A conformational analysis of histamine, and its protonated or deprotonated forms: An ab initio study

ARTICLE *in* JOURNAL OF MOLECULAR STRUCTURE THEOCHEM · DECEMBER 2003

Impact Factor: 1.37 · DOI: 10.1016/j.theochem.2003.08.024

4 AUTHORS:

Istvan Mandity

University of Szeged

38 PUBLICATIONS **580** CITATIONS

SEE PROFILE

Gabor Paragi

University of Szeged

31 PUBLICATIONS **193** CITATIONS

SEE PROFILE

Ferenc Bogár

University of Szeged, Hungarian Academy of…

75 PUBLICATIONS **486** CITATIONS

SEE PROFILE

Imre G. Csizmadia

University of Miskolc

534 PUBLICATIONS **7,299** CITATIONS

SEE PROFILE

ELSEVIER

Journal of Molecular Structure (Theochem) 666–667 (2003) 143–152

THEO CHEM

www.elsevier.com/locate/theochem

A conformational analysis of histamine, and its protonated or deprotonated forms: an ab initio study

I.M. Mandity[a,*], G. Paragi[b], F. Bogár[b], I.G. Csizmadia[c,d,e]

[a]*Institute of Pharmaceutical Chemistry, Szent-Gyorgyi Medical Center, University of Szeged, Eotvos utca 6, Szeged H-6720, Hungary*

[b]*Protein Chemistry Research Group of Hungarian Academic of Science, University of Szeged, Dom ter 8, Szeged H-6720, Hungary*

[c]*Department of Chemistry, University of Toronto, 80 St. George St., Toronto, Ont., Canada M5S 3H6*

[d]*Department of Medical Chemistry, Szent-Gyorgyi Medical Center, University of Szeged, Dom ter 8, Szeged H-6720, Hungary*

[e]*Global Institute of Computational Molecular and Materials Science (GIOCOMMS), 1422 Edenrose St., Mississauga, Ont., Canada L5V 1H3*

Abstract

Histamine, a neurotransmitter contains an imidazole ring which may be protonated or deprotonated. The present study was dedicated to the two tautomeric and their protonated and deprotonated forms. Throughout the whole study, the side chain nitrogen was kept in its protonated form. Potential energy surface scanning and reaction path calculation between two optimized conformations were carried out using restricted Hartree-Fock method with 3-21G basis set (RHF/3-21G).

Keywords: Histamine; Conformers; RHF/3-21G; DDRP; Conformational analysis

1. Introduction

Histamine is an important biological molecule, which has different activities in animal organisms. (The standard nomenclature for this molecule is 1*H*-imidazole-4(5)-ethanamine. However, (2-aminoethyl)imidazole and following Ganellin, β-(4-imidazolyl)ethylamine, are also used.) This compound also appears in plant tissues. Histamine mediates with at least three different biological receptors: H_1, H_2 and H_3 [1].

The two nitrogens of the imidazole ring are in the 1, 3 position. The H^+ can be localized on the 1 or on the 3 nitrogen of the aromatic system, and the ring can be deprotonated and protonated, as shown in Fig. 1.

This biogenic amine is formed by the metabolization [2] of an important amino acid Histidine (His). We might mention, in passing, that histidine is an essential amino acid. This amino acid must be presented in sufficient quantities in the diet for proper functioning of the human body. Histamine may be oxidized by the monoamine oxidize enzyme and by

* Corresponding author.
E-mail address: mandity@ovrisc.mdche.u-szeged.hu (I.M. Mandity).

0166-1280/$ - see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.theochem.2003.08.024

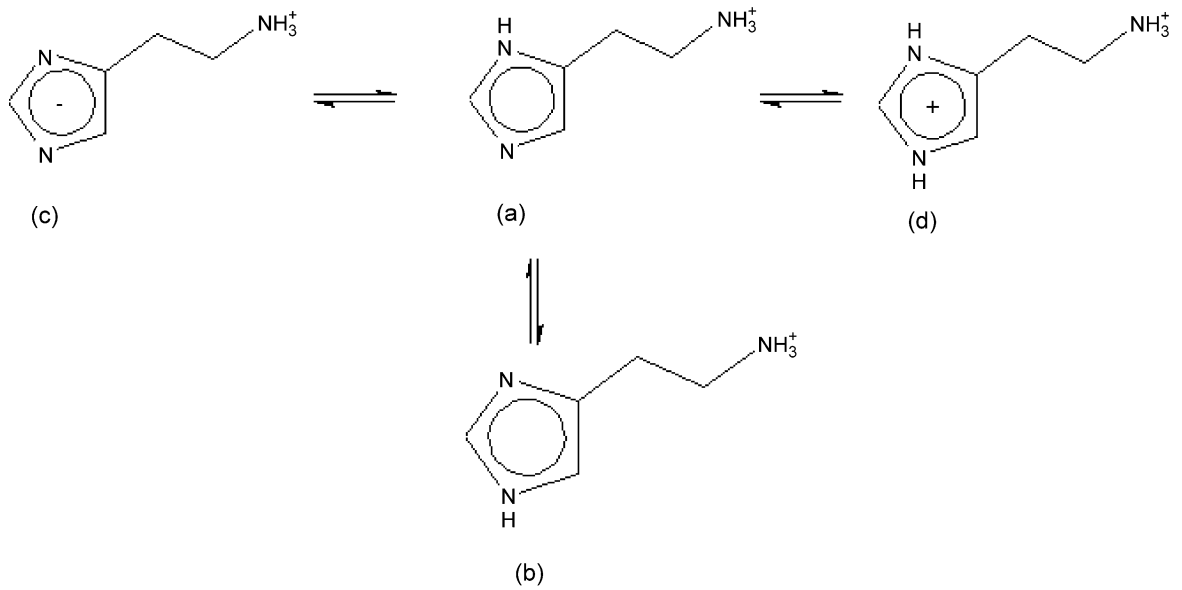

Fig. 1. The four forms of histamine. (a) Side chain protonated histamine, tautomeric form 1. (b) Side chain protonated histamine, tautomeric form 2. (c) Side chain protonated ring deprotonated histamine. (d) Side chain protonated ring protonated histamine.

the diamine oxidize enzyme as well, which is shown in Fig. 2.

When a systematic protonation is made on the imidazole ring, one would expect that such a change would manifest itself in the potential energy surface (PES). It may alter the appearance of the surface, or even its topology as well as the location and the energy values of the optimized minima.

2. Computational method

The molecular structure, stereochemistry, and geometry of protonated, deprotonated and the two tautomeric forms of histamine were exclusively defined in terms of their *z*-matrix internal co-ordinate system. PES were calculated with 144 points at 30° increments at the RHF/3-21G level of theory. Corresponding minima from the PES were selected and full optimizations were carried out successively at the RHF/3-21G level of theory. Further reaction path analysis were performed between two minima using the Dynamically Defined Reaction Path method (DDRP) [3]. The reaction path investigation was also performed with RHF/3-21G energy calculation. According to our knowledge, it was the first time when this method was used at this level of theory. We also made semiempirical study with DDRP, but the transition state structure seemed to be irrelevant. The GAUSSIAN98 [4] program was used to carry out all the ab initio computations, and the DDRP calculations were performed with modified Tinker program package [3,5] in combination with the GAUSSIAN98 code.

3. Results and discussions

3.1. Conformational analysis

The four compounds studied [6] conformationally in the present work are shown in Fig. 3. All of them were treated as double rotors. Torsional angle χ_1 was associated with the rotation of the imidazole group, while torsional angle χ_2 was associated with the rotation of the $-CH_2-NH_3^+$ group.

The conformational PES as described by the equation $E = E(\chi_1, \chi_2)$ was computed and plotted

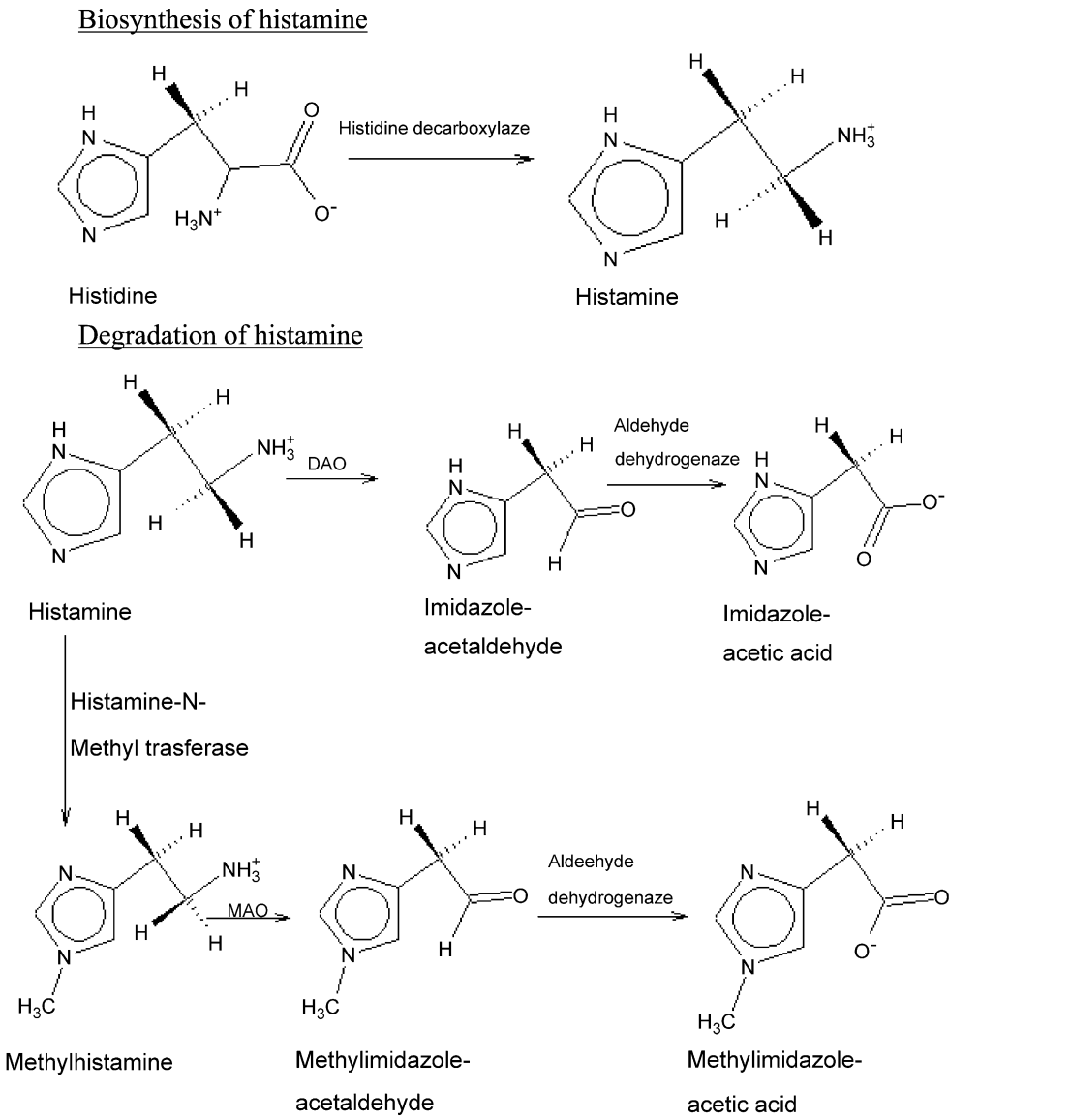

Fig. 2. A schematic representation of the metabolism of histamine.

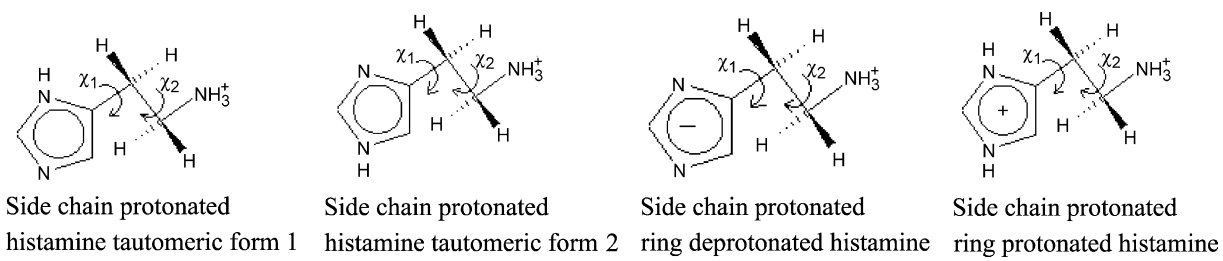

Fig. 3. Structure of the four compounds studied.

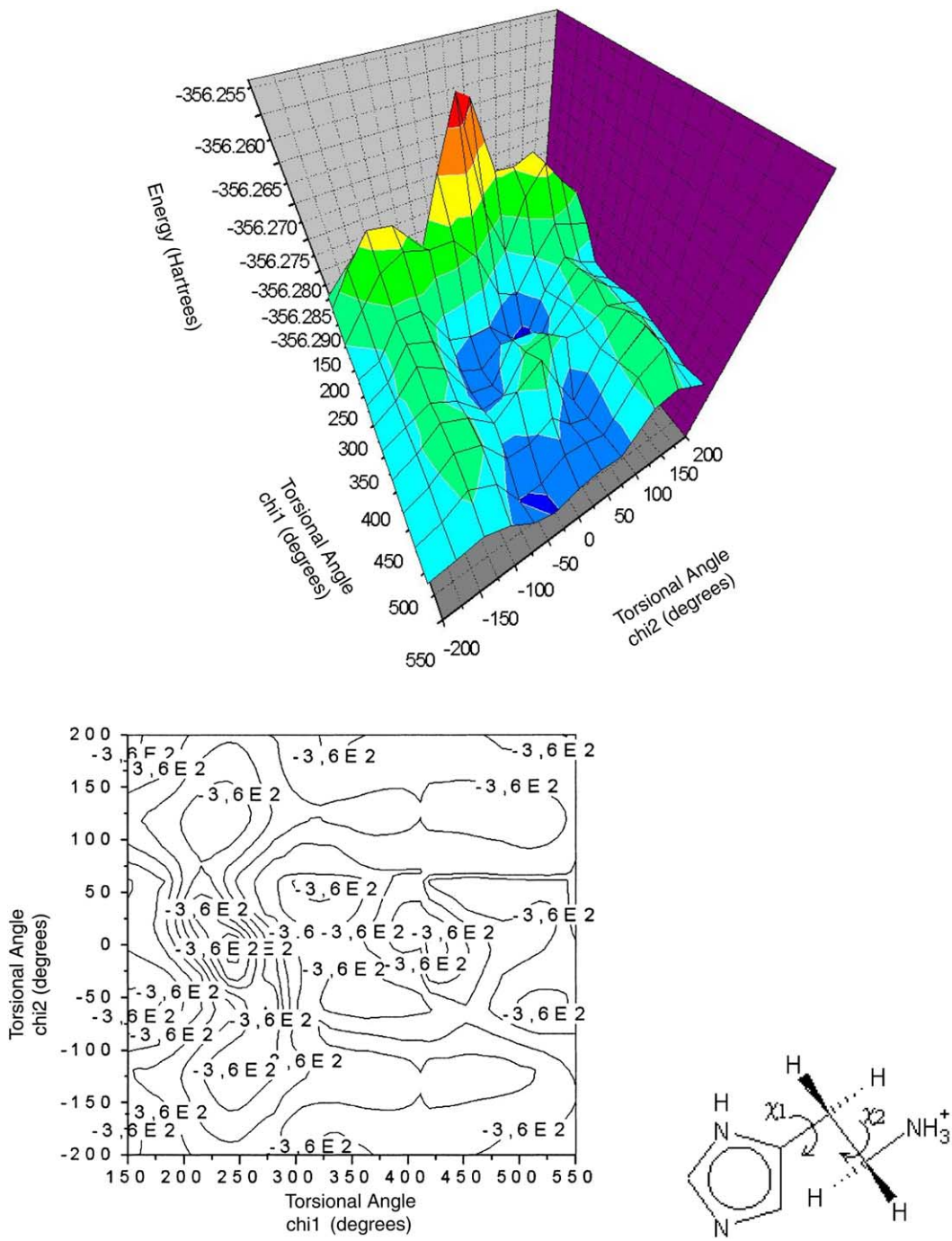

Fig. 4. Side chain protonated histamine tautomeric form 1 conformational surface (up) and contour (bottom).

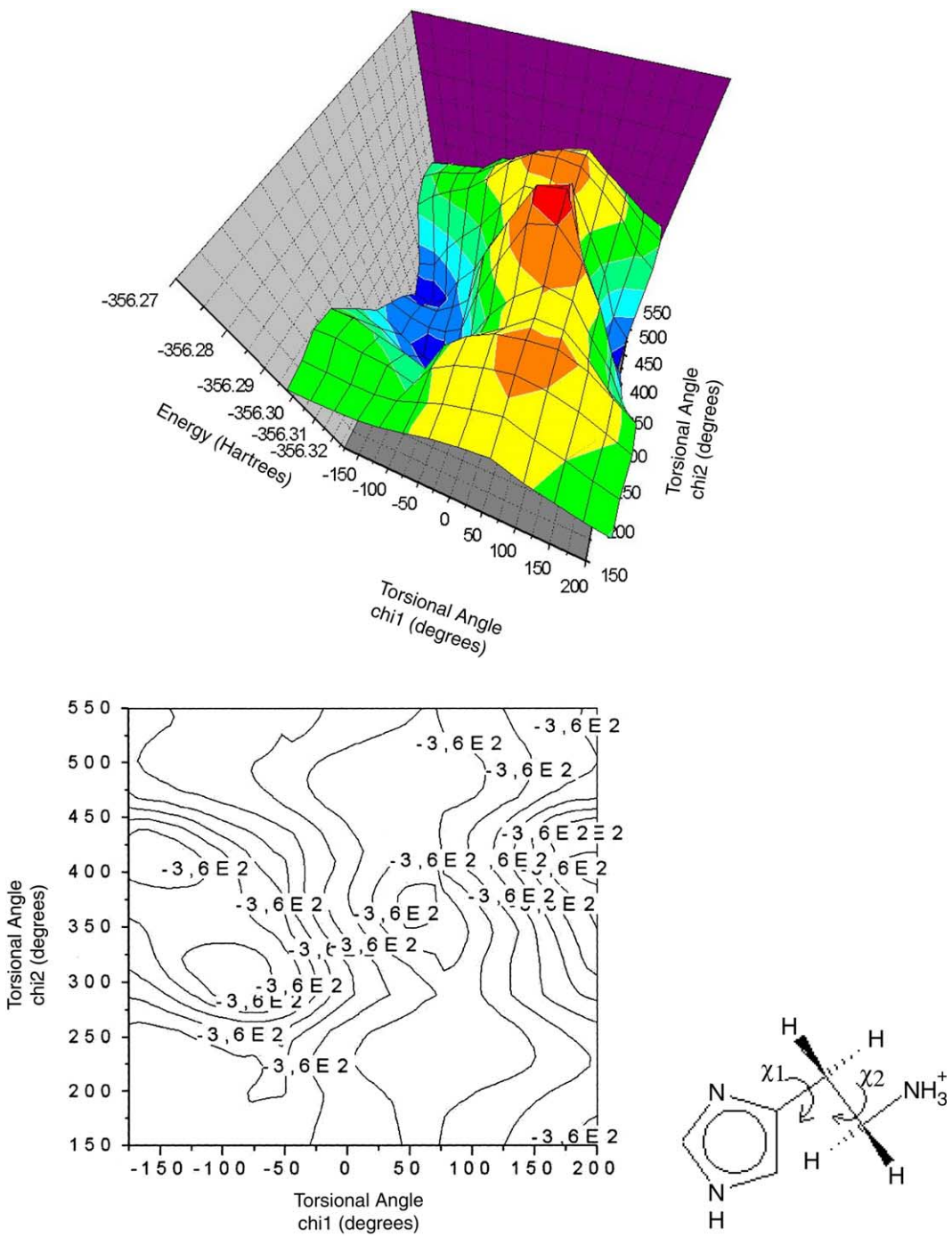

Fig. 5. Side chain protonated histamine tautomeric form 2 conformational surface (up) and contour (bottom).

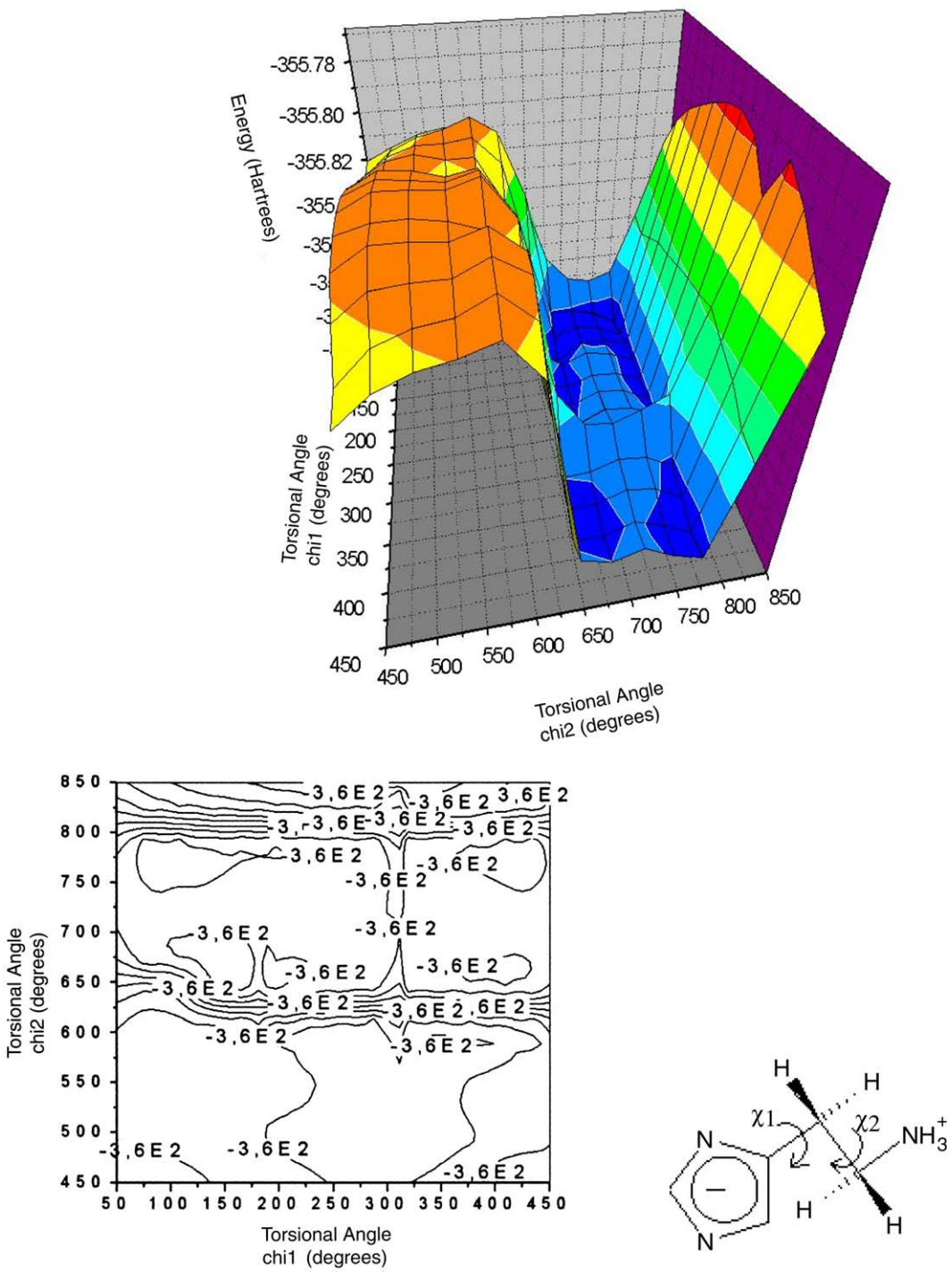

Fig. 6. Side chain protonated ring deprotonated form of histamine conformational surface (up) and contour (bottom).

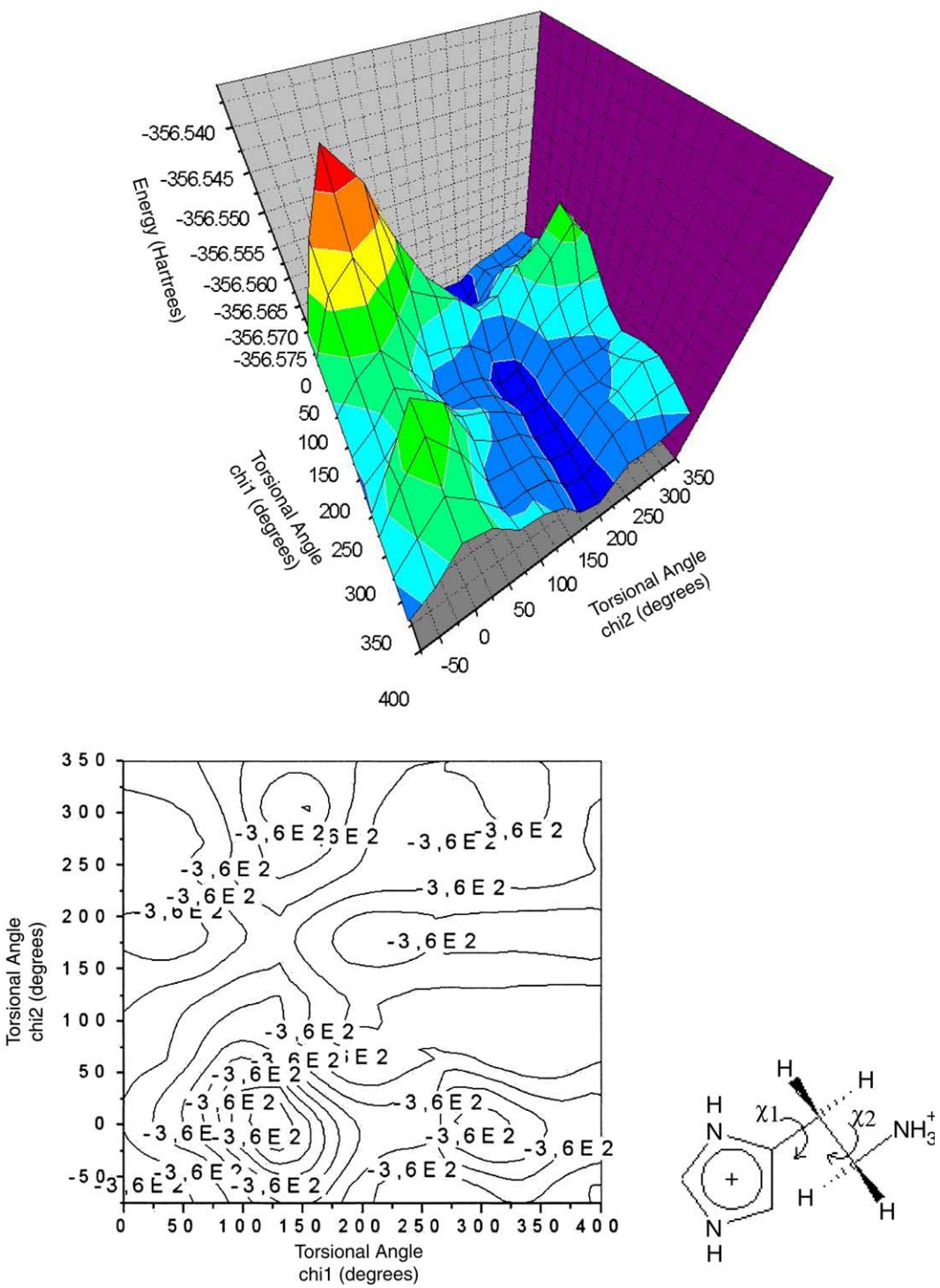

Fig. 7. Side chain protonated ring protonated form of histamine conformational surface (up) and contour (bottom).

Table 1
Optimized energy (in Hartree) and dihedral angles (in degree) of minima for side chain protonated histamine tautomeric form (1)

χ_1 (degree)	χ_2 (degree)	Energy (Hartree)
333.82021	61.84213	−356.28784
513.82021	−58.15787	−356.28874
453.82021	61.84213	−356.28629
333.82021	−58.15787	−356.28673

Table 2
Optimized energy (in Hartree) and dihedral angles (in degree) of minima for side chain protonated histamine tautomeric form (2)

χ_1 (degree)	χ_2 (degree)	Energy (Hartree)
−103.20718	318.45509	−356.32642
−163.20718	408.45509	−356.32774

Table 3
Optimized energy (in Hartree) and dihedral angles (in degree) of minima for side chain protonated ring deprotonated histamine

χ_1 (degree)	χ_2 (degree)	Energy (Hartree)
436.98255	762.27031	−355.90826
406.98255	642.27031	−355.90450
106.98255	792.27031	−355.90946
106.98255	642.27031	−355.91193

for each of the four forms of side chain protonated histamine. The graphical representation of the four PESs are shown in Figs. 4–7, respectively.

The conformational and energetic characteristics of the optimized structures of the four forms of side chain protonated histamine are summarized in Tables 1–4. The conformers which have the lowest total energy are shown in Fig. 8. The conformer of side chain protonated histamine

Table 4
Optimized energy (in Hartree) and dihedral angles (in degree) of minima for side chain protonated ring protonated histamine

χ_1 (degree)	χ_2 (degree)	Energy (Hartree)
35.04327	181.8951	−356.57623
245.04327	181.8951	−356.57514

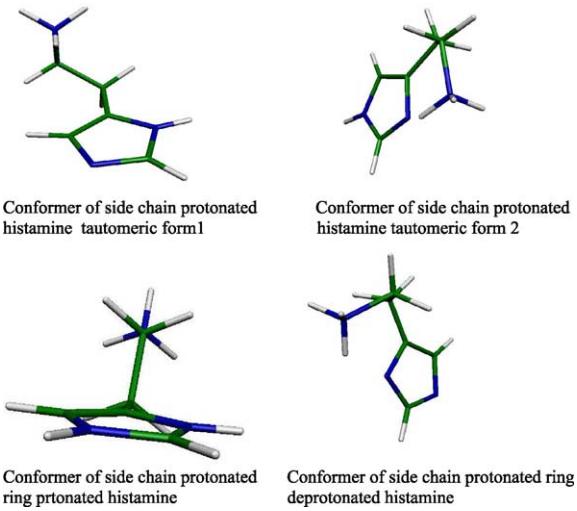

Fig. 8. The four conformers, which have the lowest total energy.

tautomer (1), the conformer of side chain protonated histamine tautomer (2) and the conformer of side chain protonated ring deprotonated histamine have intramolecular hydrogen bound between one of the hydrogens of the NH_3^+ group and one of the nitrogens in the imidazole ring. The conformer of the side chain protonated ring protonated histamine is the *anti* conformer.

3.2. The path way between two minima of side chain protonated histamine tautomeric form (1) (DDRP)

The PES can help us to see how the molecule from an optimized conformation can transform into another one. However, it is always an important question the height of the potential barrier between the two minima, and the transition state of the molecule. Furthermore, the scanning of the whole PES is a very time consuming task, which cannot be performed in many cases. The reaction path methods simplify these tasks, and furthermore, they can help us to scan the 'physically interesting' part of the surface. With the DDRP method, we connected successfully the two minima of the side chain protonated histamine tautomeric form (1). The change of the energy and conformation along the path is shown in Fig. 9. The frequency analysis showed that the conformation belongs to the maximal energy on the path was

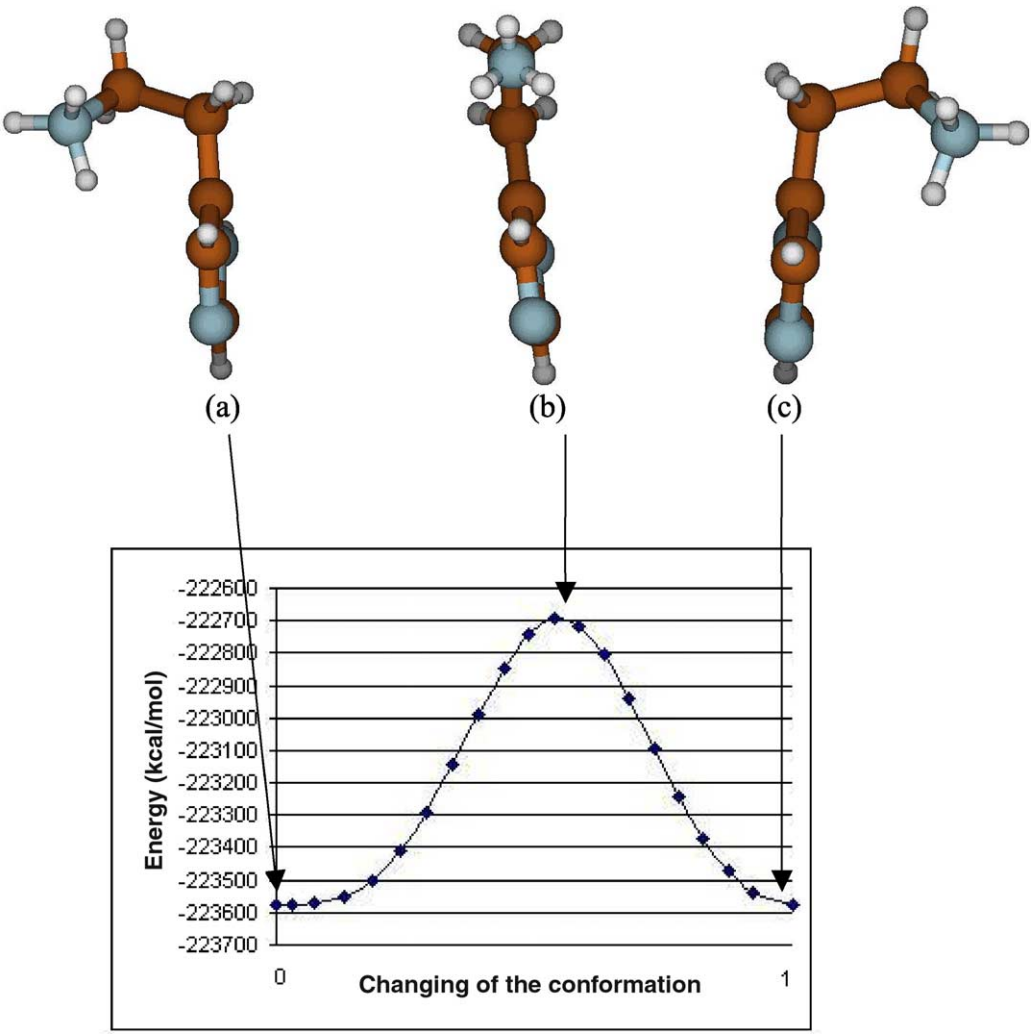

Fig. 9. The changing of the energy and conformation during the path.

a transition state. The conformation of the transition is shown in Fig. 9(b). The height of the potential barrier along the path is 853.15567 kcal/mol.

Acknowledgements

One of us (IGC) would like to thank the Ministry of Education for a Szent-Györgyi Visiting Professorship.

References

[1] A. Hernandez-Laguna, Z. Cruz-Rodriguez, Y.G. Smeyers, G.A. Arteca, J.-L.M. Abboud, O. Tapia, J. Mol. Struct. (Theochem) 335 (1995) 77–87.
[2] B.G. Katzug, Basic and Clinical Pharmacology, eighth ed., Lange Medical Books/McGraw-Hill, Toronto/New York, 2001.
[3] L.L. Stachó, M.I. Bán, Theor. Chim. Acta 83 (1992) 433.
[4] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi,

V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, and J.A. Pople, GAUSSIAN'98, Revision A.7, Gaussian, Inc., Pittsburgh, PA, 1998.

[5] P. Ren, J.W. Ponder, J. Comput. Chem. 23 (2002) 1497–1506.

[6] D.M. Gasparo, D.R.P. Almeida, S.M. Dobo, L.L. Torday, A. Varro, J.Gy. Papp, J. Mol. Stuct. (Theochem) 585 (2002) 167–179.