ELSEVIER

Journal of Molecular Structure: THEOCHEM 725 (2005) 63–68

THEO CHEM

www.elsevier.com/locate/theochem

Geometrical isomerism and conformational charges of selected open-ring enaminones in its neutral and protonated forms

Juan C. Garro Martínez[a,*], Graciela N. Zamarbide[a], Mario R. Estrada[a], Eduardo A. Castro[b]

[a]*Area de Química-Física, Departamento de Química, Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis, San Luis 5700, Argentina*

[b]*CEQUINOR, Departamento de Química, Universidad Nacional de La Plata, C.C. 962, La Plata 1900, Argentina*

Received 28 October 2004; accepted 20 January 2005
Available online 8 June 2005

Abstract

Enaminones are chemical compounds consisting of an amino group linked through a C=C to a carbonyl group. They combine the ambident nucleophility of enamines with the ambident electrophility of enones. Open-ring enaminones probed to be excellent prodrugs of model primary amines because their transportation ability trough biological membranes, while some cyclic enaminones have been reported as effective anti-epiletic agents. Selected open-ring enaminones, has been subjected to quantum chemical studies with the assumption that their flexibility wills allow more precise complexation with the corresponding receptor. Various conformers were investigated in a search for structural coincidences with the anti-convulsants cyclic enaminones.

Keywords: Enaminone; Ab initio geometry optimization; Conformation and site of protonation

1. Introduction

Enaminones (Fig. 1a), a group of organic compounds containing the conjugated system N–C=C–C=O, combine the ambident nucleophility of enamines (sites a, c and e) with the ambident electrophility of enones (sites b and c).

Such enaminones, formed between a primary amine and a 1,3-dicarbonyl compound are easily prepared, isolated and store at room temperature conditions since the carbonyl group, conjugated to the enamine moiety gives this system enough stability. A number of reviews has been published about the chemistry of enaminones [1–3], their physicochemical properties and biological uses, particularly as anti-convulsant agents [4,5]. However, no extensive structure–stability relationships, except for the experimental works of Larsen and co-workers [6] have been reported.

In spite of the interest that these compounds present, only theoretical works at semiempirical level of theory [7,8] and a quantum chemical study on the prototype enaminone: 2-propenal-3-amine [9], have been published.

Biologically active enaminones can be classified into two types:

-*Open-chain enaminones* (Fig. 1b) when the characteristic group is part of a chain. These compounds may be potential pro-drugs since they could release biologically active primary amines [2,4].

-*Cyclic enaminones* (Fig. 1c) when the characteristic group is part of a ring, showing structural similarities with known anti-epileptic or anti-convulsant drugs.

As an example, the activity of DM5 (Fig. 2) at the voltage-dependent sodium channel binding site is comparable to that of class 1 anti-convulsants: phenytonin, carbamazepine and lamotrigine.

Numerous open-chain enaminones have been investigated with the assumption that their flexibility will

* Corresponding author.
E-mail address: jcgarro@unsl.edu.ar (J.C. Garro Martínez).

0166-1280/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.theochem.2005.01.038

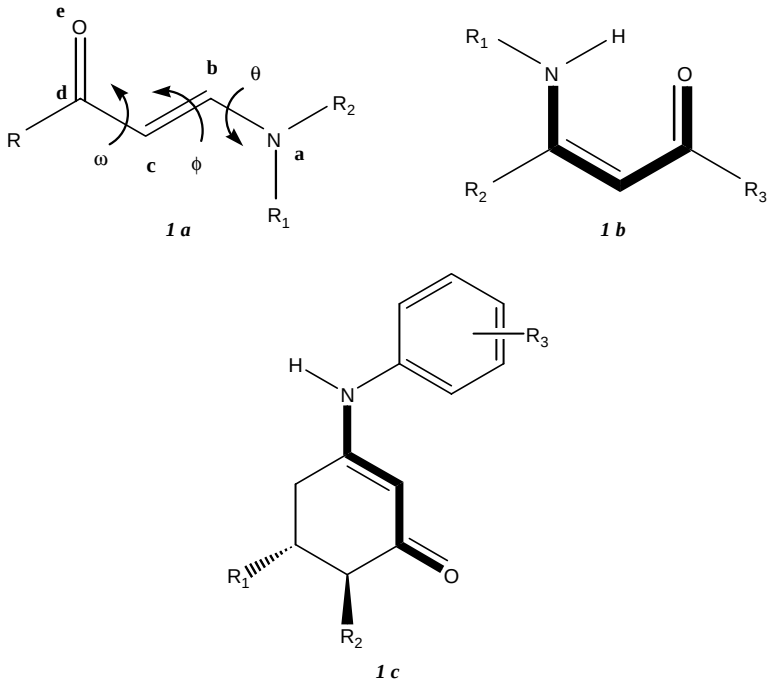


Fig. 1. (a) enaminone, (b) open-chain enaminone and (c) cyclic enaminone.

allow more precise complexation with the corresponding receptor.

The present paper deals with the theoretical determination of geometrical isomerism, and conformational charges of some open-chain enaminones, selected from recently reported experimental works on anti-convulsants agents.

2. Molecular computations

Using the GAUSSIAN 98 program system [10], ab initio computations have been carried out at the HF/6-31G and HF/6-31+G* levels of theory.

Five neutral molecules of open-ring enaminones (Fig. 3) were subjected to full molecular geometry optimization.

Table 1 sums up the difference between studied enaminones.

Although primary and secondary acyclic enaminones can exist in three tautomeric forms (oxo, imino and enol), there has been collected a great deal of evidence using NMR, UV, IR and X-ray analyses showing that the ground state of enaminones is best characterized by the oxo tautomeric form [11].

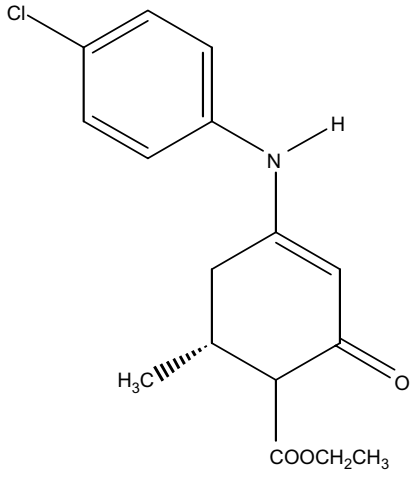
An oxo-enaminone can exist in four isomers A, B, C and D as shown in Fig. 4.

3. Results and discussion

Results of molecular geometry optimization, at two levels of theory, for most stable structures of all the isomers of molecules I, II, III, IV and V are shown in Table 2, including torsional angles and hydrogen bond distances.

As it can be seen, the four expected geometrical forms were found. However, A isomer is the more stable structure for all molecules on study. This can be explained because the hydrogen bond type (**1**) between the hydrogen of the amino group and the oxygen of the carbonyl, close a six-member ring.

For an enaminone, which may be a pro-drug, to release a primary amine (R–NHR), that may be an actual drug,



DM5

Fig. 2. DM5 an active anti-convulsant.