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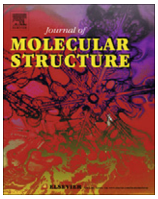

Conformational profile and vibrational assignments of hippuric and 4-aminohippuric acids

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ABSTRACT

The structural stability of hippuric acid and 4-aminohippuric acid was investigated for comparison purpose by the DFT-B3LYP and *ab initio* MP2 calculations with the 6-311G** basis set. From the calculations at both levels of theory the near-planar *Ctcnp* structure was predicted to be the lowest energy minimum for the two acids. The stability of the corresponding planar structure (*Ctcp*) was predicted to significantly decrease (6 kcal/mol) as going from the parent acid to the 4-amino derivative. The *Tgcnp* structure was predicted to be about 1 kcal/mol higher in energy than the most stable *Ctcnp* structure in both acids. The NH_2 inversion barrier was estimated from the planar *Ctcp* structure to be about 4 kcal/mol. The zwitterion structure was predicted to be about 45 and 50 kcal/mol higher in energy than the ground state conformation in the two acids, respectively, as a result of strong conjugation between the N atom of the —NH moiety and the carbonyl —C=O of the benzoyl group. The vibrational frequencies of the lowest energy *Ctcnp* conformer of hippuric and 4-aminohippuric acids were computed at the B3LYP/6-311G** level of theory. A comparison of the vibrational assignments for the two acids was provided on the basis of combined experimental and theoretical data.

1. Introduction

The structural stability of the phenoxyacetic acid herbicide and its 2,3,4,5,6-pentafluoro and 2,4-dichloro derivatives has been recently investigated at the DFT-B3LYP/6-311G** and MP2/6-311G** levels of theory [1,2]. Comprehensive vibrational assignments for the three acids were also provided by combining experimental infrared and Raman spectra and theoretical data [1,2]. From the calculations contradicted results were obtained by the DFT and the Møller–Plesset levels about the nature of the first and the second stable structures of both phenoxyacetic acid and its pentafluoride [1].

The planar *Tttp* (*transoid* O=C—O—H) of phenoxyacetic acid was predicted at the DFT-B3LYP level to be about 0.5 and 1.3 kcal/mol lower in energy than the non-planar *Cgcpp* and *Tgcpp* (*cisoid* O=C—O—H) forms, respectively. The stability of the *Tttp* form was reported to be a result of a 5-membered H-bonding between the phenoxy oxygen atom and the hydroxyl hydrogen atom. However, at the MP2 and the MP4(SDQ) levels the *Cgcpp* form of the acid was predicted to be about 0.8 and 1.4 kcal/mol lower in energy than the *Tgcpp* and *Tttcp* structures, respectively [1].

For 2,4-dichlorophenoxyacetic acid the *Cgcpp* structure was predicted by the DFT-B3LYP and MP2 levels to be the lowest energy minima for the acid [2]. Similar to the case of the parent and pentafluoro acids, the two levels disagreed about the nature of the second stable structure of the dichloride. At the DFT-B3LYP level of calculations the planar *Tttp* (*transoid* O=C—O—H) and the non-planar *Tgcpp* (*cisoid* O=C—O—H) forms were predicted to be 0.7 and 1.5 kcal/mol, respectively, higher in energy than the *Cgcpp* conformation. At the MP2 level the two high-energy *Tttp* and *Tgcpp* forms were predicted to be 2.7 and 1.4 kcal/mol, respectively, higher in energy than the ground state *Cgcpp* structure.

On the basis of the fact that Møller–Plesset calculations account for the non-bonding O⋯H interactions better than DFT calculations do [3], the *Cgcpp* and the *Tgcpp* conformations were adopted as the low and the high-energy structures of phenoxyacetic, 2,3,4,5,6-pentafluoro- and 2,4-dichlorophenoxy acids [1,2]. The stability of the non-planar *Cgcpp* and *Tgcpp* conformers and the prediction of a significant change in the calculated total dipole moments as going from one conformer to another in all three acids implied that steric forces and dipolar interactions play a very competitive role in governing the ground state structure of the phenoxyacetic acids [1,2].

As a continuation of the interest in the properties of biologically active carboxylic acids, the structure and vibrational spectra of 4-aminohippuric acid were analyzed in the present study and compared to the parent hippuric acid. The energies of the two molecules in their possible structures were optimized at the DFT-B3LYP and the *ab initio* MP2 calculations using the 6-311G** basis

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set. The vibrational frequencies were computed at the B3LYP level. The vibrational assignments of the normal modes were made on the basis of the calculated and available observed infrared and Raman spectra of the molecule. A detailed comparison of the vibrational assignments of the infrared and Raman spectra of the two acids were also carried out. The results of the work are presented herein.

2. Computational detail

The GAUSSIAN 03 program [4], running on a 128-node high-performance e-1350 IBM cluster was employed to carry out the DFT-B3LYP and MP2 calculations utilizing the 6-311G** basis set. The possible structures of hippuric acid and 4-aminohippuric acid were optimized and their energies and dipole moments were calculated at both levels of theory. The relative energies of the more stable conformations for the two acids are shown in Tables 1 and 2. The lowest three structures of hippuric acid were also calculated using the MP4(SDQ)/6-311G** level of theory (Table 1). The possible conformations of the zwitterions in the parent acid and its 4-amino derivative were also calculated. Fig. 1S shows the structure of the zwitterion of the *ZCtcp* form. The lowest energy structures (the *Ctcnp* form) of the two acids are shown in Fig. 1. The calculated optimized structural parameters and total energies of the possible conformations for the molecules are listed in Tables 1S–6S.

The optimized structural parameters of hippuric acid and 4-aminohippuric acid in their low-energy near-planar *Ctcnp* conformation (Tables 5S and 6S) were used to calculate the vibrational wavenumbers at the B3LYP/6-311G** level of theory. Comprehensive assignments of the normal vibrational modes of the two acids were proposed on the basis of calculated and experimental infrared and Raman spectra. The vibrational assignments are listed in Table 3. The infrared and Raman spectra of hippuric and 4-aminohippuric acids (Figs. 2 and 3) were obtained from the link: //www.aist.go.jp/RIODB/SDBS, Nos. 1717 and 1163, respectively.

3. Discussion

The interesting structural and biological properties of hippuric acid and their 4-amino derivative [5–10] have prompted us to investigate its conformational stability and vibrational spectra in the present study. In an early study Karabacak and co-authors investigated the molecular structure and vibrational spectra of hippuric acid [10]. They reported that there are four conformers for hippuric acid. These four structures were adopted only the planar structure where the phenyl group is planar with respect to the molecular plane [10]. In the present work the structural stability of hippuric acid and its 4-amino derivative was investigated thoroughly to explore the nature of the real ground state conformation of the two acids. The structural stability of hippuric acid is determined by a complex internal rotation of several rotors and the benzene ring as well. In addition, the stability of the zwittwerion structures was also investigated in the study.

From the calculations, hippuric acid and 4-aminohippuric acid were predicted by the DFT-B3LYP and MP2 calculations to exist predominantly in the near-planar *Ctcnp* conformation (Fig. 1), and not in the planar *Ctcp* form as reported for the parent hippuric acid [10]. The repulsive interaction between the N—H and the ring C—H bond seem to destabilize the molecules in the planar *Ctcp* structure which was calculated to be 1–2 kcal/mol higher in energy than the corresponding near-planar form in both acids (Tables 1 and 2). The non-bonding $H\cdots H$ distance between the NH and CH (ring) moieties was calculated to be about 2 Å at all levels; which is short enough for intramolecular repulsive interaction that is expected to slightly destabilize the planar structure as compared with the near-planar one. The $H_{11}N_9C_1C_2$ torsional angle (Fig. 1) was calculated to be about 14° and 17° in hippuric acid and 4-aminohipperic acid, respectively. This shows the effect of the $H\cdots H$ steric hinderance in destabilizing the the planar structures of the acids. Similar to aniline [11] the two N—H bonds of the amino group in 4-aminohippuric acid are predicted to be directed symmetrically towards the same side of the benzene ring. The NH_2 inversion barrier was estimated from the planar *Ctcp* structure (Table 3S) to be about 4 kcal/mol as compared to 3.5 kcal/mol in the case of aniline [11].

A comparison between the calculated structural parameters of the near-planar ground state (*Tgcnp*) of the two acids by the DFT-B3LYP and Møller–Plesset calculations shows a noticeable difference in the calculated $O_{13}C_{12}C_{10}N_9$, $C_{12}C_{10}N_9C_1$ torsional angles (Tables 1 and 2). This significant change is due to the fact that the MP2 calculations account better for non-bonding interactions than the DFT calculations [1,3,12]. Furthermore, the zwitterion structures (Fig. 1S) in the two acids were predicted to be approximately 50 kcal/mol higher in energy than the ground state conformation as a result of the conjugation between the amino N atom and the benzoyl carbonyl group (Tables 1 and 2). The conjugation effect increases the sp^2 character of the nitrogen atom and creates a partial π character along the C—N bond; which significantly stabilizes the planar and not the pyramidal -NH moiety.

Table 1

Calculated[a] relative energies ΔE (kcal/mol) of the main possible structures of hippuric acid (*C* = cis, *T* = trans, *g* = gauche, *n* = near, *p* = planar, *pp* = perpendicular, *Z* = zwitterion) at the B3LYP/6-311G**, MP2/6-311G** and MP4(SDQ)/6-311G** levels of theory.

Structure[b]	B3LYP/6-311G**		MP2/6-311G**	
	(ϕ_1, ϕ_2, ϕ_3, ϕ_4, ϕ_5, ϕ_6)	ΔE	(ϕ_1, ϕ_2, ϕ_3, ϕ_4, ϕ_5, ϕ_6)	ΔE
Ctcnp	(−2, 166, 3, −18, 0, 162)	0.000	(−5, 168, 5, −26, 0, 156)	0.000
Ctcp	(0, 180, 0, 0, 0, 180)	0.191	(0, 180, 0, 0, 0, 180)	0.808
Tgcnp	(179, 99, 6, −22, 1, 157)	2.346	(−159, 65, 9, −27, 1, 143)	1.082
Ctcpp	(0, 180, 0, 90, 0, 180)	4.261	(0, 180, 0, 90, 0, 180)	3.543
Ttcp	(180, 180, 0, 0, 0, 180)	3.010	(180, 180, 0, 0, 0, 180)	3.395
ZCtcp	(0, 180, 0, 0, 125, −125)	46.114	(0, 180, 0, 0, 125, −125)	46.584
MP4(SDQ)/6-311G**				
Ctcnp			(−2, 166, 3, −18, 0, 162)	0.000
Ctcp			(0, 180, 0, 0, 0, 180)	0.653
Tgcnp			(−159, 65, 9, −25, 1, 142)	1.198

[a] The calculated total energies (hartree) of the *Ctcnp* conformer of hippuric acid are: −629.006483, −627.276727 and −627.326399 at the DFT, MP2 and MP4 levels of theory, respectively. See Tables 1S and 2S for more details.

[b] ϕ_1, ϕ_2, ϕ_3, ϕ_4, ϕ_5 and ϕ_6 are the optimized $O_{13}C_{12}C_{10}N_9$, $C_{12}C_{10}N_9C_1$, $C_{10}N_9C_1O_8$, $O_8C_1C_2C_3$, $H_{15}O_{14}C_{12}O_{13}$, $H_{11}N_9C_1C_{10}$ torsional angles, respectively (see Fig. 1). For zwitterions, ϕ_5 and ϕ_6 are the two $HN_9C_1C_{10}$ torsional angles.