying calculations, the band at 1630 cm^{-1} was assigned to the COO^- asymmetric stretching mode of the zwitter ion and the band at 1724 cm^{-1} was assigned to redshifted $C=O$ stretch within neutral clusters. We show that zwitter ion formation of amino acids readily occurs with only few water molecules available even under extreme conditions.

DOI: 10.1103/PhysRevLett.128.033001

The three-dimensional structure, function, and dynamics of peptides and proteins are almost exclusively governed by noncovalent interactions [1–4]. Despite the importance of amino acids as the building blocks of life, the question of whether the smallest amino acid glycine was formed on primitive Earth or was delivered to our home planet remains to date intriguing, yet unanswered [5–8]. Detection of amino acids in meteorites and comets supports the hypothesis that impact of these extraterrestrial bodies on infant Earth could have brought in prebiotic building blocks, including amino acids that ignited primordial evolution [9–16]. Although glycine precursors, such as CH_3NH_2, NH_2CHO, and CH_3CN, have been detected in the interstellar medium (ISM), the presence of glycine in ISM remains inconclusive and thus controversial [17–20]. Glycine exists in vacuum in its nonionic (or neutral) form, NH_2CH_2COOH, but its hydrophilic amino and carboxyl groups can strongly interact with water via hydrogen bonding. In aqueous solutions at ambient conditions, this leads to proton transfer and, thus, to its well-known zwitter ionic form, $^+NH_3CH_2COO^-$. The addition of a single water molecule to glycine was found to be not sufficient to observe charge separation in helium nanodroplets [21].

At such ultracold conditions, a distinctive feature of chemical reactions is their aggregation-induced character due to growing the cluster in a stepwise manner by adding the molecules one by one [22,23]. The corresponding mechanism leading to proton transfer, e.g., for HCl, greatly differs from that of the very same reaction at high temperatures due to thermal activation at constant cluster size [24,25]. Thus, not only the reaction pathway but also the required number of water molecules may be different at ultralow compared to ambient temperatures [22–25]. Moreover, in the case of glycine-water clusters, the energy differences between nonionic and zwitter ionic species are very small in the relevant cluster size regime [26], which hampers computational predictions. For decades the nagging but open question was how many water molecules are required to invoke zwitter ionization, with proposals ranging from only three up to nine water molecules [26–28].

The spectroscopic fingerprints of glycine [29] are expected to differ significantly depending on its dissociation state. Therefore, unfolding the chemistry of glycine in the abundant interstellar cold ($\sim 10-20$ K) water ices holds the key for its detection in ISM. Prior to searches in space, however, laboratory measurements need to answer the question of whether glycine is bound to remain neutral, or if it can zwitter ionize at the extreme conditions of the chemical habitats as provided by icy comets or extraterrestrial meteorites [30,31].

Previous studies suggested that the interaction with photons (UV, X, γ, or cosmic rays) or impinging particles (e.g., ions and protons) followed by thermalization at these very low temperatures triggers the formation of complex organic molecules and amino acids on astrophysical ice surfaces found in dense cold molecular clouds, meteorites or cometary bodies [32,33]. Experiments mimicking the conditions of icy mantles revealed that glycine itself can form on ices containing CO_2, NH_3, CH_3OH, H_2O, CO, and HCN [34,35]. Yet, the molecular mechanism and even the form in which glycine molecules exist in space (i.e., nonionic or zwitter ionic) is still under debate [36,37] since detection in the gas-phase interstellar medium has been unsuccessful until now [18,20].

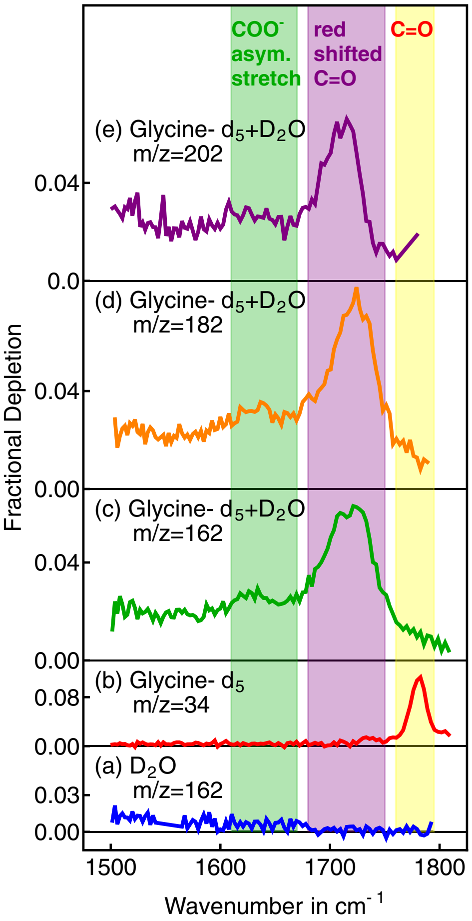

FIG. 1. IR depletion spectra obtained for helium droplets doped with D_2O clusters, glycine- d_5 monomer, and a combination of glycine-d_5 and D_2O, measured at different mass channels in the frequency range between 1500 and 1800 cm^{-1}. (a) IR spectrum of pure D_2O clusters at mass channel $m/z = 162$, yielding no band in the investigated frequency range. (b) IR spectrum of pure glycine-d_5 at mass channel $m/z = 34$. (c)–(e) IR spectra of $(\text{glycine-}d_5) - (D_2O)_n$ clusters at mass channels $m/z = 162$, 182 and 202 recorded at a pressure of 2 mPa. The yellow, purple, and green shaded regions indicate the bands assigned to the $C = O$ stretch of glycine-d_5 monomer (1782 cm^{-1}), the red-shifted $C = O$ stretch of nonionic $(\text{glycine-}d_5) - (D_2O)_n$ clusters (1724 cm^{-1}) and the asymmetric stretch of the COO^- group in zwitter ionic $(\text{glycine-}d_5) - (D_2O)_n$ clusters (1630 cm^{-1}), respectively. Note that $m/z = 202$ corresponds to a microsolvated glycine-d_5-cluster containing at least 7 water molecules. The signal-to-noise ratio is reduced compared to the measurements at lower mass channels, because only fewer measurements were carried out and averaged.

In our present study we put a spotlight on the question of whether glycine—once it is formed under extreme astrophysical conditions—will be present in nonionic or zwitter ionic forms, or both. To mimic such very low temperatures in the realm of laboratory spectroscopy, we used superfluid helium nanodroplets at 0.37 K as ultracold nanotraps to embed nonionic glycine, which was sublimed by heating in an oven. Subsequently, single water molecules were added to the helium nanodroplets in a second pickup chamber under controlled water vapor pressure to adjust the water content at the molecular level.

Using such a cryolab approach, we report in what follows an infrared spectroscopic study of glycine-water systems isolated in helium droplets. The details of the experiments are described in the Supplemental Material [38], Sec. 1 as well as in preceding literature [60]. Our previous study [21] of glycine monomer and glycine-H_2O covered the frequency range $1000 - 1450\ \mathrm{cm}^{-1}$. We are now using the ultrabright FELIX radiation source [61], allowing us to record depletion spectra in the frequency range between $1500 - 1800\ \mathrm{cm}^{-1}$. Importantly, this frequency range covers both the COO^- asymmetric stretching mode, which serves us as the unambiguous fingerprint of the onset of zwitter ion formation, as well as the $C = O$ stretch of the neutral COOH state [62,63]. To avoid a possible overlap with the well-known bending mode of water clusters (at $1600 - 1650\ \mathrm{cm}^{-1}$) as well as with the NH bending resonance ($\sim 1600\ \mathrm{cm}^{-1}$) of the NH_3^+ group, we switched to fully deuterated $(\text{glycine-}d_5)\text{-}(D_2O)_n$ clusters [64–66]. This provides us a clean spectroscopic window to unambiguously probe the existence of zwitter ions under outer space conditions.

First, we recorded the individual depletion IR spectra of the pure components, D_2O and glycine-d_5. The partial pressure of D_2O was set to 2×10^{-5} mbar, corresponding to preferred pickup of more than six water molecules (see Supplemental Material [38]). Under these conditions, the IR spectrum shows no absorption in the $1500 - 1800\ \mathrm{cm}^{-1}$ frequency region, taken at a mass channel attributed to $(D_2O)_{n\geq 9}$ cluster fragments $[m/z = 162, (D_2O)_8D^+]$ and also for smaller water clusters, no absorption is expected in this frequency range [Fig. 1(a)]. For glycine-d_5, the temperature of the sublimation oven was optimized to 95 °C. At this temperature droplets preferentially pickup single glycine molecules, as was confirmed by a systematic variation of pick-up pressure via temperature changes in the oven (see Supplemental Material [38]). In this way, a spectrum of pure glycine-d_5 was recorded at mass channel $m/z = 34$, corresponding to the $CD_2ND_2^+$ mass fragment. The spectrum features a single band at 1782 cm^{-1}, which is assigned to the $C = O$ stretch of the carboxylic group (COOD) of monomeric nonionic glycine-d_5 [Fig. 1(b)].

To prepare microhydrated $(\text{glycine-}d_5) - (D_2O)_n$ clusters, helium droplets were subsequently doped with glycine-d_5 and D_2O at a partial pressure of 2×10^{-5} mbar. The IR spectra were recorded at mass channels $m/z = 162$, 182, and 202, which are expected to have major contributions from clusters of glycine with five, six and seven water molecules, yielding the fragments $(\text{glycine-}d_5)(D_2O)_4D^+$, $(\text{glycine-}d_5)(D_2O)_5D^+$, and $(\text{glycine-}d_5)(D_2O)_6D^+$ upon ionization, respectively. However, as fragmentation upon ionization leads to loss of water molecules, every mass

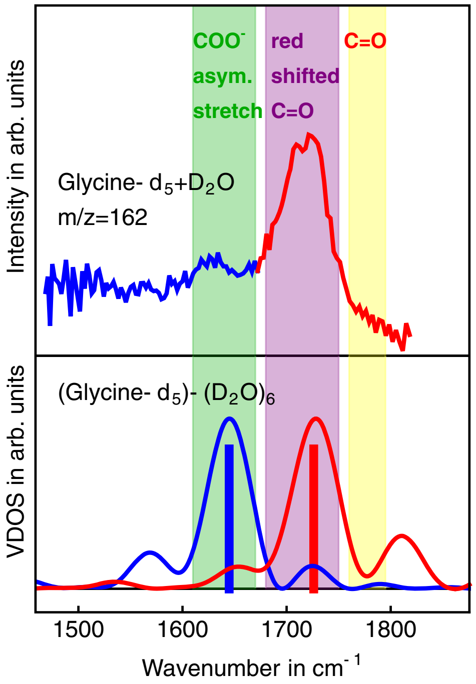

FIG. 2. Comparison of the IR spectrum of $(\text{glycine-}d_5) - (D_2O)_n$ clusters recorded at mass channel $m/z = 162$ (top panel) with the vibrational density of states of $(\text{glycine-}d_5) - (D_2O)_6$ according to on-the-fly semiclassical dynamics (bottom panel). The harmonic frequencies of the $C = O$ stretch of nonionic $(\text{glycine-}d_5) - (D_2O)_6$ clusters and the asymmetric stretch of the COO^- group within zwitter ionic $(\text{glycine-}d_5) - (D_2O)_6$ clusters are shown by red and blue sticks, respectively. The anharmonic spectra (solid lines) have been obtained from divide-and-conquer semiclassical simulations of these modes. Frequency scaling with respect to the $C = O$ stretch of pure glycine-d_5 serving as an intrinsic reference is applied (see Supplemental Material [38], Sec. 6). Please note, that, e.g., dissociated clusters with $n = 10$ are predicted to show redshifted bands (see Fig. S9 in Ref. [38]). Thus, higher clusters might contribute to the broad absorbance below 1630 cm^{-1}.

channel and hence the depletion spectrum will always in addition contain contributions from clusters with a larger number of water molecules (see Supplemental Material [38], Sec. 2). Therefore, mass selective measurements provide information on the minimum number of water molecules involved. However, for an unambiguous determination of cluster size pressure dependent intensity measurements, pick-up depletion curves are mandatory.

We want to note that the spectra of all three recorded mass channels contain two bands centered at 1630 and 1724 cm^{-1} [Figs. 1(c)–1(e)]. As these features are not observed in either the D_2O or the glycine-d_5 spectrum, we assign the bands to microhydrated $(\text{glycine-}d_5) - (D_2O)_n$ clusters. Further assignment is made based on a comparison of the experimental spectra to predicted vibrational resonances of $(\text{glycine-}d_5) - (D_2O)_n$ clusters, which include anharmonic shifts and mode couplings on top of the harmonic estimates as obtained from divide-and-conquer semiclassical dynamics simulations [67,68] that have been focused on these key vibrational modes (see Supplemental Material [38], Sec. 6). Experimentally, a band at 1743.3 cm^{-1}, observed in the Ar matrix was assigned to the glycine-water complex [69].

Based on these computations we assign the absorption band centered at 1630 cm^{-1} to the asymmetric carboxylate anion COO^- stretch of zwitter ionic $(\text{glycine-}d_5) - (D_2O)_n$ and the band at 1724 cm^{-1} to the redshifted $C = O$ stretch of the COOD group of glycine-d_5 in corresponding nonionic clusters (Fig. 2 and Fig. S9 [38]). The intensities of the bands at 1630 and 1724 cm^{-1} suggest that, compared to the zwitter ionic cluster, a larger amount of nonionic $(\text{glycine-}d_5) - (D_2O)_n$ clusters is formed in the helium droplets, taking into account the predicted intensities. This is attributed to the unique stepwise aggregation process in helium nanodroplets, involving rapid cooling of the embedded molecules. Therefore, addition of a water molecule to a $(\text{glycine-}d_5) - (D_2O)_n$ might result in geometries in which this process of zwitter ionization is not facilitated, or even possible, despite being energetically favorable. Similarly, as observed for other clusters, in helium droplets, local minima next to the global minimum of the potential energy surface can be populated even at 0.37 K [23].

Is there finally a chance to pinpoint the minimum number of water molecules required to zwitter ionize glycine at these ultralow temperatures? While we cannot discriminate the number of water molecules based on the mass-selected IR spectra alone, the cluster size can be determined by pressure-dependent intensity measurements, so-called pickup curves. In helium droplets, the pickup probability of solutes as a function of partial pressure follows approximately a Poisson distribution, which can be utilized to identify the number of molecules contributing to a given signal (see Supplemental Material [38] for details) [70].

The pick-up curve recorded at a resonant frequency of 1724 cm^{-1}, i.e., the center frequency of the band assigned to neutral $(\text{glycine-}d_5) - (D_2O)_n$ yields a minimum number of two water molecules (see Fig. S9 [38]). This is in accordance with the assignment of the 1724 cm^{-1} band to nonionic $(\text{glycine-}d_5) - (D_2O)_n$ clusters, which are predicted to exist even for smaller cluster sizes.

In Fig. 3, top, we show the pick-up curve of the band at 1630 cm^{-1} at a mass channel of $m/z = 142$, corresponding to all glycine clusters with at least four water molecules. As this band is assigned to the stretching vibration of COO^- of the zwitter-ionic cluster, only clusters with the number of water molecules necessary for zwitter ionization will contribute to this signal. The depletion curve shows an increase up to a D_2O partial pressure of 2.0 mPa, for higher pressures the signal intensity is found to decrease again. While we expect an overlap of several cluster sizes to

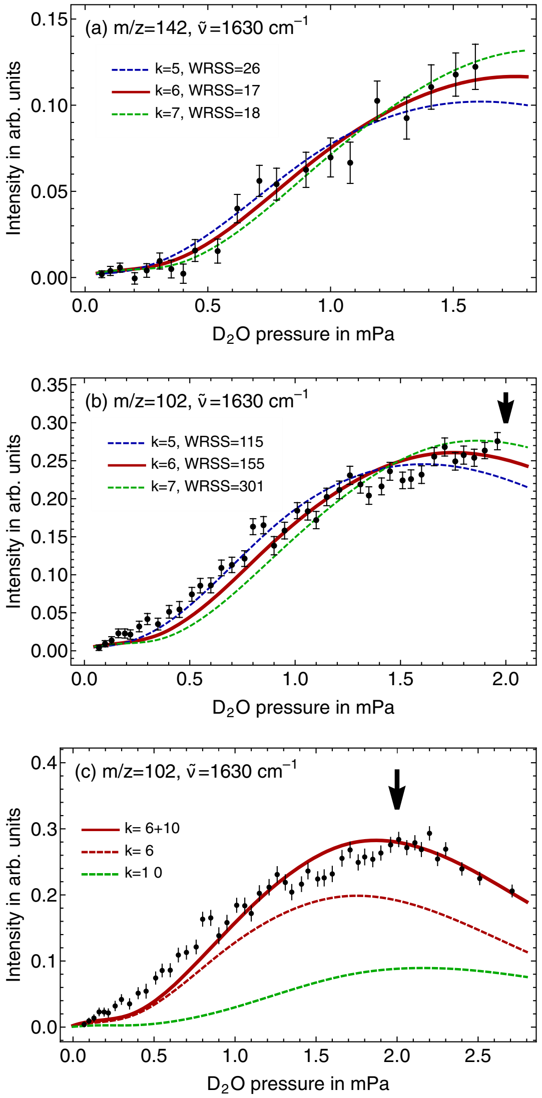

FIG. 3. Fit of the pick-up curve at 1630 $\mathrm{cm^{-1}}$ of the zwitter ionic $(\text{glycine-}d_5)-(\mathrm{D_2O})_6$ clusters. (a) Depletion signal as a function of $\mathrm{D_2O}$ partial pressure at mass channel $m/z = 142$ (black dots) in comparison with reference pick-up curves for $k = 5$, 6, and 7. The quality of the fit is evaluated based on the weighted residual sum of squares (WRSS). The best fit (smallest WRSS) is obtained for $k = 6$ and $k = 7$. b) Depletion signal as a function of $\mathrm{D_2O}$ partial pressure at mass channel $m/z = 102$ (black dots). The best fit (smallest WRSS) is obtained for $k = 5$ and $k = 6$. c) Fits of the pick-up curve for a combination of clusters with six to ten water molecules (red line), showing the individual contribution of six (dashed red line) and ten (dashed green line) clusters.

contribute to the measured pick-up curve, the maximum of the Poisson distribution will be shifted to higher pressures with increasing cluster size. Thus, we expect a contribution also of higher cluster sizes and therefore a broad plateau at higher pressures. Thus, information on the minimum number of water molecules can be extracted from the fit to rising edge of the pick-up curve, which is dominated by the cluster of smallest size. Including the data points in the medium pressure range of the pick-up curve, we find best agreement for $k = 6$ and 7 molecules of water for $m/z = 142$ and $k = 5$ and 6 water molecules for $m/z = 102$, as shown in Fig. 3, middle. Therefore, we find overall best agreement for $k = 6$ molecules of water, while fits restricted to $k = 5$ or $k = 7$ give poorer agreement for $m/z = 142$ or $m/z = 102$, respectively. A global fit to pick-up curves recorded at several mass channels yields the same result, which shows the robustness of our approach (Fig. S8 [38]). This means that clusters with *at least* six water molecules contribute to this signal, while contributions from larger clusters are expected to dominate the curve at higher water pressures. If we fit the pick-up curve up to a water pressure of 2.5 mPa, which includes these contributions from larger clusters, we find that even clusters with ten water molecules contribute to the signal (Fig. 3, bottom).

The assignment of the 1630 $\mathrm{cm^{-1}}$ band to the smallest zwitter ionic cluster $(\text{glycine-}d_5)-(\mathrm{D_2O})_6$ and the 1724 $\mathrm{cm^{-1}}$ band to nonionic $(\text{glycine-}d_5)-(\mathrm{D_2O})_n$ cluster is furthermore supported by comparison of the experimental spectra to simulated anharmonic spectra of the nonionic and zwitter ionic clusters. Specifically, the redshifted $\mathrm{C=O}$ stretching resonance of the COOD group and the asymmetric stretching band of the $\mathrm{COO^-}$ group of glycine- d_5 have been computed within the divide-and-conquer approach to the multiple coherent states semiclassical initial value representation for several water clusters (see Supplemental Material [38], Sec. 6, Fig. S9) [67,68]. By comparison, we find an excellent agreement to the experimental data when considering six water molecules as the minimum number for which the zwitter ionic form is present in experiment, see Fig. 2. Details of the experimental setup, the data analysis, and the theoretical work can be found in Supplemental Material [38], which includes Refs. [39–59].

Based on a combination of experimental and theoretical investigations of perdeuterated glycine-water clusters, we discovered that zwitter ionization of the simplest amino acid at very low temperature mimicking outer space conditions is already possible if six water molecules are available. Therefore, we propose that on icy objects in the interstellar medium, not only the nonionic neutral species should be present, but, in particular, zwitter ionic amino acids should be highly abundant. Based on a direct comparison of the measured infrared spectra with computed anharmonic spectra, we assigned the bands at 1630 and 1724 $\mathrm{cm^{-1}}$ to the $\mathrm{COO^-}$ asymmetric stretch of zwitter ionic glycine in water clusters and to the strongly redshifted $\mathrm{C=O}$ stretch of nonionic microhydrated glycine- d_5, respectively. Thus, given the ubiquitous presence of extraterrestrial water ices, infrared spectroscopic surveys aiming at detecting amino acids in outer space should focus on both species.

Funded by the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) under Germany's Excellence Strategy—EXC 2033—Projektnummer 390677874. D. M. thanks DFG for partial support via his grant MA 1547/11-2. F. G., R. C., and M. C. acknowledge financial support from the European Research Council (Grant Agreement No. 647107—SEMICOMPLEX-ERC-2014-CoG) under the European Union's Horizon 2020 research and innovation program, and from the Italian Ministry of Education, University, and Research (MIUR: FARE program Grant No. R16KN7XBRBproject QURE). Computational resources have been provided by HPC@ZEMOS, HPC-RESOLV, and BoViLab@RUB. FELIX is supported by the Stichting voor Fundamenteel Onderzoek der Materie (FOM) and LASERLAB-EUROPE grant 654148. We thank Stefan Henkel for carefully reading the manuscript and helpful discussions.

---

[*] Corresponding author.
martina.havenith@rub.de

[1] A. M. Rijs, G. Ohanessian, J. Oomens, G. Meijer, G. Von Helden, and I. Compagnon, Angew. Chem. Int. Ed. **49**, 2332 (2010).

[2] J.-Y. Shen *et al.*, Nat. Commun. **4**, 2611 (2013).

[3] L. Purushottam, S. R. Adusumalli, U. Singh, V. Unnikrishnan, D. G. Rawale, M. Gujrati, R. K. Mishra, and V. Rai, Nat. Commun. **10**, 2539 (2019).

[4] A. L. Lehninger, D. L. Nelson, and M. M. Cox, *Lehninger Principles of Biochemistry* (Worth Publishers, New York, 2000).

[5] S. L. Miller, Science **117**, 528 (1953).

[6] J. Oró, Nature (London)**190**, 389 (1961).

[7] A. P. Johnson, H. J. Cleaves, J. P. Dworkin, D. P. Glavin, A. Lazcano, and J. L. Bada, Science **322**, 404 (2008).

[8] J. L. Bada, Chem. Soc. Rev. **42**, 2186 (2013).

[9] K. Kvenvolden, J. Lawless, K. Pering, E. Peterson, J. Flores, C. Ponnamperuma, I. R. Kaplan, and C. Moore, Nature (London) **228**, 923 (1970).

[10] J. E. Elsila, D. P. Glavin, and J. P. Dworkin, Meteorit. Planet. Sci. **44**, 1323 (2009).

[11] K. Altwegg *et al.*, Sci. Adv. **2**, e1600285 (2016).

[12] M. P. Bernstein, J. P. Dworkin, S. A. Sandford, G. W. Cooper, and L. J. Allamandola, Nature (London) **416**, 401 (2002).

[13] G. M. Caro, U. Meierhenrich, W. Schutte, B. Barbier, A. A. Segovia, H. Rosenbauer, W.-P. Thiemann, A. Brack, and J. Greenberg, Nature (London) **416**, 403 (2002).

[14] Z. Martins, M. C. Price, N. Goldman, M. A. Sephton, and M. J. Burchell, Nat. Geosci. **6**, 1045 (2013).

[15] N. Goldman, E. J. Reed, L. E. Fried, I.-F. W. Kuo, and A. Maiti, Nat. Chem. **2**, 949 (2010).

[16] K. Hadraoui *et al.*, Astron. Astrophys. **630**, A32 (2019).

[17] E. G. Bøgelund, B. A. McGuire, M. R. Hogerheijde, E. F. van Dishoeck, and N. F. Ligterink, Astron. Astrophys. **624**, A82 (2019).

[18] S. Kwok, Astron. Astrophys. Rev. **24**, 8 (2016).

[19] P. Redondo, C. Barrientos, and A. Largo, Astrophys. J. **836**, 240 (2017).

[20] M. Cunningham *et al.*, Mon. Not. R. Astron. Soc. **376**, 1201 (2007).

[21] M. Kaufmann, D. Leicht, R. Schwan, D. Mani, G. Schwaab, and M. Havenith, Phys. Chem. Chem. Phys. **18**, 28082 (2016).

[22] A. Gutberlet, G. Schwaab, Ö. Birer, M. Masia, A. Kaczmarek, H. Forbert, M. Havenith, and D. Marx, Science **324**, 1545 (2009).

[23] D. Mani *et al.*, Sci. Adv. **5**, eaav8179 (2019).

[24] R. Pérez de Tudela and D. Marx, Phys. Rev. Lett. **119**, 223001 (2017).

[25] R. Pérez de Tudela and D. Marx, Chem.—Eur. J. **26**, 11955 (2020).

[26] R. Pérez de Tudela and D. Marx, J. Phys. Chem. Lett. **7**, 5137 (2016).

[27] R. Ramaekers, J. Pajak, B. Lambie, and G. Maes, J. Chem. Phys. **120**, 4182 (2004).

[28] C. M. Aikens and M. S. Gordon, J. Am. Chem. Soc. **128**, 12835 (2006).

[29] F. Gabas, R. Conte, and M. Ceotto, J. Chem. Theory Comput. **13**, 2378 (2017).

[30] L. I. Cleeves, E. A. Bergin, C. M. D. Alexander, F. Du, D. Graninger, K. I. Öberg, and T. J. Harries, Science **345**, 1590 (2014).

[31] M. R. Hogerheijde *et al.*, Science **334**, 338 (2011).

[32] P. Boduch *et al.*, J. Phys. Conf. Ser. **629**, 012008 (2015).

[33] S. Esmaili, A. D. Bass, P. Cloutier, L. Sanche, and M. A. Huels, J. Chem. Phys. **148**, 164702 (2018).

[34] K. I. Öberg, Chem. Rev. **116**, 9631 (2016).

[35] M. Lattelais, O. Risset, J. Pilme, F. Pauzat, Y. Ellinger, F. Sirotti, M. Silly, P. Parent, and C. Laffon, Int. J. Quantum Chem. **111**, 1163 (2011).

[36] A. Belloche, H. S. Müller, K. M. Menten, P. Schilke, and C. Comito, Astron. Astrophys. **559**, A47 (2013).

[37] P. Ehrenfreund and S. B. Charnley, Annu. Rev. Astron. Astrophys. **38**, 427 (2000).

[38] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.128.033001 for details of the experimental setup, the data analysis, and the theoretical work, which includes Refs. [39–59].

[39] M. Choi, G. Douberly, T. Falconer, W. Lewis, C. Lindsay, J. Merritt, P. Stiles, and R. Miller, Int. Rev. Phys. Chem. **25**, 15 (2006).

[40] F. Weigend, M. Häser, H. Patzelt, and R. Ahlrichs, Chem. Phys. Lett. **294**, 143 (1998).

[41] S. Grimme, J. Chem. Phys. **118**, 9095 (2003).

[42] F. Weigend and R. Ahlrichs, Phys. Chem. Chem. Phys. **7**, 3297 (2005).

[43] J. P. Perdew, K. Burke, and M. Ernzerhof, Phys. Rev. Lett. **77**, 3865 (1996).

[44] B. Hammer, L. B. Hansen, and J. K. Nørskov, Phys. Rev. B **59**, 7413 (1999).

[45] S. Grimme, J. Antony, S. Ehrlich, and H. Krieg, J. Chem. Phys. **132**, 154104 (2010).

[46] F. Neese, Wiley Interdiscip. Rev. **8**, e1327 (2018).

[47] E. J. Heller, Acc. Chem. Res. **14**, 368 (1981).

[48] R. P. Feynman and A. R. Hibbs, *Quantum Mechanics and Path Integrals* (MacGraw-Hill, New York, 1965).

[49] M. F. Herman and E. Kluk, Chem. Phys. **91**, 27 (1984).
[50] K. G. Kay, J. Chem. Phys. **100**, 4377 (1994).
[51] W. H. Miller, J. Chem. Phys. **53**, 3578 (1970).
[52] A. L. Kaledin and W. H. Miller, J. Chem. Phys. **118**, 7174 (2003).
[53] M. Ceotto, S. Atahan, G. F. Tantardini, and A. Aspuru-Guzik, J. Chem. Phys. **130**, 234113 (2009).
[54] M. Ceotto, S. Atahan, S. Shim, G. F. Tantardini, and A. Aspuru-Guzik, Phys. Chem. Chem. Phys. **11**, 3861 (2009).
[55] N. De Leon and E. J. Heller, J. Chem. Phys. **78**, 4005 (1983).
[56] M. Ceotto, G. F. Tantardini, and A. Aspuru-Guzik, J. Chem. Phys. **135**, 214108 (2011).
[57] G. Di Liberto, R. Conte, and M. Ceotto, J. Chem. Phys. **148**, 014307 (2018).
[58] F. Gabas, G. Di Liberto, and M. Ceotto, J. Chem. Phys. **150**, 224107 (2019).
[59] R. Conte, F. Gabas, G. Botti, Y. Zhuang, and M. Ceotto, J. Chem. Phys. **150**, 244118 (2019).
[60] D. Mani, T. Fischer, R. Schwan, A. Dey, B. Redlich, A. Van Der Meer, G. Schwaab, and M. Havenith, RSC Adv. **7**, 54318 (2017).
[61] D. Oepts, A. Van der Meer, and P. Van Amersfoort, Infrared Phys. Technol. **36**, 297 (1995).
[62] J. Oomens, J. D. Steill, and B. Redlich, J. Am. Chem. Soc. **131**, 4310 (2009).
[63] C. Kapota, J. Lemaire, P. Maître, and G. Ohanessian, J. Am. Chem. Soc. **126**, 1836 (2004).
[64] J. M. Voss, K. C. Fischer, and E. Garand, J. Phys. Chem. Lett. **9**, 2246 (2018).
[65] K. C. Fischer, S. L. Sherman, J. M. Voss, J. Zhou, and E. Garand, J. Phys. Chem. A **123**, 3355 (2019).
[66] R. Schwan *et al.*, Angew. Chem. Int. Ed. **58**, 13119 (2019).
[67] M. Ceotto, G. Di Liberto, and R. Conte, Phys. Rev. Lett. **119**, 010401 (2017).
[68] F. Gabas, G. Di Liberto, R. Conte, and M. Ceotto, Chem. Sci. **9**, 7894 (2018).
[69] L. Kócs, E. E. Najbauer, G. Bazsó, G. Magyarfalvi, and G. r. Tarczay, J. Phys. Chem. A **119**, 2429 (2015).
[70] M. Lewerenz, B. Schilling, and J. Toennies, J. Chem. Phys. **102**, 8191 (1995).