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The conformational behavior and H-bond structure of asparagine: A theoretical and experimental matrix-isolation FT-IR study

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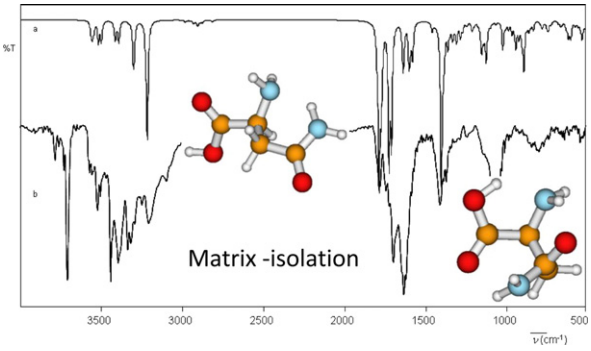
HIGHLIGHTS

- ► Ab initio exploration of the conformational landscape of asparagine.
- ► Three intramolecular H-bonds in the most stable form.
- ► A strong H-bond interaction between the side chain and the backbone.
- ► Experimental identification by matrix-isolation FT-IR spectroscopy.
- ► A mean frequency deviation of 7.6 cm^{-1}.

GRAPHICAL ABSTRACT



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ABSTRACT

Due to the high importance of the structural properties of peptides, the conformational behavior of one of their elementary building blocks, asparagine, has been investigated in this work. Matrix-isolation FT-IR spectroscopy is a suitable technique to investigate the intrinsic properties of small molecules. Asparagine has been subjected to matrix-isolation FT-IR spectroscopy supported with DFT and MP2 calculations. DFT optimization of asparagine resulted in 10 stable conformations with $\Delta E_{DFT}<10$ kJ.mol^{-1}. Compared to a previous study, one new conformation has been revealed. Further optimization at the MP2/6-31++G** level resulted in seven conformations with $\Delta E_{MP}<10$ kJ.mol^{-1}. A conformation containing the three intramolecular H-bonds, i.e. $C=O^{sc}\ldots HN^{bb}$, $C=O^{bb}\ldots HN^{sc}$ and $OH^{bb}\ldots N^{bb}$ appeared to be the most stable one at both levels despite the large negative entropy contribution due to these 3 H-bonds. At the sublimation temperature of 353 K, the DFT method predicts four and the MP2 method six conformations to be present in the experimental matrix-isolation spectrum. These conformations have different intramolecular H-bonds, which has allowed to identify at least 4 low energy conformations in the FT-IR spectrum. Detailed comparison between theory and experiment resulted in a mean frequency deviation of 7.6 cm^{-1}.

1. Introduction

One of the most intriguing questions in biophysical chemistry is how protein sequences determine the unique structure. This question, known as the protein folding problem, is of great importance because understanding protein folding mechanisms is a key to successful manipulation of protein structure and most important their functionality, which is directly related to their conformational flexibility [12]. As elementary building block of proteins, the intrinsic conformational properties and energies of amino acids determine, to a large extend, the functionality of proteins and polypeptides [26]. In addition, the amino acid residues in proteins correspond to the low-energy conformations [30].

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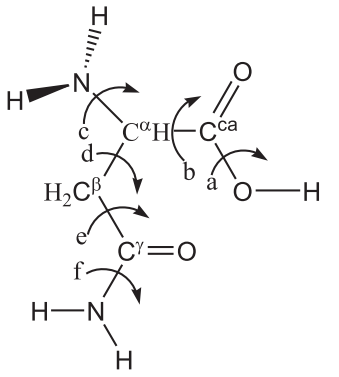

Fig. 1. Numbering and possible internal rotation axes (°) for asparagine.

A very suitable methodology to study the intrinsic properties of small molecules is matrix-isolation FT-IR spectroscopy. In a matrix, a molecule is essentially not involved in any interactions. Furthermore the obtained FT-IR spectra can be possibly used to detect amino acids in interstellar space [35].

Due to the importance of the conformational behavior and energetics of amino acids many of them have been subjected to ab initio studies, e.g. [14,17,19,24,36,37]. All of these studies have revealed more than one stable conformation with four typical kinds of backbone structure characterized by an intramolecular H-bond, i.e. OH…N, NH_2…O=C, NH_2…O(H) and NH_2…O=C. The occurrence of several stable conformations could give rise to very complex FT-IR spectra. This is probably the reason why matrix-isolation FT-IR studies have only been performed for relatively simple amino acids such as glycine [32], alanine [21], isoleucine [6] and cysteine. [11] In this study, the somewhat more complex amino acid asparagine is subjected to a matrix-isolated FT-IR study, supported by a theoretical approach.

The NH_2 group in the side chain of asparagine allows the formation of additional H-bonds. However, it is well known that the amino group in an amide group is an extremely weak base due to considerable resonance so that the side chain proton-acceptor capabilities are only located in the C=O group.

Asparagine was the first amino acid isolated (1806) in its crystalline form from asparagus juice in which it is abundant [39]. Asparagine plays an important role in the metabolic control of cell functions in nerve and brain tissue [25]. It is essential for the synthesis of glycoproteins and a large number of proteins as it is involved in the liver for converting an amino acid into another [1,18,24,29,31].

An extended theoretical ab initio investigation of asparagine has been performed by the group of Lin [10]. A set of 972 conformational trial structures was optimized at successive DFT(B3LYP)/6-311G* and DFT(B3LYP)/6-311++G** levels of theory. 62 stable conformations were found and these were subjected to MP2 single point energy calculations. The shifted vibrations of some H-bond involved stretching modes of the representative conformations have also been reported. The stabilities for side chain conformations of asparagine in solutions have been theoretically studied by Kimura [20]. The asparagine dipeptide has also been theoretically studied using the HF and MP2 methodology by Aleman et al., [1] who have concluded that the gauche conformations are dominant.

As far as experimental data are concerned, IR and Raman spectra of solid asparagine and its ND_3^+ and ND_2 deuterated derivatives have been recorded and a general assignment of the fundamental vibrations has

Table 1
DFT(B3LYP)/6-31++G** and MP2/6-31++G** energies, zero-point vibrational energies (ZPE), relative energies (ΔE) and dipole moments (μ) for the most stable asparagine conformations.

Conformation	Type of backbone	Energy (a.u.)	ZPE[a] (a.u.)	Total energy[b] (a.u.)	ΔE[c] (kJ.mol^{-1})	μ (D)	ΔE[d] (kJ.mol^{-1})
DFT							
ASN1	I $N^{bb}H…O^{sc}+N^{sc}H…O^{bb}$	−492.495198	0.132662	−492.362536	0.00	2.76	0.00
ASN7	I $NH…O^{sc}$	−492.493090	0.131703	−492.361387	3.02	5.04	5.19
ASN2	II $N…HN^{sc}$	−492.493249	0.131932	−492.361317	3.20	3.89	0.51
ASN6	I $NH…O^{sc}$	−492.493029	0.132355	−492.360674	4.89	4.22	5.65
ASN10	IV $OH…O^{sc}$	−492.492234	0.131740	−492.360494	5.36	6.75	8.20
ASNX	I $O..HN^{sc}$	−492.491739	0.132551	−492.359188	8.79	3.31	[e]
ASN3	II $N…HN^{sc}$	−492.491005	0.131868	−492.359137	8.92	4.08	10.63
ASN8	II $NH…O^{sc}$	−492.490041	0.131015	−492.359026	9.22	3.59	12.64
ASN4	II	−492.490027	0.131165	−492.358862	9.65	4.73	12.84
ASN9	III $N…HN^{sc}$	−492.490735	0.131910	−492.358825	9.74	5.44	11.51
ASN5[f]	III	−492.490017	0.131376	−492.358641	10.23	2.24	13.01
MP2							
ASN1	I $N^{bb}H…O^{sc}+N^{sc}H…O^{bb}$	−491.132046	0.135066	−490.996980	0.00	3.28	0.00
ASN2	II $N…HN^{sc}$	−491.128841	0.134205	−490.994636	6.16	4.14	8.58
ASN3	II $N…HN^{sc}$	−491.128719	0.134249	−490.994470	6.59	4.46	10.38
ASN4	II	−491.127798	0.133740	−490.994058	7.67	4.99	12.05
ASN5	III	−491.127581	0.133987	−490.993594	8.89	2.46	12.97
ASN6	I $NH…O^{sc}$	−491.127864	0.134358	−490.993506	9.12	4.20	10.54
ASN7	I $NH…O^{sc}$	−491.127663	0.134341	−490.993322	9.61	5.32	10.96
ASN8	II $NH…O^{sc}$	−491.126501	0.133753	−490.992747	11.11	3.39	15.52
ASN9	III $N…HN^{sc}$	−491.126732	0.134158	−490.992574	11.57	5.75	14.23
ASN10	IV $OH…O^{sc}$	−491.125992	0.133691	−490.992301	12.29	7.02	15.52
ASNX	I $O..HN^{sc}$	−491.125917	0.134893	−490.991024	15.64	3.58	[e]

[a] ZPE values scaled with the uniform scaling factor 0.97.
[b] ZPE corrected energies included.
[c] Energy difference between the different conformations relative to the most stable conformation ASN1.
[d] Values obtained by Chen et al. [10]
[e] No values reported for this conformation. [10]
[f] ASN is included as most stable conformations with amino acid backbone type III.