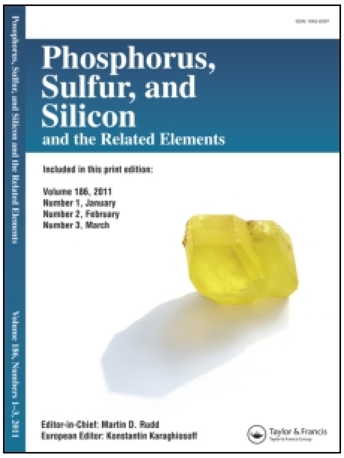

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Slow Inversion of Stereoisomers of 4-Amino-1-benzylpiperid-4-yl Phosphonic Acids and Their Esters

Rafał Latajka[a]; Roman Gancarz[a]; Paweł Kafarski[a]
[a] Institute of Organic Chemistry, Biochemistry, and Biotechnology, Wrocław University of Technology, Wrocław, Poland

To cite this Article Latajka, Rafał , Gancarz, Roman and Kafarski, Paweł(2002) 'Slow Inversion of Stereoisomers of 4-Amino-1-benzylpiperid-4-yl Phosphonic Acids and Their Esters', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 6, 1575 — 1577

To link to this Article: DOI: 10.1080/10426500212212

URL: http://dx.doi.org/10.1080/10426500212212

Phosphorus, Sulfur and Silicon, 2002, Vol. 177:1575–1577

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290093360

SLOW INVERSION OF STEREOISOMERS OF 4-AMINO-1-BENZYLPIPERID-4-YL PHOSPHONIC ACIDS AND THEIR ESTERS

Rafał Latajka, Roman Gancarz, and Paweł Kafarski
Institute of Organic Chemistry, Biochemistry, and Biotechnology, Wrocław University of Technology, Wrocław, Poland

(Received July 29, 2001; accepted December 25, 2001)

Depending on the pH of the medium or temperature, one or two phosphorus signals were observed on ^{31}P NMR spectra of 4-aminopiperid-4-yl phosphonic acids, indicating slow conformational ring interconversion. The experimental data have been correlated with theoretical results obtained by calculations using semiempirical methods (PM3), DFT, and the Poralized Continuum Model (PCM) for the description of water environment.

Keywords: Cyclic GABA analogues; DFT; PCM; phosphonates; ^{31}P NMR

INTRODUCTION

4-Aminobutyric acid (GABA) is one of the most widely distributed inhibitory neurotransmitters in central nervous system (CNS).[1] In recent years GABA-related drugs have shown promising properties as antiepileptic, antispastic, and antidepressive agents.[2] For this reason, a number of new potential analogues which are more selective for GABA receptors have been found.[3] Among them, the piperidine-4-sulfonic acid has been found to be a highly potent GABA antagonist. Also, the replacement of the carboxylic moiety by a phosphonic acid function gave similar activity. In the course of our studies on the synthesis of new phosphonic GABA analogues, we have observed a peculiar, fully reversible conformational equilibrium in this group of compounds, which is easily detectable by NMR spectroscopy. Depending on the pH of the

---

Address correspondence to Rafał Latajka, Institute of Organic Chemistry, Biochemistry, and Biotechnology, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland. E-mail: latajka@kchf.ch.pwr.wroc.pl

medium and temperature, one or two phosphorus signals were observed in ^{31}P NMR spectra of 4-aminopiperid-4-yl phosphonic acid derivatives. Our experimental studies have shown that the occurrence of this phenomenon is connected with processes of protonation and solvatation of amino group.[4]

RESULTS AND DISCUSSION

Spectroscopic data suggested that in acidic solution, where two phosphorus signals were observed, predominates form where phosphonic group is in axial position to piperidine ring. In basic medium only one equatorial form was observed.[4] Theoretical calculations were made for the model case of dimethyl ester of 1-aminocyclohexa-1-yl phosphonic acid. The results for gas phase, obtained by use MNDO-PM3 and DFT methods, are presented in Table I. They suggested that the greatest stability is observed for two isomers, where phosphonic group is in equatorial orientation to cyclohexane ring (compounds I and II).

In the case when amino group is protonated, the situation is different (see Table II). The calculations which were made (using PM3 method) for the protonated form of compounds I and III have shown that in this case axial form (III) is more stable then equatorial (I)—the difference in values of energy is 1.24 kcal/mol. The influence of water solvent ($\varepsilon = 78.39$) was investigated by means of Polarized Continuum Model (PCM). In this case, for unprotonated forms the difference of values of

TABLE I Structural Parameters Obtained by PM3 and DFT Methods (Bond Lengths in Å, Angles in Degrees)

Parameter	I	II	III	IV
r(C—N)	1.488	1.488	1.491	1.497
r(C—P)	1.897	1.881	1.887	1.883
r(P=O)	1.459	1.463	1.462	1.459
Θ(P—C—N)	114.02	110.1	103.7	94.1
Θ(C—P=O)	118.6	118.7	119.5	120.8
Θ(C—P—O)	104.1	101.5	103.5	102.4
ϕ(P—C—C—C)	−170.1	173.4	−80.0	87.4
ϕ(N—C—C—C)	65.6	−68.0	168.0	−170.0
E^{BLYP*}	−937.21528	−937.20578	−937.21330	−937.20625
ΔE^{BLYP**}	0.0	5.96	1.24	5.67
$E^{G96PW91*}$	−937.38851	−937.37936	−937.38554	−937.37824
$\Delta E^{G96PW91**}$	0.0	5.74	1.86	6.44

*Values of energy in atomic units (1 a.u. = 627.5092 kcal/mol).

**Values of energy in kcal/mol.

TABLE II Energetic Properties of Conformers of Dimetyl Ester of 1-Aminocyclohexa-1-yl Phosphonic Acid

	Equatorial structure (I)		Axial structure (III)	
	E(a.u.)	ΔE (kcal/mol)	E(a.u.)	ΔE (kcal/mol)
Gas phase				
NH_2	−937,21528	0,0	−937,21330	1,24
NH_3^+	−937,58432	2,33	−937,58803	0,0
Water				
NH_2	−937,22135	0,0	−937,22065	0,44
NH_3^+	−937,66507	3,05	−937,66993	0,0
ΔG_{hydr}^*				
NH_2	−3,81		−4,61	
NH_3^+	−50,67		−51,39	
Energy* of protonation				
Gas phase	−231,6		−222,8	
Water	−278,4		−281,9	

*In kcal/mol.

energy is lower than in gas phase, whereas for protonated compounds difference in values of energy between axial and equatorial structures increase to 3.05 kcal/mol (see Table II).

The results of theoretical calculations are in good agreement with experimental data obtained by means of NMR spectroscopy.

REFERENCES

[1] J. Kehler, B. Ebert, O. Dahl, and P. Krogsgaard-Larsen, *Tetrahedron*, **55,** 771–780 (1999).
[2] F. Fonnum, *Psychopharmacology*, **18,** 173–182 (1987).
[3] R. I. Brinkworth, E. J. Lloyd, and P. R. Andrews, *Nat. Prod. Rep.*, **5,** 363–386 (1988).
[4] R. Gancarz, R. Latajka, A. Halama, and P. Kafarski, *Magn. Reson. Chem.*, **38,** 867–871 (2000).