



PHYSICAL CHEMISTRY 2012

^{11th} International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

Under the auspices of the
University of Belgrade

Proceedings

The Conference is dedicated to
Professor Ivan Draganić

September 24-28, 2012
Belgrade, Serbia

ISBN 978-86-82475-27-9 <i>Volume 1</i> ISBN 978-86-82475-28-6 <i>Volume II</i>

Title: PHYSICAL CHEMISTRY 2012 (Proceedings)

Editors: S. Anić and Ž. Čupić

Published by: Society of Physical Chemists of Serbia, Studenski trg 12-16, 11158, Belgrade, Serbia

Publisher: Society of Physical Chemists of Serbia

For Publisher: S. Anić, President of Society of Physical Chemists of Serbia

Printed by: “Jovan” Printing and Publishing Company; 200 Copies;

Number of pages: 6+ 497; **Format:** B5; Printing finished in September 2012.

Text and Layout: “Jovan”

200- Copy printing

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PHYSICAL CHEMISTRY 2012

*11th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry*

*Under the auspices of the
University of Belgrade*

*Organized by
The Society of Physical Chemists of
Serbia*

*in co-operation
with*

Institute of Catalysis Bulgarian Academy of Sciences

*Boriskov Institute of Catalysis of Siberian Branch of the Russian Academy
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QUANTUM MECHANICAL AND SPECTROSCOPIC INVESTIGATIONS OF POTENT ANTIEPILEPTIC DRUG 1-(4-CHLORO-PHENYL)-3-PHENYL-SUCCINIMIDE

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Abstract

This study represents an integrated approach towards understanding the vibrational, electronic, NMR, reactivity and structural aspects of 1-(4-Chloro-phenyl)-3-phenyl-succinimide (CPPS). Theoretical calculations were performed by density functional theory (DFT)/B3LYP method using 6-311++G(d,p) basis set. The scaled theoretical wavenumber showed very good agreement with the experimental values. HOMO-LUMO energy gap for the title molecule has been analyzed. Furthermore, molecular electrostatic potential map (MEP) of the compound has been calculated.

Introduction

Succinimides and their derivatives have been considered as an important class of nitrogen-containing heterocycles. There has been increasing interest in the study of succinimides due to their anticonvulsant activity. Ethosuximide [1] is a succinimide anticonvulsant, used mainly in absence seizures. Methsuximide is an anticonvulsant with the therapeutic efficacy due to its pharmacologically active metabolite, *N*-desmethylnmethsuximid [2]. Phensuximide used to treat epilepsy and other seizure disorders [3].

Moreover, we are performing the synthesis and the properties relevant to pharmacokinetics of two series of newly synthesized succinimide derivatives [4]. Compound 1-(4-Chloro-phenyl)-3-phenyl-succinimide (CPPS) is one of the four agents picked as the best candidate for compromising the human intestinal absorption and plasma protein binding properties. To the best of our knowledge the spectroscopic properties of CPPS have not yet been studied in detail.

Experimental details

The chemical structure and purity of the synthesized compound was confirmed by its melting point, ¹H and ¹³C NMR, FT-IR and UV spectra. FT-IR spectra were recorded with a Bomem MB 100 spectrophotometer. The ultraviolet absorption spectrum of CPPS was examined in the range 200-500 nm using Shimadzu 1700 UV/Vis spectrophotometer. The UV pattern was taken from a 10⁻⁵ molar solution of CPPS, solved in ethanol. ¹H and ¹³C NMR spectra were recorded in CDCl₃ using

TMS as an internal standard on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz, respectively.

Computational details

All the calculations were performed using Gaussian 03 program package. Geometry of CPPS was fully optimized with DFT/B3LYP/6-311++G(d,p) method. The harmonic frequencies were calculated by B3LYP method using 6-311++G(d,p) basis set and then scaled by 0.9686. The assignments of the calculated wavenumbers were aided by the animation option of Gauss View 3.0 graphical interface from Gaussian programs. Furthermore, the theoretical vibrational spectra of the title compound are interpreted by means of Potential Energy Distribution (PED) using VEDA 4 program. ^1H and ^{13}C NMR chemical shifts are calculated with GIAO approach by applying B3LYP/6-311++G(d,p) method. The frontier molecular orbital energies and HOMO-LUMO energy gap are also calculated in the same method. UV absorption energies of this compound were calculated by TD-DFT method in ethanol solvent. To investigate the reactive sites of CPPS, the molecular electrostatic potentials for the 0.002 a.u. isosurfaces of electron density was evaluated using the B3LYP/6-311++G(d,p) method.

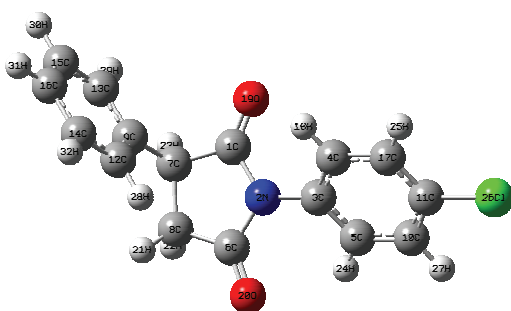


Figure 1. Optimized geometry of CPPS.

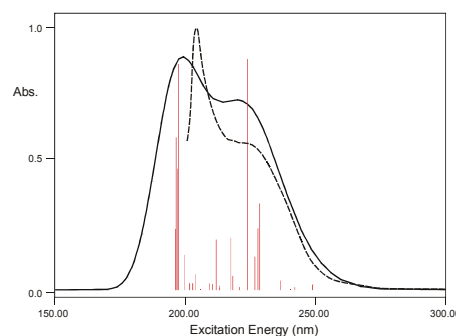


Figure 2. Experimental and predicted UV spectra of CPPS.

Results and Discussions

The molecular structure of the CPPS belongs to C1 point group symmetry. The optimized molecular structure of the title molecule was obtained from Gaussian 03 program as shown in Fig. 1. The minimum energy of the title compound was calculated by structure optimization at B3LYP/6-311++G(d,p) is -1282.59117675 a.u. To the best of our knowledge, exact experimental data on the geometrical parameters of CPPS are not available in the literature.

For CPPS the very weak absorption band at 3098 and 3062 cm^{-1} in FT IR are assigned to C-H stretching modes of the phenyl ring systems. The bands at 3031 and 2975 cm^{-1} are assigned to asymmetric and symmetric C-H stretching modes of the CH_2 -group, respectively. The pattern of band observed at 1781 and 1707 cm^{-1} in FT IR are assigned C=O stretch vibrations. The pattern of band

observed at 1625, 1283 and 1167 cm^{-1} are assigned as C-C stretching vibrations of the aromatic systems (skeletal vibrations). The aromatic C-H in- and out-of-plane bending vibrations are at 1196 and 950, 929, 842 cm^{-1} , respectively. In our present study the C-N stretching band is found to be present at 1234 cm^{-1} . All the calculated wavenumbers show excellent agreement with the experimental data.

In ^1H NMR spectra two doublets of doublets at 2.95 and 3.32 ppm mark the methylene hydrogens in the succinimide ring. The hydrogen atom of C-H group appears at higher chemical shift of 4.14 ppm due to influence of phenyl ring. Peaks at 7.22-7.46 ppm indicate the presence of aromatic hydrogen atoms, i.e. in the benzene rings. C3 and C4 in succinimide ring appear at lower chemical shift of 36.99 and 45.79 ppm due to neighbouring electronegative carbonyl groups. C2 and C5 of carbonyl groups are at 174.51 and 176.35 ppm. Peaks at 127.3-136.8 ppm were due phenyl groups. The predicted chemical shift values of DFT were in close agreement with the experimental.

As can be seen from the Figure 2, electronic absorption spectrum of CPPS shows three bands at 202, 204, and 224 nm, respectively. From TD-DFT calculation, the theoretical absorption bands are predicted at 193, 197 and 223 nm and can easily be seen that they correspond well with the experimental. The frontier orbitals, HOMO and LUMO determine the way a molecule interacts with other species. The frontier orbital energy gap for CPPS is -5.61 eV.

Molecular electrostatic potential surface map indicates that the most suitable atomic sites for electrophilic attack are O(19) and O(20) atoms, while the most probable sites which could be involved in nucleophilic process are at C(7) and C(8) atoms of succinimide ring.

Conclusion

Based on the density functional theory (DFT)/B3LYP/6-311++G(d,p) method, vibrational, electronic, NMR, reactivity and structural aspects of 1-(4-Chloro-phenyl)-3-phenyl-succinimide (CPPS) were studied in detail and the results were also compared with the experimental.

Acknowledgments

This work has been financially supported by Ministry of Education and Science, Republic of Serbia, under Grant No. 172035, 172013 and HP-SEE European project.

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CIP Volume I

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

544(082)
621.35(082)
66.017/.018(082)

MEĐUNARODNA konferencija iz fundamentalne i
primenjene fizičke hemije (11 ; 2012 ;
Beograd)

Physical Chemistry 2012 : proceedings.
#Vol. #1 / 11th International Conference on
Fundamental and Applied Aspects of Physical
Chemistry, September 24-28, 2012, Belgrade ;
[editors S.[Slobodan] Anić and Ž.[Željko]
Čupić ; organized by Society of Physical
Chemists of Serbia ... et al.]. - Belgrade :
Society of Physical Chemists of Serbia, 2012
(Belgrade : Jovan). - VI, 498 str. : ilustr.
; 24 cm

"The Conference is dedicated to Professor
Ivan Draganić" --> nasl. str. - Tiraž 200. -
Bibliografija uz svaki rad.

ISBN 978-86-82475-27-9
1. Društvo fizikohemičara Srbije (Beograd)
a) Физичка хемија - Зборници b)
Електрохемијско инжењерство - Зборници c)
Наука о материјалима - Зборници
COBISS.SR-ID 193432332