Published in final edited form as:

J Phys Chem Lett. 2019 March 21; 10(6): 1325–1330. doi:10.1021/acs.jpclett.9b00208.

Laser Ablation Assists Cyclization Reactions of Hydantoic Acid: A Proof for the Near Attack Conformation Theory?

Lucie Kolesníková, Iker León, Elena R. Alonso, Santiago Mata, and Jose L. Alonso*

Grupo de Espectroscopia Molecular (GEM), Unidad Asociada CSIC, Laboratorios de Espectroscopia y Bioespectroscopia, Edificio Quifima, Universidad de Valladolid, 47011 Valladolid, Spain

Abstract

In the course of the investigation of the rotational spectrum of prebiotic hydantoic acid by Fourier transform microwave spectroscopy coupled with a laser ablation source in a supersonic expansion, rotational signatures of two cyclic molecules – hydantoin and 2,5-oxazolidinedione – have been unexpectedly observed along with the four most stable conformers of hydantoic acid. Interestingly, two of them presented folded geometric arrangements that might act as precursors in the cyclization reactions assisted by laser ablation. They could play the role of Near Attack Conformations in the framework of the NACs theory for intramolecular reactions. Detailed analysis of the spectrum further revealed the simultaneous formation of other species in the jet showing the laser ablation of solid organic precursors constitutes an alternative tool in the generation of new chemical species.

Organic solids with relatively high melting points present very low vapor pressures, posing difficulties to their study in the gas phase. For these species, laser ablation offers an efficient approach in which the energy of a high-intensity pulsed laser is used for fast desorption of non-volatile samples. The ablation plume is governed by very complex physical and chemical processes^{1–3} generating numerous transient species^{4–6} that may constitute important intermediates in chemical reactions. Nowadays, substantial advances in laser ablation procedures have made possible the transfer of many thermally fragile molecules into the gas phase to probe them in the isolation conditions of a supersonic expansion using high-resolution Fourier transform microwave techniques.⁷ We have recently applied this approach to the spectroscopic characterization of hydantoin⁸ and glycine, which play an essential role in interstellar chemistry as precursors of glycine. Hydantoic acid (HA) is considered as an intermediate on the hydrolytic way from hydantoin to glycine.^{10,11} It has also been proposed to participate in the prebiotic synthesis of primitive proteins.^{12,13} We report here the first structural study of isolated HA and mainly, about the amazing chemical species unexpectedly found in the supersonic jet of our laser ablation experiment.

*Corresponding Author: jlonso@qf.uva.es. Phone: +34 983186348; Fax: +34 983186349.

Notes

The authors declare no competing financial interests.

Solid HA (m.p. 176 °C) was ablated using the third harmonic (355 nm) of a picosecond Nd:YAG laser and the vaporized products were examined between 2 to 8 GHz by chirped-pulse Fourier transform microwave (CP-FTMW) spectroscopy^{14,15} (see Section 1 of Supporting Information). The broadband record, shown in Figure 1, revealed a congested rotational spectrum with many rotational lines which disappeared when laser ablation was turned off. Known decomposition lines,¹⁶ as well as water complexes, were first identified and removed from the spectrum. Most of the remaining lines were seen to present a hyperfine structure arising from ^{14}N nuclear quadrupole coupling interactions. They were initially attributed to HA species since it possesses $^{14}\text{N}_\text{C}$ and $^{14}\text{N}_\text{t}$ nuclei in its backbone (see Figure 2a) with a nuclear quadrupole moment ($I = 1$). The ^{14}N nuclear quadrupole coupling interaction splits the rotational energy levels giving rise to a very complex hyperfine structure as shown in the upper insets in Figure 1. On the other hand, the HA molecule contains five rotatable bonds (see Figure 2a), and therefore the conformational space is potentially vast. The presence of polar functional groups that can act as a proton donor or acceptor multiplies the possibilities of intramolecular hydrogen bonds and lead to a multi-conformational behavior that could explain the complex rotational spectrum observed.

The identification of the coexisting conformers of HA was based on a systematic procedure already employed in our previous studies of amino acids¹⁷ and dipeptides¹⁸ that involved the combination of theoretical and experimental data (see Section 2 of the Supporting Information). Relying on the theoretical predictions, we have identified the four lowest-energy conformers, labeled as $\text{C}_5\text{-I}$, $\text{C}_7\text{-I}$, $\text{C}_7\text{-II}$, and $\text{C}_5\text{-II}$ in Figure 2b. The ^{14}N nuclei introduced hyperfine rotational probes at defined sites of HA which act as a reporter of the chemical environment of N_C and N_t quadrupolar nuclei. It constitutes a precious tool in conformational identification.¹⁹ In this context, further measurements were performed under the higher resolution of our narrowband cavity-based FTMW spectrometer,²⁰ so the hyperfine structure could be fully resolved and analyzed (see Section 2 in the Supporting Information). This provided accurate values of the rotational constants and the diagonal elements of the nuclear quadrupole coupling tensor for the observed conformers in Table 1. Conformational identification is achieved by comparing the experimentally determined molecular properties with those predicted theoretically. Rotational constants (A, B, C) and quadrupole coupling constants (χ_{aa} , χ_{bb} , χ_{cc}) were all consistent for conclusive identification. The four observed conformers of HA are found in both extended and folded configurations in which the backbones are stabilized by different types of intramolecular hydrogen bonds that allow closure of five- (C_5) and seven-membered (C_7) rings. The topology of the theoretical electron densities was achieved visualizing the non-covalent interactions (NCI) with the NCI plot method²¹ (see Figure S1 in the Supporting Information) to quantify the energy related to HBs.

Once the transitions of the four HA conformers were discarded, an unusually large number of lines showing ^{14}N nuclear quadrupole hyperfine structure remained unassigned in the rotational spectrum. Surprisingly, some of these lines were discovered to belong to hydantoin (see the lower inset of Figure 1), the heterocyclic molecule recently studied in our laboratory.⁸ We checked for the presence of HA in our spectral records of laser ablated hydantoin¹², and no lines of HA were found. This observation necessary prompted the following question: Does the acyclic HA cyclize into cyclic hydantoin by laser ablation? If

so, a new ring bond $N_1-C=O$ should be formed, and a water molecule should be eliminated. Intuitively, a chance of the productive formation of this bond is expected to be enhanced if the participating reactive centers of nitrogen and carbon atoms are in a near position resembling the bond to be formed in the transition state. This situation is called a Near Attack Conformation (NAC) that can proceed to the transition state. It is the core of Lightstone and Bruice's theory^{22–25} that proposes the conformers having a proper geometric arrangement (NAC conformers) as the doors through which the intramolecular reactions, such as cyclization, occur. In our case, the flexibility of the HA backbone allowed for the stabilization of the C_7-II folded conformer in which the proximity of the two potentially reactive amine $-N_1H_2$ and carboxylic $-COOH$ ends are tightly held by a strong $N_1-H\cdots O=C$ intramolecular hydrogen bond. This conformational pre-organization might play the role of NAC explaining the cyclization of HA into hydantoin as schematically shown in Figure 3a.

At this point, an important question arises. If we assume that the C_7-II conformer is responsible for the formation of hydantoin in the frame of the NAC approach, the presence of the other C_7-I folded conformer should conduct, by the elimination of ammonia (see Figure 3b), to the formation of another cyclic compound, 2,5-oxazolidinedione. It is the simplest member of the α -amino acid N-carboxy anhydrides family that play an essential role in the molecular evolution on the prebiotic Earth.^{26–28} C_7-I conformer brings together the terminal $-COOH$ carboxylic and $H_2NC(O)-$ reactive amide groups through a strong $O-H\cdots O=C$ intramolecular interaction. Like C_7-II , it can act as NAC leading to the formation of 2,5-oxazolidinedione.

Is 2,5-oxazolidinedione molecule in our supersonic expansion? It has never been spectroscopically characterized so no previous rotational data exists to prove its presence as a cyclization product of the laser ablation of HA. With this aim, we undertook a theoretical study of 2,5-oxazolidinedione to provide values of the molecular parameters that allow its spectroscopic identification (see Section 3 of the Supporting Information). Guided by the theoretical prediction, a careful search for its spectral signatures was carried out. Astonishingly, four *b*-type transitions could be identified in the broadband spectrum (see lower inset of Figure 1). We have extended the rotational spectrum of laser ablated HA up to 15 GHz, and more *b*-type transitions were ultimately measured validating the detection of 2,5-oxazolidinedione. Detailed analysis of the ^{14}N nuclear quadrupole hyperfine structure (see Section 3 of the Supporting Information) provided the precise set of spectroscopic constants listed in Table 2, which are in excellent agreement with the predicted ones. Notice that the experimental value of the nuclear quadrupole coupling constant $\chi_{cc} = -4.79$ MHz is very similar to that of the amide nitrogen in hydantoin of $\chi_{cc} = -4.73$ MHz⁸ which corroborates the existence of pyrrolic nitrogen ($-N<$)²⁹ for both heterocyclic rings.

The exhaustive dissection of the broadband rotational spectrum granted the detection of other eleven monomeric species, nine of them already detected in space, and four molecular complexes (see Section 4 of the Supporting Information). They are summarized in Chart 1 where they are categorized according to the heteroatom they bear. Many are common on Earth, while others are quite exotic. For example, cyanoacetylene and cyanomethanimine are unstable by terrestrial standards and were previously produced in laboratories by electric

discharge or pyrolysis methods.^{30–32} The four observed complexes, also collected in Chart 1, indicate the presence of the non-polar N₂ and CO₂ as well as HCN. All the species from Chart 1 point to the rich chemistry taking place during the laser ablation event. It is interesting to note that several species from Chart 1, such as cyanoacetylene, vinyl cyanide, or methyl isocyanate could also be observed in the rotational spectrum of laser ablated hydantoin. On the other hand, no signs for rotational signatures of hydantoic acid and 2,5-oxazolidinedione could be identified, which is another strong indication for the NAC mechanism.

In summary, two cyclic species, hydantoin and 2,5-oxazolidinedione, have been unexpectedly detected in the course of the conformational study of the acyclic hydantoic acid by laser ablation (LA) coupled with Fourier transform microwave techniques. Interestingly, two of the four coexisting conformers unveiled for hydantoic acid adopt folded C₇ configurations that might act as NACs precursors of the transition state in a cyclization reaction assisted by laser ablation that conducts to the formation of the above cyclic compounds. These findings might constitute the first gas-phase evidence for the NAC approach introduced by Lightstone and Bruce from theoretical calculations.^{22–24} The present results may open new ways towards proposals of reaction mechanisms taking place under extreme conditions of the laser ablation process.

Last but not least, the great diversity of chemical species generated in the presently reported laser ablation experiment of HA shows new potentials of laser ablation of organic solids. If this is combined with the high-resolution and specificity of Fourier transform microwave techniques in a supersonic expansion, it may constitute a novel tool in the generation and characterization of new chemical species. Studies in this direction are currently underway in our laboratory to generate new unstable molecules of astrophysical interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The financial funding from Ministerio de Ciencia e Innovación (CTQ2013-40717-P and CTQ2016-76393-P), Junta de Castilla y León (Grant VA077U16) and European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013)/ERC-2013SyG, Grant Agreement n. 610256 NANOCOSMOS, are gratefully acknowledged. E. R. A. thanks Ministerio de Ciencia e Innovación for FPI grant (BES-2014-067776).

References

- (1). Bäuerle, D. Laser Processing and Chemistry. Springer Berlin Heidelberg; Berlin, Heidelberg: 2011.
- (2). Russo RE, Mao X, Gonzalez JJ, Zorba V, Yoo J. Laser Ablation in Analytical Chemistry. *Anal Chem.* 2013; 85:6162–6177. [PubMed: 23614661]
- (3). Stafe, M, Marcu, A, Puscas, NN. Pulsed Laser Ablation of Solids: Basics, Theory and Applications. Springer Berlin Heidelberg; Berlin, Heidelberg: 2014.
- (4). Serrano J, Moros J, Laserna JJ. Sensing Signatures Mediated by Chemical Structure of Molecular Solids in Laser-Induced Plasmas. *Anal Chem.* 2015; 87:2794–2801. [PubMed: 25668318]

- (5). Serrano J, Moros J, Javier Laserna J. Molecular Signatures in Femtosecond Laser-Induced Organic Plasmas: Comparison with Nanosecond Laser Ablation. *Phys Chem Chem Phys*. 2016; 18:2398–2408. [PubMed: 26695078]
- (6). Sovova K, Dryahina K, Spáňal P, Kyncl M, Cívik S. A Study of the Composition of the Products of Laser-Induced Breakdown of Hexogen, Octogen, Pentrite and Trinitrotoluene Using Selected Ion Flow Tube Mass Spectrometry and UV-Vis Spectrometry. *Analyst*. 2010; 135:1106–1114. [PubMed: 20419263]
- (7). Alonso, JL, López, JC. Microwave Spectroscopy of Biomolecular Building Blocks. *Gas-Phase IR Spectroscopy and Structure of Biological Molecules*. Rijs, AM, Oomens, J, editors. Springer International Publishing; Cham: 2015. 335–401.
- (8). Alonso ER, Kolesníková L, Alonso JL. Laser Ablated Hydantoin: A High Resolution Rotational Study. *J Chem Phys*. 2017; 147
- (9). Alonso ER, Kolesníková L, Białkowska-Jaworska E, Kisiel Z, León I, Guillemin J-C, Alonso JL. Glycinamide, a Glycine Precursor, Caught in the Gas Phase: A Laser-Ablation Jet-Cooled Rotational Study. *Astrophys J*. 2018; 861:70.
- (10). Kayanuma M, Kidachi K, Shoji M, Komatsu Y, Sato A, Shigeta Y, Aikawa Y, Umemura M. A Theoretical Study of the Formation of Glycine via Hydantoin Intermediate in Outer Space Environment. *Chem Phys Lett*. 2017; 687:178–183.
- (11). Pascal, R, Boiteau, L, Commeyras, A. From the Prebiotic Synthesis of α -Amino Acids Towards a Primitive Translation Apparatus for the Synthesis of Peptides. *Prebiotic Chemistry*. Walde, P, editor. Springer Berlin Heidelberg; Berlin, Heidelberg: 2005. 69–122.
- (12). Abou Mrad N, Ajram G, Rossi J-C, Boiteau L, Duvernay F, Pascal R, Danger G. The Prebiotic C-Terminal Elongation of Peptides Can Be Initiated by N-Carbamoyl Amino Acids. *Chem Eur J*. 2017; 23:7418–7421. [PubMed: 28378889]
- (13). Danger G, Plasson R, Pascal R. Pathways for the Formation and Evolution of Peptides in Prebiotic Environments. *Chem Soc Rev*. 2012; 41:5416–5429. [PubMed: 22688720]
- (14). Shipman, ST, Pate, BH. New Techniques in Microwave Spectroscopy. *Handbook of High-Resolution Spectroscopy*. John Wiley & Sons, Ltd; Chichester, UK: 2011.
- (15). Brown GG, Dian BC, Douglass KO, Geyer SM, Shipman ST, Pate BH. A Broadband Fourier Transform Microwave Spectrometer Based on Chirped Pulse Excitation. *Rev Sci Instrum*. 2008; 79
- (16). Peña I, Cabezas C, Alonso JL. The Nucleoside Uridine Isolated in the Gas Phase. *Angew Chem Int Ed*. 2015; 54:2991–2994.
- (17). Peña I, Sanz ME, López JC, Alonso JL. Preferred Conformers of Proteinogenic Glutamic Acid. *J Am Chem Soc*. 2012; 134:2305–2312. [PubMed: 22191520]
- (18). Cabezas C, Varela M, Alonso JL. The Structure of the Elusive Simplest Dipeptide Gly-Gly. *Angew Chem Int Ed*. 2017; 129:6520–6525.
- (19). Alonso JL, Vaquero V, Peña I, López JC, Mata S, Caminati W. All Five Forms of Cytosine Revealed in the Gas Phase. *Angew Chem Int Ed*. 2013; 52:2331–2334.
- (20). Bermúdez C, Mata S, Cabezas C, Alonso JL. Tautomerism in Neutral Histidine. *Angew Chem Int Ed*. 2014; 53:11015–11018.
- (21). Johnson ER, Keinan S, Mori-Sánchez P, Contreras-García J, Cohen AJ, Yang W. Revealing Noncovalent Interactions. *J Am Chem Soc*. 2010; 132:6498–6506. [PubMed: 20394428]
- (22). Lightstone FC, Bruice TC. Ground State Conformations and Entropic and Enthalpic Factors in the Efficiency of Intramolecular and Enzymatic Reactions. 1. Cyclic Anhydride Formation by Substituted Glutarates, Succinate, and 3,6-Endoxo- 4-Tetrahydrophthalate Monophenyl Esters. *J Am Chem Soc*. 1996; 118:2595–2605.
- (23). Lightstone FC, Bruice TC. Separation of Ground State and Transition State Effects in Intramolecular and Enzymatic Reactions. 2. A Theoretical Study of the Formation of Transition States in Cyclic Anhydride Formation. *J Am Chem Soc*. 1997; 119:9103–9113.
- (24). Bruice TC, Lightstone FC. Ground State and Transition State Contributions to the Rates of Intramolecular and Enzymatic Reactions. *Acc Chem Res*. 1999; 32:127–136.
- (25). Hur S, Bruice TC. The near Attack Conformation Approach to the Study of the Chorismate to Prephenate Reaction. *Proc Natl Acad Sci*. 2003; 100:12015–12020. [PubMed: 14523243]

- (26). Kricheldorf HR. Polypeptides and 100 Years of Chemistry of Alpha-Amino Acid N-Carboxyanhydrides. *Angew Chem Int Ed*. 2006; 45:5752–5784.
- (27). Biron J-P, Pascal R. Amino Acid N-Carboxyanhydrides: Activated Peptide Monomers Behaving as Phosphate-Activating Agents in Aqueous Solution. *J Am Chem Soc*. 2004; 126:9198–9199. [PubMed: 15281806]
- (28). Pascal, R, Boiteau, L, Commeyras, A. From the Prebiotic Synthesis of α -Amino Acids Towards a Primitive Translation Apparatus for the Synthesis of Peptides. *Prebiotic Chemistry*. Walde, P, editor. Springer Berlin Heidelberg; Berlin, Heidelberg: 2005. 69–122.
- (29). Tanjaro C, Subramanian R, Karunatilaka C, Kukolich SG. Microwave Measurements of ^{14}N and ^2D Quadrupole Coupling for (Z)-2-Hydroxypyridine and 2-Pyridone Tautomers. *J Phys Chem A*. 2004; 108:9531–9539.
- (30). Takano S, Sugie M, Sugawara K, Takeo H, Matsumura C, Masuda A, Kuchitsu K. Microwave Spectra, Dipole Moments, and Energy Difference of E and Z C-Cyanomethanimine (HCN Dimer). *J Mol Spectrosc*. 1990; 141:13–22.
- (31). Zaleski PD, Seifert AN, Steber AL, Muckle TM, Loomis AR, Joanna FC, Oscar Martinez J, Kyle NC, Philip RJ, Jan MH, et al. Detection of E-Cyanomethanimine toward Sagittarius B2(N) in the Green Bank Telescope PRIMOS Survey. *Astrophys J Lett*. 2013; 765:L10.
- (32). McCarthy MC, Chen W, Travers MJ, Thaddeus P. Microwave Spectra of 11 Polyne Carbon Chains. *Astrophys J Suppl Ser*. 2000; 129:611.

Figure 1.

The broadband spectrum of laser-ablated hydantoic acid. The upper insets show the individual transitions of the four observed conformers with partially resolved nuclear quadrupole hyperfine structure. The lower insets depict rotational transitions belonging to the discovered cyclic species.

Figure 2.

(a) A sketch of hydantoic acid showing the rotations around the single bonds. N_t and N_c refer to the terminal and central ^{14}N nuclei, respectively. (b) Three-dimensional structures of the four observed conformers of hydantoic acid showing the intramolecular interactions.

Figure 3. Conformer-dependent cyclization reactions leading to (a) hydantoin and (b) 2,5-oxazolidinedione, the two cyclic species detected in the rotational spectra of laser ablated hydantoic acid.

Chart 1.

Summary of the 17 species detected in the jet-cooled CP-FTMW spectra of laser ablated hydantoic acid. The star behind the chemical name shows that a given species has been detected in space.

Table 1
Experimental and calculated spectroscopic parameters for the four observed conformers of hydantoic acid.

Parameter ^a	C5-I		C7-I		C7-II		C5-II	
	Experiment	Theory ^b	Experiment	Theory ^b	Experiment	Theory ^b	Experiment	Theory ^b
A /MHz	5508.64096 (63) ^c	5442	4794.0228 (20)	4746	5195.4 (12)	5227	4376.153 (23)	4396
B /MHz	1010.67310 (24)	1014	1266.88614 (47)	1273	1160.2744 (19)	1158	1239.285 (11)	1212
C/MHz	861.96668 (19)	867	1103.59640 (40)	1109	1032.3768 (14)	1015	1224.5233 (90)	1185
$\chi_{aa}(N_c)$ /MHz	2.6105 (90)	2.81	1.372 (11)	1.48	2.057 (14)	2.22	... ^d	1.47
$\chi_{bb}(N_c)$ /MHz	2.145 (15)	2.29	0.698 (16)	0.52	0.384 (48)	0.82	... d	0.24
$\chi_{cc}(N_c)$ /MHz	-4.756 (15)	-5.11	-2.070 (16)	-2.00	-2.440 (48)	-3.05	... d	-1.70
$\chi_{aa}(N_t)$ /MHz	2.0661 (94)	2.21	1.7569 (86)	2.08	1.299 (21)	1.49	... d	1.79
$\chi_{bb}(N_t)$ /MHz	1.977 (17)	1.74	1.559 (14)	1.94	1.562 (94)	2.21	... d	-2.71
$\chi_{cc}(N_t)$ /MHz	-4.043 (17)	-3.95	-3.316 (14)	-4.02	-2.862 (94)	-3.69	... d	0.92
E/cm^{-1}	...	0	...	322	...	865	...	769
G/cm^{-1}	...	0	...	389	...	950	...	723

^a A , B , and C are the rotational constants; χ_{aa} , χ_{bb} , and χ_{cc} are the diagonal elements of the nuclear quadrupole coupling tensor for the central (N_c) and terminal (N_t) ^{14}N nuclei; E and G represent the relative energy and Gibbs free energy ($T=298\text{ K}$), respectively, with respect to the global minimum.

^b B2PLYPD/aug-cc-pVTZ level of the theory.

^c The numbers in parentheses are 1σ uncertainties in units of the last decimal digit.

^d Due to the weakness of individual hyperfine components, only central frequencies were analyzed.

Table 2
Experimental and calculated spectroscopic parameters for 2,5-oxazolidinedione.

Parameter ^a	Experimental	Theory ^b
<i>A</i> /MHz	6550.6445 (14) ^c	6587
<i>B</i> /MHz	2391.76565(60)	2382
<i>C</i> /MHz	1772.88748(54)	1769
χ_{aa} /MHz	2.5587(80)	2.62
χ_{bb} /MHz	2.2353 (69)	2.35
χ_{cc} /MHz	−4.7940 (69)	−4.97

^a *A*, *B*, and *C* are the rotational constants; χ_{aa} , χ_{bb} , and χ_{cc} are the diagonal elements of the nuclear quadrupole coupling tensor for the ¹⁴N nuclei.

^b B2PLYPD/aug-cc-pVTZ level of the theory.

^c The numbers in parentheses are 1 σ uncertainties in units of the last decimal digit. The complete table is given in the Supporting Information.