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Thermal decomposition of allantoin as probed by matrix isolation FTIR spectroscopy

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ABSTRACT

The optimized geometries, energies of the possible conformers of allantoin (2,5-dioxo-4-imidazolidinyl urea, the diureide of glyoxylic acid) as well as the barriers for conformational interconversion have been calculated using the density functional theory [DFT(B3LYP)/6-311++G(d,p)] method. The calculations predicted the existence of four conformers (**gC**, **tT**, **g′C**, and **g′T**; where the first and second symbols in the name of the conformers designate the conformation around the exocyclic NHC–NHCO and CNH–CO axes, respectively), with the **gC** form contributing to more than 98% of the population in gas phase at room temperature. This conformer is different from that corresponding to the monomeric unit found in crystalline *RS*-allantoin (**g′C**; Mootz, D. *Acta Crystallogr.* **1965**, *19*, 726), stressing the importance of intermolecular H-bonding in determining the structure of the crystal. Upon sublimation under vacuum (10^{-6} mbar), the compound was found to undergo extensive decomposition to urea, isocyanic acid, NH_3, and carbon. The identification of the decomposition products was made by using matrix isolation infrared spectroscopy. In consonance with the theoretical predictions, the allantoin molecules surviving thermal decomposition were found to undergo conformational isomerization and be present in the cryogenic argon matrix in both the **gC** and **g′C** conformations. The solid state room temperature infrared spectrum of allantoin was also investigated and assigned.

1. Introduction

Allantoin (2,5-dioxo-4-imidazolidinyl urea; $C_4H_6N_4O_3$; Fig. 1) is also called 5-ureidohydantoin or glyoxyldiureide and is the diureide of glyoxylic acid. It is a product of purine metabolism and known since long ago to exist in nature, for example, in allantoic and amniotic fluids, in fetal urine and in many plants and bacteria.[1–8] Allantoin is active in skin-softening and rapid skin cells regeneration. It removes corneocytes by loosening the intercellular kit or the desmosomes (protein bridges) that maintain the adhesion of corneocytes to each other. It then exfoliates dry and damaged cells and boosts the radiant appearance of the skin, whose surface becomes smoother and softer. Due to these properties, allantoin has been used in cosmetic industry in several forms (e.g., lotions, creams, suntan products, shampoos, lipsticks, and various aerosol preparations), as well as in topical pharmaceutical preparations for treatment of skin diseases for many years.[4,9–11]

From a more fundamental perspective, allantoin is also an interesting compound, in which different types of intra- and intermolecular H-bond interactions can be expected to be relevant in determining its structural preferences, spectroscopic properties, and reactivity. In particular, the fragmentation reactions exhibited by the compound appeared to us particularly appealing for investigation since the structure of the allantoin ring, with two sequential –C(=O)–N(H)– fragments, looked a good candidate to act as a precursor of isocyanic acid, a well known biologically pernicious substance that can easily react with amino terminus residues of proteins (or side chains of lysine and arginine residues) to form carbamoylated

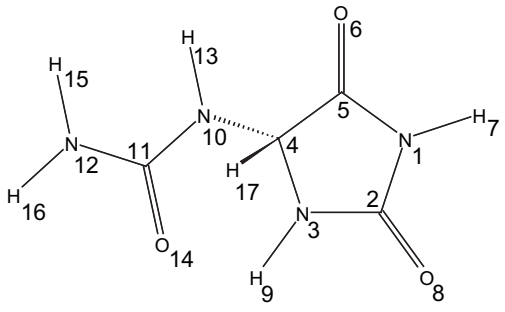

Figure 1. Allantoin, with the adopted atom labeling scheme.

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proteins, which have been observed in several states of disease.[12–15] Indeed, 1-phenyl-tetrazolone, which has structural similarities to allantoin possessing a single –C(=O)–N(H)– fragment in its heterocyclic ring has been recently shown to decompose easily to phenylazide and isocyanic acid.[16]

In spite of both its many applications and expected interesting molecular properties and reactivity, allantoin has not yet been much studied from the structural point of view, though many publications describe procedures for its analytical determination, in particular in a biochemical context.[17–20] The molecule has a chiral center and may then exist as *R*- and *S*-enantiomeric forms. Contrary to what happens for the enantiomerically pure substance, for which no crystal data has yet been reported, the crystalline structure of *RS*-allantoin was obtained by X-ray diffraction.[21] The crystal was found to belong to the $P2_1/c$ space group (a=8.024, b=5.153, c=14.797 Å, β=93.01°), with four molecules in the unit cell, exhibiting an intricate three-dimensional H-bond network in which the three carbonyl oxygens, three imido, and two amino hydrogen atoms take part. The monomeric unit in the crystal was found to have the C_4–N_{10}–C_{11}–O_{14} axis in the cis conformation and a conformation around the C_4–N_{10} bond that directs the O_{14} atom to above the heterocyclic ring, so that the molecule assumes a 'scorpion like' geometry.[21]

Kahn and Tipton[22] performed simple HF/6-31G(d,p) calculations on the isolated molecule of allantoin and reported the existence of four different conformers, with the form similar to the monomeric structure found in the *RS*-allantoin crystal being the second most stable one. According to the HF/6-31G(d,p) calculations, the most stable conformer (by 12.8 kJ mol^{-1}) has also a cis C_4–N_{10}–C_{11}–O_{14} axis, but in this case the ureido group is directed toward the outside part of the molecule. Two additional conformers of higher energy bearing a trans C_4–N_{10}–C_{11}–O_{14} fragment were also described by Kahn and Tipton.[22] NMR data[22] showed that in solution of both DMSO or $CHCl_3$ allantoin should exist in a conformation with a cis C_4–N_{10}–C_{11}–O_{14} axis as well, though no precise identification of the relevant form could be undertaken.

Previously reported reactivity studies on allantoin have focused mainly on its racemization reaction.[22,23] To the best of our knowledge, no further structural or spectroscopic studies were reported on allantoin hitherto.

In the present investigation, we performed a detailed study of the potential energy surface of allantoin using the density functional theory (DFT) approach and investigated the thermal fragmentation of the compound taking place upon sublimation. The identification of the decomposition products was made by using matrix isolation infrared spectroscopy. In addition, we obtained and assigned the room temperature infrared spectrum of the compound. This enabled us to obtain further information on the most relevant intermolecular interactions that stabilize the **g′C** conformer in this phase over the thermodynamically most stable **gC** conformer.

2. Experimental and computational methods

Allantoin was provided by Prof. Mustafa Korkmaz, Hacettepe University, Ankara, spectroscopic grade (>98 %). The matrices were prepared by co-deposition of argon (99.99990% purity, obtained from Air Liquide) and the vapors generated upon sublimation of allantoin onto the cooled (10 K) CsI substrate of the cryostat (APD Cryogenics close-cycle helium refrigeration system with a DE-202A expander). A glass vacuum system and standard manometric procedures were used to deposit the isolating gas. Allantoin was placed in a specially designed mini-oven assembled inside the cryostat and thermoelectrically heated.

The matrix isolation IR spectra were collected, with 0.5 cm^{-1} spectral resolution, on a Nicolet 6700 Fourier Transform infrared spectrometer, equipped with a deuterated triglycine sulfate (DTGS) detector and a Ge/KBr beamsplitter. The infrared spectrum of the neat *RS*-allantoin crystal in KBr pellet at room temperature was obtained in a BOMEM MB104 FTIR spectrometer, with resolution 4 cm^{-1}.

Differential Scanning Calorimetry (DSC) measurements were made in a Perkin–Elmer DSC7 calorimeter over the temperature range 25–255 °C, with scanning rate 10 °C min^{-1}. Data acquisition and determination of the onset temperatures were performed with the Perkin–Elmer 1020 Series Thermal Analysis System Software. The samples were hermetically sealed in aluminum pans, and an empty pan was used as reference. A 20 mL min^{-1} nitrogen purge was employed. Temperature calibration [24] was performed with high grade standards, namely biphenyl (T_{fus}=68.93±0.03 °C) and zinc (T_{fus}=419.53 °C), and verified with naphthalene (T_{fus}=80.20±0.04 °C), benzoic acid (T_{fus}=122.35±0.02 °C), and indium (T_{fus}=156.60 °C). For heat calibration the enthalpy of fusion of indium was used ($\Delta_{fus}H$=3286±13 J mol^{-1}).[24]

The quantum chemical calculations were performed with the Gaussian 03 suit of programs[25] at the DFT level of theory, using the 6-311++G(d,p) basis set.[26,27] The three-parameter hybrid density functional abbreviated as B3LYP, which includes Becke's gradient exchange correction[28] and the Lee, Yang and Parr,[29] and Vosko, Wilk and Nusair correlation functionals[30] was selected for the calculations. Structures were optimized using the Geometry Direct Inversion of the Invariant Subspace (GDIIS) method,[31,32] with the transition state structures for conformational interconversion located using the Synchronous Transit-Guided Quasi-Newton (STQN) approach.[33] The 2D potential energy surface maps were built by varying the N_3–C_4–N_{10}–C_{11} and C_4–N_{10}–C_{11}–O_{14} dihedral angles from 0 to 360° in increments of 5° and optimizing all other structural parameters at the selected level of theory.

Vibrational frequencies were calculated at the same level of theory and scaled down by a single factor (0.978) to correct them mainly for the effects of basis set limitations, neglected part of electron correlation and anharmonicity effects, and used to assist the analysis of the experimental spectra. Normal coordinate analysis of allantoin was undertaken in the internal coordinates space as described by Schachtschneider,[34] using the program BALGA and the optimized geometries and harmonic force constants resulting from the DFT(B3LYP)/6-311++G(d,p) calculations.

3. Results and discussion

3.1. Conformational analysis

Allantoin has a chiral center, the two enantiomers being conformationally and spectroscopically equivalent. In this study we will then consider only one of the enantiomers (*S* form).

According to the 2D potential energy map shown in Figure 2, at least four conformers differing in the N_3–C_4–N_{10}–C_{11} and C_4–N_{10}–C_{11}–O_{14} dihedral angles were expected for the molecule. This number could, eventually, increase if the heterocyclic ring deviated from planarity and the imide and amide groups were pyramidalized. Hence, a detailed search for conformers was undertaken by varying the initial geometries of the imide and amide groups and also including structures with a non-planar heterocyclic ring in the set of structures submitted to full geometry optimization. All these structures corresponded to geometries located in the vicinity of the four general minima found in the preliminary relaxed scan performed to build the 2D potential energy map provided in Figure 2.

The final number of located different energy minima was 6 (Fig. 3). Nevertheless, as discussed in detail below, these six minima correspond to only four conformational states, each one associated with one of the four low potential energy valleys represented in Figure 2.