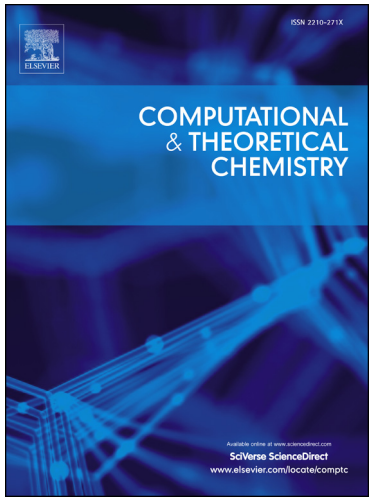


A theoretical study of the conformation and dynamic properties of 1,5-benzodiazepines and their derivatives

Rosa M. Claramunt, Ibon Alkorta, José Elguero

PII: S2210-271X(13)00282-X
DOI: http://dx.doi.org/10.1016/j.comptc.2013.07.002
Reference: COMPTC 1171

To appear in: *Computational & Theoretical Chemistry*

Received Date: 20 May 2013
Revised Date: 1 July 2013
Accepted Date: 1 July 2013

Please cite this article as: R.M. Claramunt, I. Alkorta, J. Elguero, A theoretical study of the conformation and dynamic properties of 1,5-benzodiazepines and their derivatives, *Computational & Theoretical Chemistry* (2013), doi: http://dx.doi.org/10.1016/j.comptc.2013.07.002

Computational and Theoretical Chemistry

A theoretical study of the conformation and dynamic properties of 1,5-benzodiazepines and their derivatives

Rosa M. Claramunt[a], Ibon Alkorta[b,*], José Elguero[b]

[a] *Departamento de Química Orgánica y Bio-Orgánica, Facultad de Ciencias, Universidad Nacional de Educación a Distancia (UNED), Senda del Rey 9, E-28040 Madrid, Spain*

[b] *Instituto de Química Médica, Centro de Química Orgánica "Manuel Lora-Tamayo", CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain*

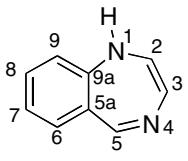
A B S T R A C T

The geometries of eighteen 1,5-benzodiazepines including their oxo and thioxo derivatives have been calculated and compared with experimental geometries determined by X-ray crystallography using as property the methylene flip angle. Protonation of 3*H*-1,5-benzodiazepine lead to a planar quasi-aromatic cation. For the non-planar structures we have calculated ring inversion barriers that are well correlated with ten experimental values determined by Dynamic NMR allowing the establishment of an empirical equation for predicting new values.

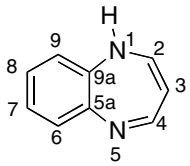
Keywords: 1,5-benzodiazepines; conformation; ring inversion; quasi-aromaticity; DFT

1. Introduction

1,5-Benzodiazepines (see below for their systematic name), although of much lesser important than 1,4-benzodiazepines [1,2,3,4], have found their place in medicinal chemistry. The most important is Clobazam (a 2,4-dione derivative) to the point that several analogs have been developed. But there are much more, some of them being represented in Fig. 1. Their main field of application is in Central Nervous System (CNS) pathologies but 1,5-benzodiazepines have found applications in other fields, the most promising being as Cholecystokinin (CCK) antagonists with possible utility as analgesics and for the treatment of Alzheimer's disease [5]. Concerning 1,5-benzodiazepinones an excellent summary can be found in the paper by Okovytyy et al. [6].



1*H*-benzo[*e*][1,4]diazepine
1,4-benzodiazepine



1*H*-benzo[*b*][1,4]diazepine
1,5-benzodiazepine