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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

In silico identification of the active conformation of open-chain enaminones with anticonvulsant activity

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Abstract A study about the relationship between molecular properties of open-chain enaminones and their anticonvulsant activity is presented in this paper. Geometry optimizations of the enaminones were performed at HF and DFT/B3LYP levels of theory using 6-31 + G(d) basis set. The HOMO and LUMO energies were obtained at the same level of theory. The solvent effect was studied through IPCM. A natural bond orbital (NBO) analysis was performed to analyze the possible association between the stability and the intramolecular hydrogen bond interaction energies. The stability order of the isomers in gas phase was the following: *cis-1* > *trans-4* > *cis-2* > *trans-3*. The IPCM method showed that the *trans*-3 isomers are more stable that the *cis*-2 when the solvent effect was taken into account. Two important intramolecular hydrogen bonds were found by NBO analysis. According to our findings, these interactions could affect the activity of the two most stable isomers (*cis*-1 and *trans*-4). By contrast, *trans*-3 isomers did not present this type of interaction. Therefore, the latter isomers have a large flexibility and can adopt a conformation similar to the conformation of active ringed enaminones. In addition, HOMO and LUMO energies suggested that the *trans*-3 isomers could be the most reactive species.

Keywords Open-chain enaminones · Anticonvulsant activity · Structure–activity relationship · Active conformation · Ab initio · NBO analysis

Introduction

The general term "enaminones" refers to a group of organic compounds containing the conjugated system N–C=C–C=O. Structural studies of this family of compounds show that the oxo form is the most stable tautomer (Garro Martinez *et al.*, 2001; Kascheres, 2003; Brbot-Šaranović *et al.*, 2000). Other studies, carried out on the simplest enaminone 2-propenal-3-amine, indicate that the enaminones present *cis* and *trans* isomers (Garro Martinez *et al.*, 2005) (Fig. 1).

It is well known that biologically active enaminones have the functional group N–C=C–C=O within a ring structure (ringed enaminones, RE). Many authors have presented the synthesis and the anticonvulsant activity of several RE (Edafiogho *et al.*, 2006; Eddington *et al.*, 2003, 2002; Abdel-Hamid *et al.*, 2002; Foster *et al.*, 1999; Anderson *et al.*, 2006; Shawali, 2010). They have pointed out that the activity of these compounds at the voltage-dependent sodium channel binding site is comparable to the activity of class 1 anticonvulsants: phenytoin, carbamazepine, and lamotrigine.

The open-chain enaminones (OCE) are compounds whose functional group N–C=C–C=O is part of a flexible chain. Recent studies indicate that the OCEs could also show anticonvulsant activity based on the assumption that

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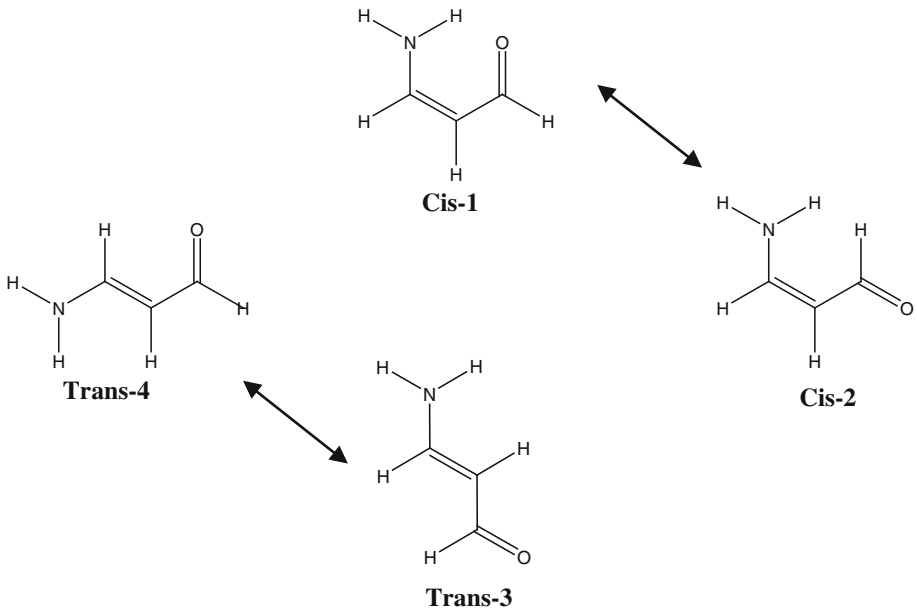

Fig. 1 Structures of the *cis* and *trans* isomers of 2-propenal-3-amine

their flexibility could allow a more precise binding to the corresponding receptor (Cheng and Ju, 2010; Mahmud *et al.*, 2010; Ivanov *et al.*, 2007).

The aim of the present paper is to establish a relationship between molecular properties (total energies in gas and condensed phases, intramolecular interaction energy $E(2)$, HOMO and LUMO energies, among others) and the anticonvulsant activity of a set of OCEs. We hope that this study could provide new structural information, such as the influence of the conformation on biological activity, in order to guide the rational synthesis of novel active compounds.

Materials and methods

Molecular modulation

The structures of OCEs were obtained from a molecular modulation analysis. This approach consists in the structural modification of an active compound to get another one with a similar structure. This technique is widely used in rational drug design (Li-Jing *et al.*, 2005; Scapecchi *et al.*, 2004; Ramurthy *et al.*, 2011).

Figure 2 shows the molecular modulation scheme used to build the OCEs studied. The active compounds A and B belong to the aniline family, compound C is a benzylamine RE, and compound D comes from an isoxasole family. The anticonvulsant activity of these precursor compounds was extracted from the literature (Edafiogho *et al.*, 2006; Eddington *et al.*, 2003, 2002; Abdel-Hamid *et al.*, 2002; Foster *et al.*, 1999; Anderson *et al.*, 2006). The OCEs *trans*-3A, *trans*-3B, *trans*-3C, and *trans*-3D were derived from the active compounds A, B, C and D, Fig. 2. The rotation of the dihedral angle defined by O=C–C=C atoms leads to the formation of *trans*-4A, *trans*-4B, *trans*-4C, and *trans*-4D conformers. The *cis*-1 and *cis*-2 isomers of each OCE were studied too (Fig. 1).

Computational details

Initial geometries were obtained from previous calculations at the HF/6-31 + G(d) level of theory (Garro Martinez *et al.*, 2005). The B3LYP hybrid functional was employed with the 6-31 + G(d) basis set (Lee *et al.*, 1988; Becke, 1993) to optimize the geometry, perform the NBO analysis (Glendening *et al.*, 1998), and to calculate all the molecular properties. Frequency calculations were carried out to confirm minimum energy conformers and to check the absence of imaginary frequencies.

The solvent effect was taken into account to examine the conformational stability in implicitly modeled condensed phase. The isodensity polarizable continuum model (IPCM) method (Miertus *et al.*, 1981; Foresman *et al.*, 1996) at the B3LYP/6-31 + G(d) level of theory was employed.

All calculations were performed with Gaussian 03 package (Frisch *et al.*, 2003). The NBO 3.1 program (Glendening *et al.* 1998) implemented in Gaussian 03 was used to analyze intramolecular charge transfer energies.

Results and discussion

Conformational study

The OCEs proposed from molecular modulation analysis were subjected to a conformational study. A full

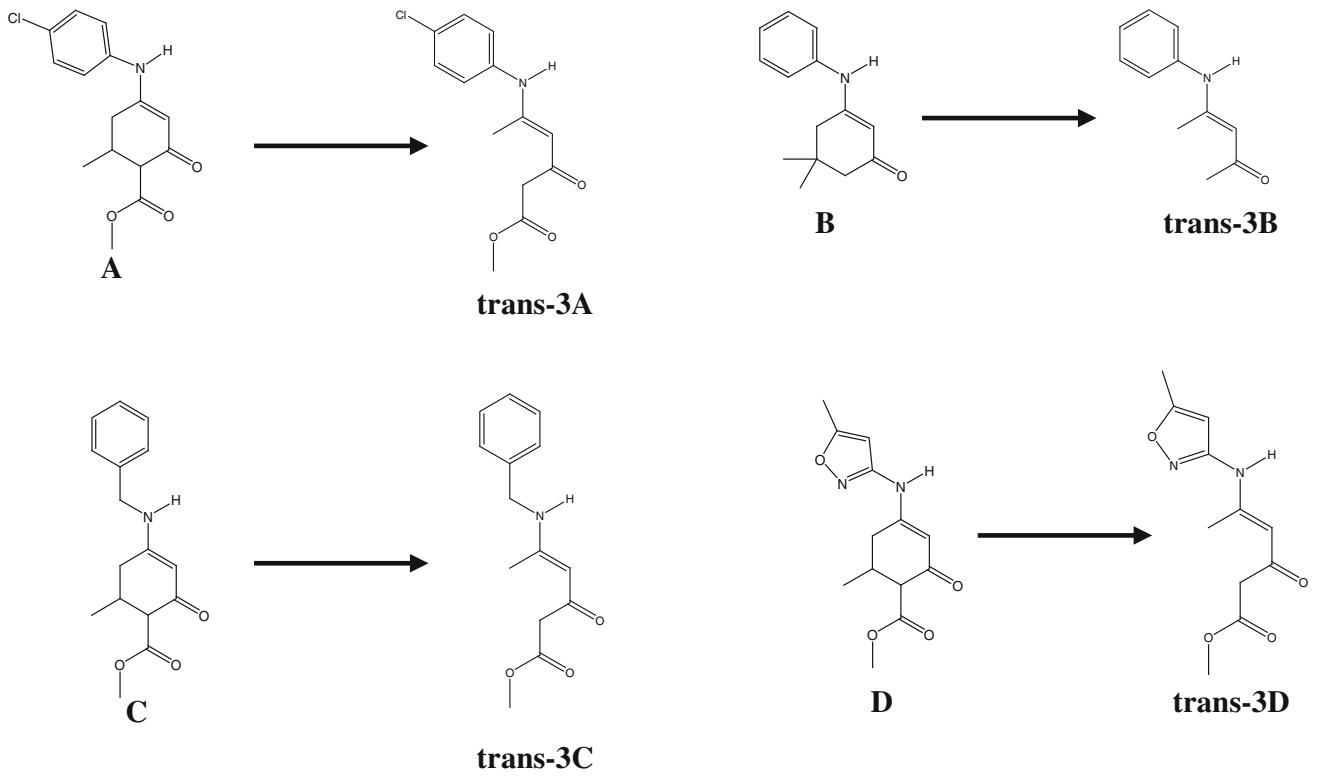

Fig. 2 Scheme of molecular modulation of active RE (**A**–**D**)

conformational study involves the evaluation of potential energy hypersurface as a function of several independent variables. However, in this work, the conformational analysis was limited to the variable of the enaminone functional group, the dihedral O=C–C=C.

The total energy ΔE (kcal mol^{-1}) and the optimized structures OCEs are shown as supplementary material, Table 1S and Fig. 1S. The results indicate that the stability of the A, B, C, and D conformational isomers decreases in the following order: *cis-1* > *trans-4* > *cis-2* > *trans-3*. It is well known that the *cis* isomers are the most stables ones. However, we have found that the *trans*-4 isomers have higher stability than the *cis*-2 isomers. In order to support these results and to investigate the existence of any intramolecular stabilizing interaction, an NBO analysis was performed. Although *cis*-2 isomers are more stable than *trans*-3, the ΔE is not significant (average value of 0.6 kcal mol^{-1}). Any little change in the electronic and molecular structure in these isomers, such as the solvent effect, could alter this stability order.

Solvent effect

The previous calculations were performed in gas phase without considering any solvent. The solvent has an important role in the molecular properties determination. The IPCM method with a dielectric constant of $\varepsilon = 78.39$ (dielectric constant of water) was used to study the solvent effect. The results, shown in Table 1, indicate the course and magnitude of conformational changes produced by considering the solvent on the OCEs.

Figure 3 shows the ΔE (kcal mol^{-1}) of the conformers in gas and condensed phases. The stability order obtained with IPCM method for the families B, C, and D is *cis-1* > *trans-4* > *trans-3* > *cis-2*. The family A stability order is not affected by the presence of the solvent and is the same as in gas phase. According to these results, the *cis*-1 is the most stable isomer in gas and condensed phases. Moreover, there is a significant decrease of ΔE of *trans*-4, *trans*-3, and *cis*-2 isomers. The values of ΔE in condensed phase could be explained considering the possible formation of an intramolecular hydrogen bond on the surface of the molecule. These hydrogen bonds would prevent the interaction of the polar groups with solvent and reduce the compounds aqueous solubility (Kuhn *et al.*, 2010).

Molecular orbital energies

The lowest unoccupied molecular orbital (LUMO) energy describes the electron-accepting character and is essential to understand the charge transfer processes that occur when a molecule interacts with biological receptors (Honorio and da Silva, 2003). The data in Table 2 show that the *trans*-4

Table 1 Total energies (Hartree) for DFT calculation in gas and condensed phases

Compounds	B3LYP/6-31 + G(d) Total energy	DFT/IPCM (ε = 78.39)[a] Total energy	Compounds	B3LYP/6-31 + G(d) Total energy	DFT/IPCM (ε = 78.39)[a] Total energy
Cis-1A	*−1,244.47596*	*−1,244.49637*	*Cis*-1C	*−824.19388*	*−824.21523*
Trans-4A	−1,244.46318	−1,244.49130	*Trans*-4C	−824.18172	−824.20946
Cis-2A	−1,244.45654	−1,244.49054	*Cis*-2C	−824.17548	−824.20153
Trans-3A	−1,244.45548	−1,244.48580	*Trans*-3C	−824.17306	−824.20324
Cis-1B	*−556.99998*	*−557.01325*	*Cis*-1D	*−837.99861*	*−838.02365*
Trans-4B	−556.98653	−557.00553	*Trans*-4D	−837.98269	−838.01845
Cis-2B	−556.98207	−557.00360	*Cis*-2D	−837.97726	−838.00956
Trans-3B	−556.98206	−557.00452	*Trans*-3D	−837.97646	−838.01523

The minimum energy conformers are highlighted in italics

[a] Dielectric constant of water

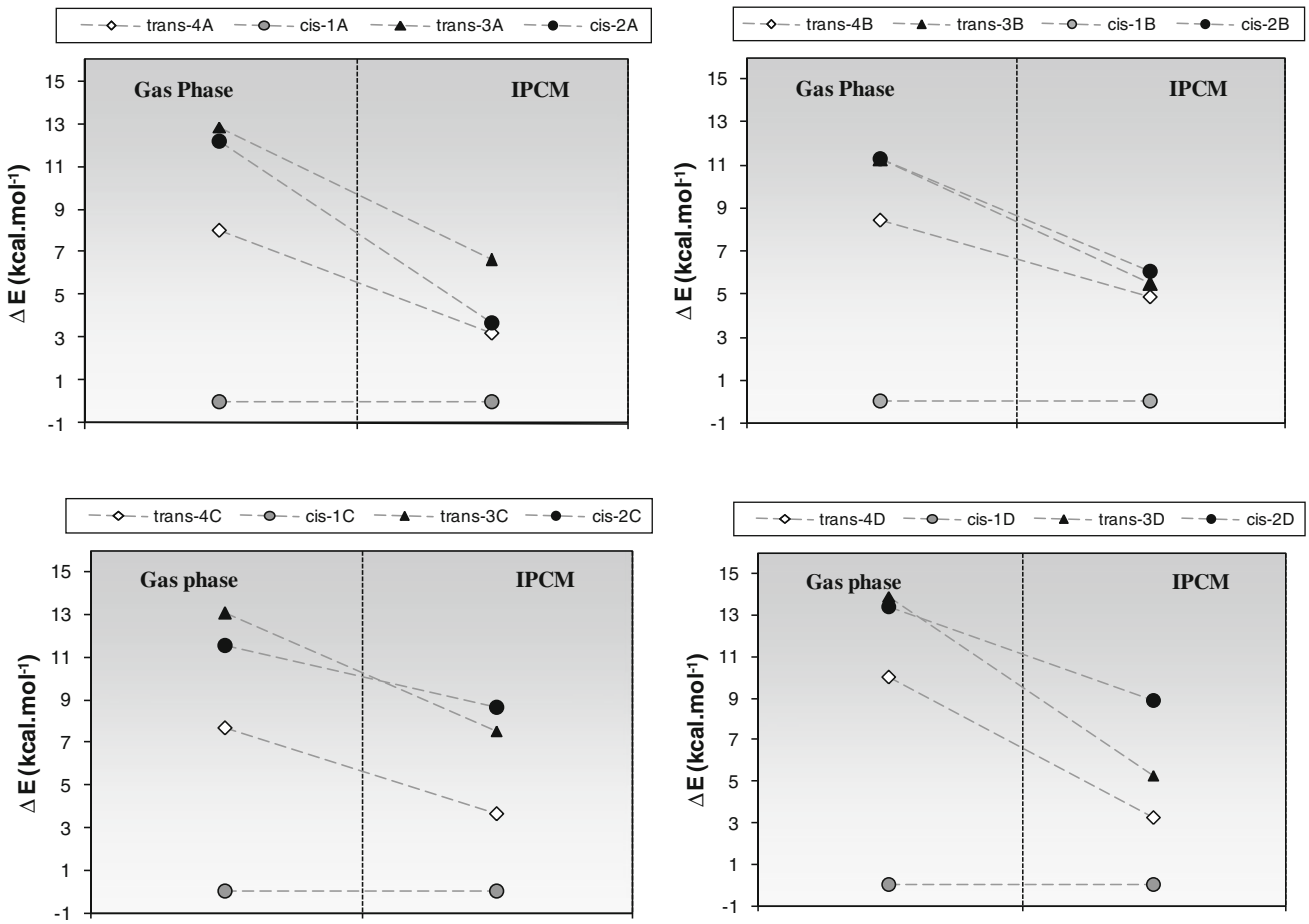

Fig. 3 Plots ΔE (kcal mol^{-1}) for isomers of OCE in gas phase: B3LYP/6-31 + G(d) and condensed phase: IPCM/B3LYP/6-31 + G(d)

isomers have low LUMO energy values indicating that these isomers could act as electron acceptors and that they could interact with the biological receptor through a charge transfer mechanism. The energy difference between HOMO and LUMO orbitals ($\Delta E_{\mathrm{HOMO-LUMO}}$) describes the energy required for an intramolecular electron transfer and it is related to polar reactivity. Compounds with a low value of $\Delta E_{\mathrm{HOMO-LUMO}}$, as the *trans*-3 isomers, could have intramolecular electron transference and are reactive species (Table 2).

Table 2 Energies of HOMO and LUMO for OCEs

Compound	E_{HOMO}	E_{LUMO}	$\Delta E_{HOMO-LUMO}$	Compound	E_{HOMO}	E_{LUMO}	$\Delta E_{HOMO-LUMO}$
Cis-1A	−0.2267	−0.0656	−0.161	*Cis*-1C	−0.2219	−0.0457	*−0.176*
Cis-2A	−0.2294	−0.0663	−0.163	*Cis*-2C	−0.2231	−0.0442	−0.179
Trans-3A	−0.2230	−0.0647	*−0.158*	*Trans*-3C	−0.2231	−0.0454	−0.177
Trans-4A	−0.2253	*−0.0632*	−0.162	*Trans*-4C	−0.2199	*−0.0435*	−0.176
Cis-1B	−0.2160	−0.0531	−0.162	*Cis*-1D	−0.2312	−0.0608	−0.170
Cis-2B	−0.2180	−0.0533	−0.164	*Cis*-2D	−0.2343	−0.0631	−0.171
Trans-3B	−0.2132	−0.0529	*−0.160*	*Trans*-3D	−0.2296	−0.0630	*−0.166*
Trans-4B	−0.2142	*−0.0504*	−0.163	*Trans*-4D	−0.2309	*−0.0601*	−0.170

The lowest energy values of each family are highlighted in italics

Table 3 Interaction energies between donor and acceptor orbitals of OCEs isomers

Isomers	Distance O···HX	Angle X–H···O	Donor	Acceptor	$E(2)$[a] (kcal mol^{-1})	
					Gas	IPCM
Cis-1A	1.80	139.34	LP (1) O	BD*(1) N–H	4.49	4.37
			LP (2) O	BD*(1) N–H	16.14	16.21
Trans-4A	2.29	131.85	LP (1) O	BD*(1) C–H	0.50	0.50
			LP (2) O	BD*(1) C–H	0.81	0.80
Cis-1B	1.83	136.48	LP (1) O	BD*(1) N–H	4.76	4.55
			LP (2) O	BD*(1) N–H	17.68	17.36
Trans-4B	2.15	130.98	LP (1) O	BD*(1) C–H	0.51	0.53
			LP (2) O	BD*(1) C–H	0.97	0.96
Cis-1C	1.84	136.70	LP (1) O	BD*(1) N–H	4.31	4.19
			LP (2) O	BD*(1) N–H	13.29	13.29
Trans-4C	2.14	131.53	LP (1) O	BD*(1) C–H	1.44	1.51
			LP (2) O	BD*(1) C–H	3.47	3.27
Cis-1D	1.80	139.17	LP (1) O	BD*(1) N–H	4.85	4.68
			LP (2) O	BD*(1) N–H	16.21	16.49
Trans-4D	2.16	131.21	LP (1) O	BD*(1) C–H	1.34	1.39
			LP (2) O	BD*(1) C–H	3.07	3.32

[a] $E(2)$ means energy of hyperconjugative interaction (stabilization energy)

NBO analysis

In order to investigate the interaction energy between donor and acceptor orbitals, a NBO analysis (using DFT methods in gas and condensed phases) was performed on the isomers that present geometric evidence of intramolecular hydrogen bond. This analysis provides an efficient method to study intra- and intermolecular bonding and interaction among bonds and provides a convenient approach to study charge transfer or conjugative interaction in molecular systems. The interaction energy $E(2)$ represents the strength of the donor–acceptor interactions and the stabilization energy associated with these interactions (Düsman *et al.*, 2005).

As it was exposed previously, the stability order of the OCEs isomers is *cis*-1 > *trans*-4 > *cis*-2 > *trans*-3 in the gas phase and *cis*-1 > *trans*-4 > *trans*-3 > *cis*-2 in condensed phase except for compound A. The stability of *cis*-1 and *trans*-4 isomers in both phases may be due to the probable existence of an intramolecular hydrogen bond. The $E(2)$ (expressed in kcal mol^{-1}) between donor and acceptor orbitals and some geometric parameters of *cis*-1 and *trans*-4 isomers are summarized in Table 3. According to these data, there is an effective interaction energy between the oxygen lone pair (LP(2) O) and the sigma antibonding orbital (σ*) of N–H bond of the *cis*-1 isomers, and C–H bond of the *trans*-4 isomers. However, according to Table 3, the interactions are stronger for *cis*-1 than *trans*-4 isomers. In condensed phase, the $E(2)$ of the *cis*-1 isomers (∼13 and 17 kcal mol^{-1}) were not affected by the presence of the solvent. The *trans*-4 isomers present a weak CH···O interaction with values of $E(2)$ lower than 3.5 kcal mol^{-1}. The $E(2)$ value could be used to explain that the stability of *trans*-4 isomers is higher than the stability of *cis*-2 isomers.

It is well known that intramolecular hydrogen bonds affect the solubility of any compound (Ramurthy *et al.*, 2011). However, the weak interaction found in *trans*-4

isomers could have little effect on the aqueous solubility of these isomers. In contrast, the high $E(2)$ value in *cis*-1 isomers results in an increased lipophilicity, increased membrane permeability, and reduced aqueous solubility showing a negative influence on the biological activity (Ramurthy *et al.*, 2011).

Structure–activity relationships

Previous studies have quantified the biological activity of the OCEs analyzed in the present work (Garro Martinez *et al.*, 2011). The activity expressed as ED_{50} (dose of a drug that is pharmacologically effective for 50 % of the population exposed to the drug) is shown as supplementary material in Table 2S. Furthermore, other authors have presented a model of the possible pharmacophore and have indicated the importance of a carbonyl group, located at a precise distance from an aromatic ring, for the binding with the active site (Carter *et al.*, 2003; Tasso *et al.*, 2000).

The isomers stability could have an important role in the biological activity of a compound. Consequently, *cis*-1 should be the isomers with highest activity and *trans*-3 should have a low activity. However, this situation is not always found in biological systems. To illustrate our case, the ΔE and the biological activity (expressed as $LogED_{50}$) of all isomers are plotted in Fig. 4. This figure shows that the *cis*-1 isomers of compounds A, B, C, and D were not the most active ones. It can be noted that the *trans*-3 is the most active isomer, although their low stability.

The NBO analyses show that the interaction energy could be associated with the isomers stability. As it was previously explained, when $E(2)$ value is high, the isomers stability is favored; nevertheless, the anticonvulsant activity can be affected in a negative way. Considering this effect, the isomers containing intramolecular hydrogen bond that stabilizes them forming a five- or six-membered ring would be the less active compounds. This idea is based on the rationalization that a more rigid structure would prevent specific interactions and more precise binding to the corresponding receptor.

The low $\Delta E_{HOMO-LUMO}$ values suggest that the *trans*-3 isomers can be the most reactive species and therefore the most active compounds. In addition, the comparison between the *trans*-3 isomers with their precursors (Fig. 5) shows a similar space orientation of the carbonyl group and the aromatic ring. As other authors have proposed (Carter *et al.*, 2003; Tasso *et al.*, 2000), we also suppose that this space distribution is an essential part of the pharmacophore of this family of compounds.

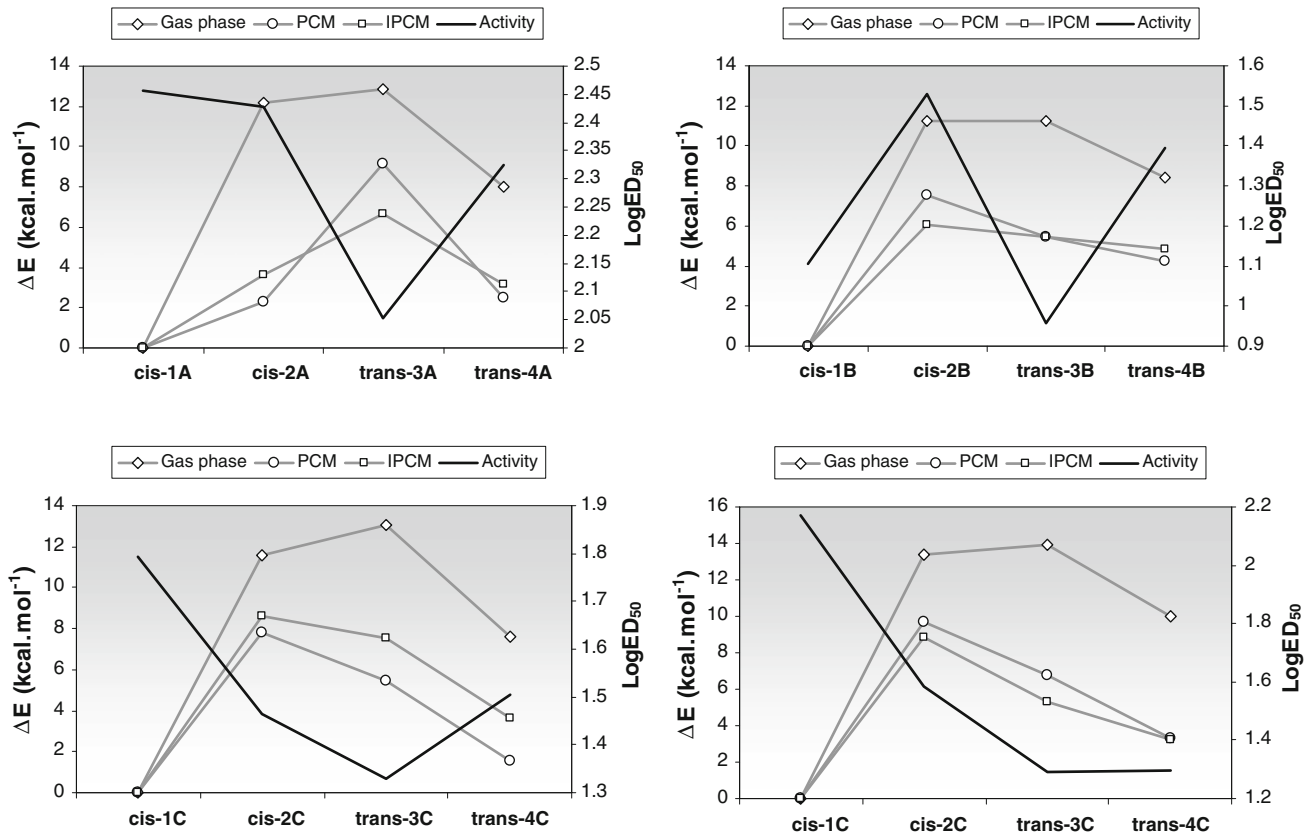

Fig. 4 Biological activity ($logED_{50}$) and ΔE (kcal mol^{-1}) for the isomers *cis* and *trans* of OCE

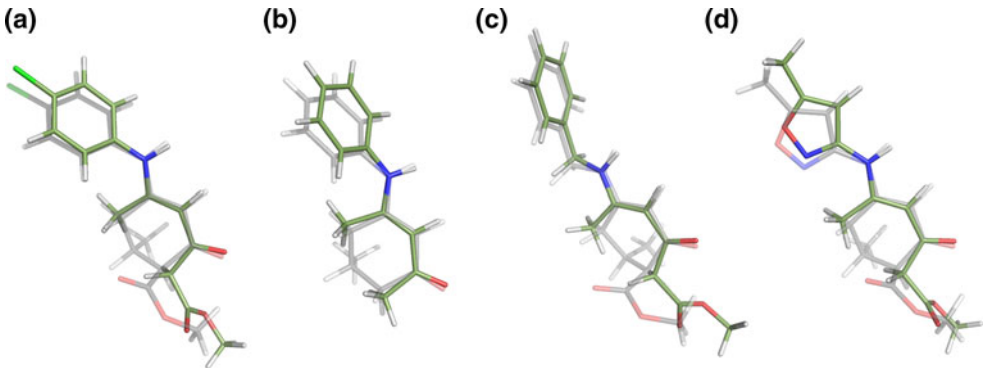

Fig. 5 Superimposition of DFT-optimized molecular structures of active RE precursors (*partially transparent stick representation*) and *trans*-3 isomers (*solid stick representation*)

Conclusions

In this paper, a stability order of four OCE isomers was established at a high DFT level of theory: *cis-1* > *trans-4* > *cis-2* > *trans-3*. The results taking into account the solvent effect showed an important decrease in ΔE of *trans*-4, *cis*-2, and *trans*-3 isomers and a possible change in the stability of *cis-2* and *trans-3* isomers. Higher stability of *cis*-1 and *trans*-4 isomers is due to the presence of intramolecular hydrogen bonds that allow the formation of a six-membered ring. The anticonvulsant activity of OCEs was related to the structural parameters and molecular properties obtained by DFT calculations. The most stable isomers (*cis*-1) have a high structural rigidity and therefore low potential to generate intermolecular hydrogen bond with the solvent or their receptor leading to a poor activity. By contrast, the high activity of *trans*-3 isomers could be explained by (a) the absence of intramolecular interactions that provide a flexible conformation and the capacity to establish intermolecular hydrogen bond with the receptor; (b) the low $\Delta E_{\mathrm{HOMO-LUMO}}$ value that turns the *trans*-3 isomers into the most reactive species; and (c) the similar space orientation of the pharmacophore group (aromatic rings and carbonyl groups) with the precursor compounds.

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