J Mol Model (2011) 17:281–287
DOI 10.1007/s00894-010-0723-7

ORIGINAL PAPER

Electronic properties of neuroleptics: ionization energies of benzodiazepines

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Received: 7 January 2010 / Accepted: 19 April 2010 / Published online: 6 May 2010
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Abstract Vertical ionization energies (VIEs) of medazepam, nordazepam and their molecular subunits have been calculated using the electron propagator method in the P3/CEP-31G* approximation. Vertical electron affinities (VEAs) have been obtained with a ΔSCF procedure at the DFT-B3LYP/6-31+G* level of theory. Excellent correlations have been achieved between IE_{calc} and IE_{exp}, allowing reliable assignment of the ionization processes. Our proposed assignment differs in many instances from that previously reported in the literature. The electronic structure of the frontier Dyson orbitals shows that the IE and EA values of the benzodiazepines can be modulated by substitution at the benzene rings. Hardness values, evaluated as (IE − EA)/2, follow the trend of the experimental singlet transition energies. Medazepam is a less hard (i.e., less stable) compound than nordazepam.

Keywords Benzodiazepines · Vertical ionization energies · Vertical electron affinities · DFT calculations · Electron propagator theory calculations

Electronic supplementary material The online version of this article (doi:10.1007/s00894-010-0723-7) contains supplementary material, which is available to authorized users.

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Introduction

Benzodiazepines are well-known drugs of wide importance in medicinal chemistry, possessing a broad spectrum of pharmacological activities [1]. The heart of a benzodiazepine consists of a seven-membered partially saturated ring with nitrogen atoms at position 1 and 4, fused with a benzene ring. Substitution at various positions on the two rings gives rise to a wide number of benzodiazepine derivatives. Accurate descriptions of the electronic and molecular structures of representative compounds are of intrinsic value. In this respect, ultraviolet photoelectron spectroscopy (UV-PES), supported by reliable theoretical calculations, may provide precious information on the outer valence molecular orbital shapes and energies [2]. In this report, we deal with the electronic structure of 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one **6** (nordazepam) and its molecular subunits **4** (ring D) and **5** (rings B and D), and with 7-chloro-5-phenyl-2,3-dihydro-1-H-1,4-benzodiazepin **3** (medazepam) and its molecular subunits **1** (ring A) and **2** (rings B and A), Fig. 1. These compounds exhibit structural units that are present in several derivatives of the same family. Experimental UV-PES studies of compounds **3**, **5** and **6** have been reported [3, 4]. The suggested assignments of the photoionization processes are, however, very different to each other. We aim to provide an accurate description of the electronic structures of medazepam and nordazepam through the computation and analysis of the outermost Dyson orbitals and the associated vertical ionization energies (VIEs) and vertical electron affinities (VEAs). To this end, we employ the ab initio electron propagator theory in the partial third order approximation (P3) [5]. P3 has been widely shown to

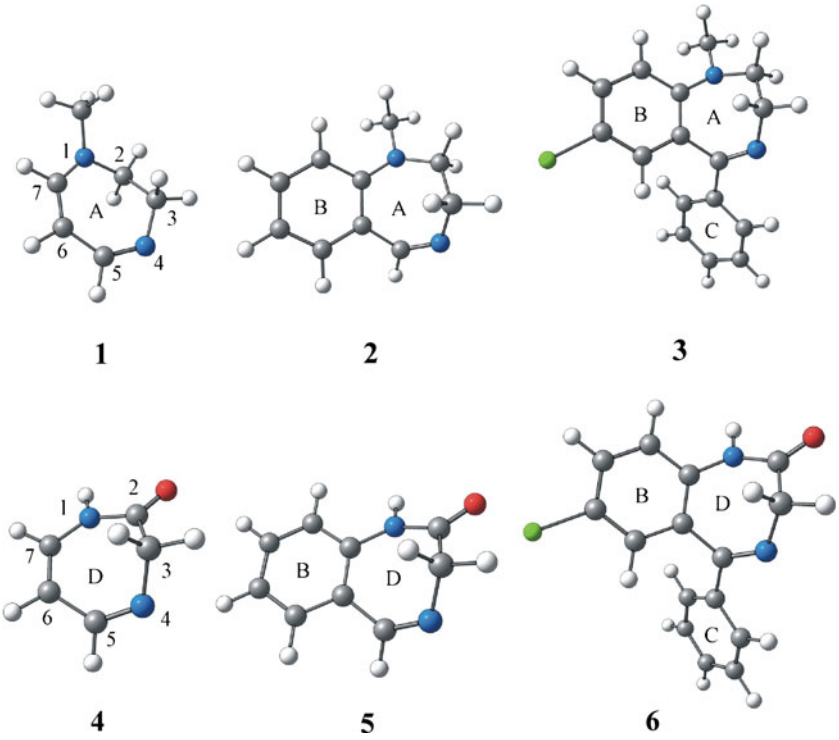

Fig. 1 Molecular structures of the investigated compounds determined by B3LYP/6-31G* calculations. Colours: white (Hydrogen), grey (Carbon), blue (Nitrogen), red (Oxygen), green (Fluorine)

give reliable interpretations of the ionization processes of a number of organic systems [6–8].

Computational details

P3 theory has been recently reviewed [9]. We briefly recall that, in this theory, for every IE there is a corresponding Dyson orbital (DO) defined by

$$\phi^{Dyson}(x_1) = N^{-1/2} \int \Psi^{*}_{cation}(x_2, x_3, x_4 \ldots\ldots, x_N) \times \Psi_{molecule}(x_1, x_2, x_3 \ldots\ldots, x_N) dx_2 dx_3 dx_4 \ldots\ldots dx_N,$$

where N is the number of electrons in the molecule and x_i is the space-spin coordinate of electron i. A so-called pole strength, which indexes the validity of the perturbative treatment, is associated with each DO. Pole strength values of between 0.85 and 1 indicate that the one-electron description of the ionization process is valid. In the P3 approximation, DOs are proportional to Hartree–Fock orbitals. The P3 approximation includes orbital electron correlation and relaxation effects associated with the ionization. The active space included all valence occupied and all unoccupied molecular orbitals in P3 calculations of **1**, **2**, **4** and **5**. In medazepam and nordazepam, we considered all valence occupied molecular orbitals and 85% of the virtual molecular orbitals.

All calculations were performed with the Gaussian 03 program [10]. Molecular structures were fully optimized at the density functional theory level (DFT) using the B3LYP functional [11, 12] and the 6-31G* basis set. Due to the size of the investigated compounds, P3 calculations were carried out with the pseudopotential (PP) CEP-31G* basis set [13]. The PP/P3 approach has been proven to be adequate for predicting VIEs [14]. Owing to the molecular size and the need for a more extended basis set, including diffuse functions, VEAs were computed by the widely used ΔSCF procedure [15, 16], by comparing the ab initio B3LYP/6-31+G* total energies of the anion and neutral molecules using the geometry of the neutral compound.

Results and discussion

The molecular structures of compounds **1–6** are shown in Fig. 1. Starting geometries were taken, when available, from X-ray data for the solid [17, 18]. To find minimum energy conformations, we performed a molecular dynamics (MD) simulation with the AMBER force field for 1 ns at 600 K and with a time step of 1 fs. The obtained conformations were optimized by AM1 calculations. The most stable structures were further fully optimized at the B3LYP/6-31G* level. Theoretical geometries are in very good agreement with experimental data [17, 18]. Minimum energy conformations were confirmed by vibrational analysis. The seven-membered ring adopts a boat structure in **3**, **4**, **5** and **6** and a twisted-boat structure in **1** and **2**. Benzene ring B is planar. Benzene ring C can rotate around the single C–C bond, producing two isoenergetic con-

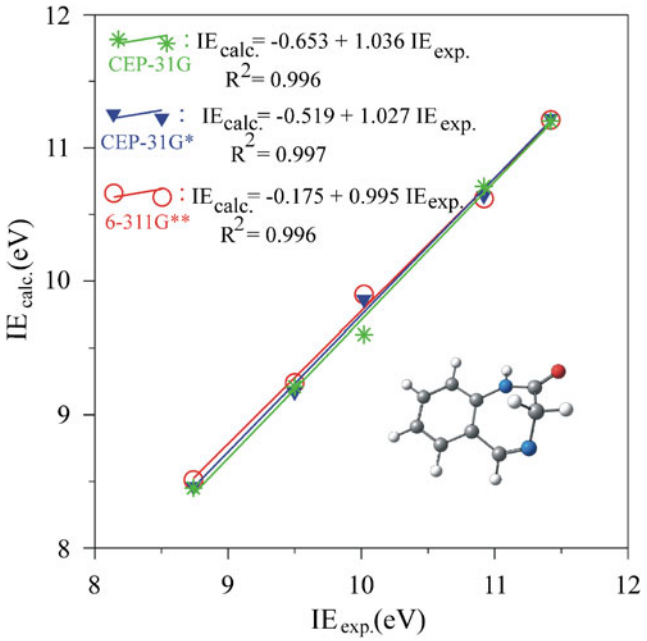

Fig. 2 IE_{calc} vs. IE_{exp} correlations for 1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5**)

formations of **3** with dihedral angles between the two benzene rings of −157.3° and 24.8°, respectively, separated by an energy barrier of 6.31 kcal mol^{-1} with a maximum at 114.8°. The corresponding values for **6** are: −136.5°, 27.7°,

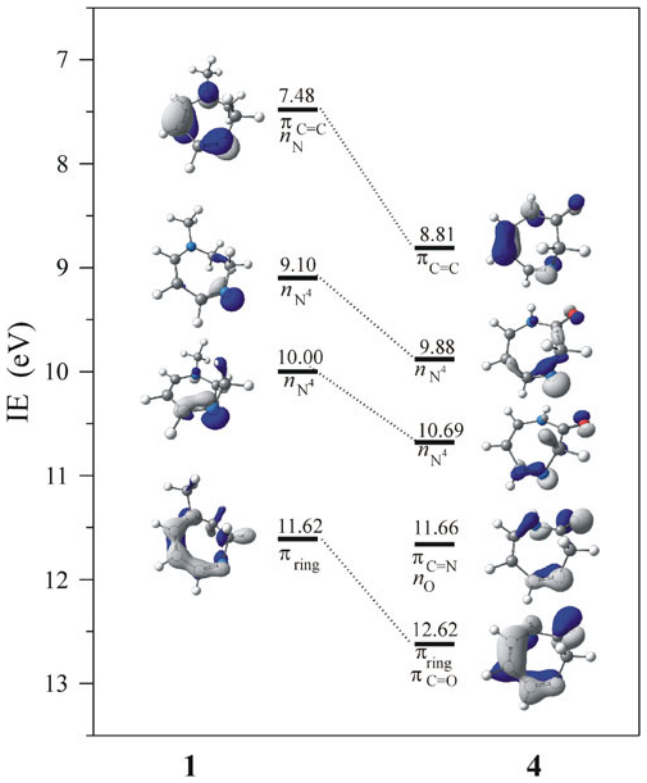

Fig. 3 Dyson orbitals and ionization energies of compounds **1** and **4**

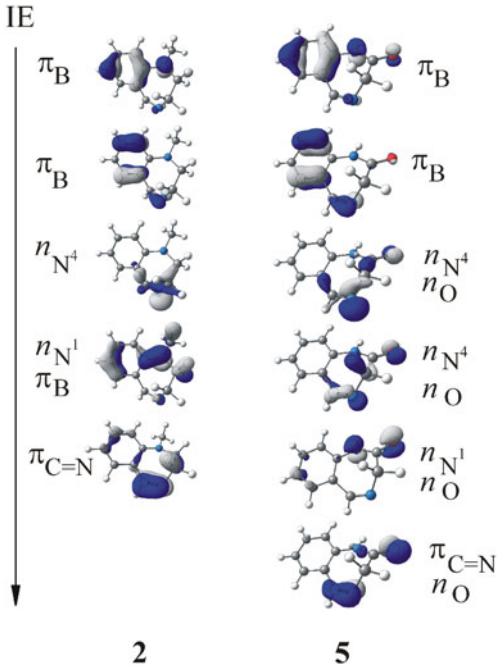

Fig. 4 Dyson orbitals of compounds **2** and **5**

5.98 kcal mol^{-1}, 123.4° (Fig. S1 of the "Electronic supplementary material"). The Cartesian coordinates of the minimum energy conformations are reported in Tables S1–S6 of the "Electronic supplementary material."

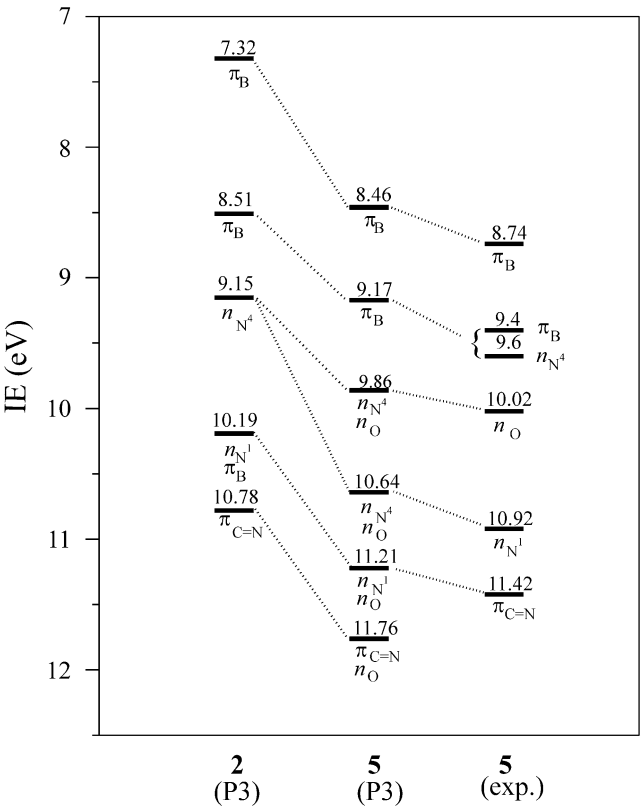

Fig. 5 Correlation diagram for compounds **2** and **5**, and comparison with experimental data

In the extensive work of Ortiz and co-workers, P3 calculations were widely and successfully carried out with the 6-311G** basis set [19]. In the present work, due to the size of the molecules we are dealing with, we used the smaller CEP-31G* basis set. A comparison of the CEP-31G* results with the 6-311G** ones and the experimental data for compound **5**, used as a test case, relative to the first five ionization energies are given in Fig. 2. It can be seen that the IE_{calc} vs. IE_{exp} correlation is similar for the two levels of theory, and that experimental numerical data are well reproduced. Considering that we would like to apply this methodology to larger related molecular systems, we also tested the use of the even smaller CEP-31G basis set. The result, reported in Fig. 2, indicates that this unpolarized double-zeta basis could also be used, although an energy shift towards smaller IE values should be expected for orbitals with large nitrogen lone pair amplitudes (third point in the correlation line of Fig. 2). The pole strength values of all of the investigated compounds were between 0.87 and 1, indicating that the one-electron description of the final state was qualitatively valid.

Our theoretical electronic structure analysis first focuses on the isolated diazepine rings A and D, and then considers the more complex systems **2**, **5** and **3**, **6**.

Vertical ionization energies

Compounds 1 and 4

The Dyson orbitals and energy levels of diazepine rings A and D are presented in Fig. 3. The first cationic final state of compound **1** is described by a rather high-energy $\pi_{C=C}$ orbital with contributions from *n*N lone pairs. The methyl group makes a small contribution through a hyperconjugative interaction. Next, two IEs at 9.10 and 10.00 eV pertain to *n*N orbitals that are mainly localized on the N^4 atom. An

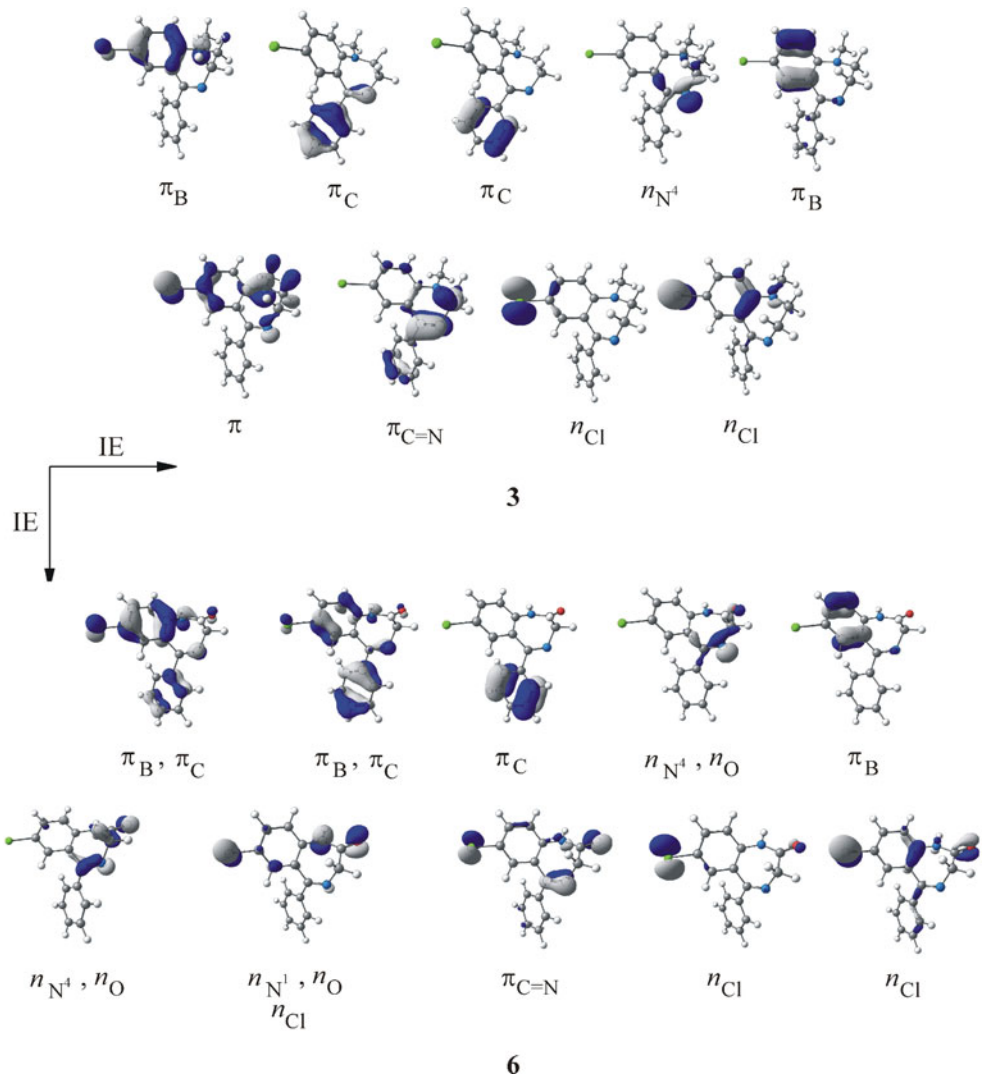

Fig. 6 Dyson orbitals for compounds **3** and **6**

in-phase π C=N^4 and C=C–C–N^1 combination characterizes the fourth ionization at 11.62 eV. Almost the same sequence of DOs characterizes the electronic structure of the diazepine ring D bearing the C=O group but lacking the CH_3 group. This substitution produces important changes in the orbital composition and the IE values of the outermost final states, which all show contributions from the *n*O lone pairs and are stabilized due to the strong electron-withdrawing power of the C=O group. Of particular significance is the 1.33 eV stabilization of the lowest-energy DO.

Compounds 2 and 5

The Dyson orbital structures of compounds **2** and **5** are shown in Fig. 4, and a correlation diagram for the corresponding IEs in Fig. 5. The fusion of rings A and D with a benzene ring to give **2** and **5** introduces the b_1- and a_2-like benzene orbitals, which make the major contributions to the first two energy levels in both compounds. These are followed by a cationic state that is essentially localized on an N^4 lone pair, which in **5** has also some *n*O amplitude. The last two DOs in Fig. 4 have π symmetry and are mainly localized on the benzene ring; the former on N^1 and the latter on the C=N bond. Both compounds show the same succession of cationic states with IE values which are about 1 eV higher in **5** than in **2**. The experimental IEs of **5** are known from photoelectron spectroscopy measurements [4] and are reported in Fig. 5 for comparison. Based on our calculations, the characterization of the electronic nature of the outermost cationic states differs in some instances from that proposed by Khvostenko et al. [4]. The most remarkable discrepancy lies in the assignment of the structured band at 9.4–9.6 eV, which we assign to the ionization from the $\pi_B(a_2)$ level at 9.17 eV, while Khvostenko et al. associate this band with two ionizations of $\pi_A(a_2)$ and *n*N^4 symmetry, respectively. Our assignment is supported by the observation that P3 calculations uniformly underestimate the experimental IE somewhat, and by the fact that it produces—as previously seen—an excellent IE_{calc} vs. IE_{exp} correlation (Fig. 2). A second main discrepancy refers to the assignment of the $\pi_{C=N}$ ionization, which Khvostenko et al. associate with the IE_5 at 11.42 eV in the photoelectron spectrum, while, in contrast, we assign it to the fifth ionization with *n*O and *n*N^1 character calculated at 11.21 eV. Our calculations predict the $\pi_{C=N}$ at 11.76 eV, which, on the basis of the correlation line in Fig. 2, should be found at the beginning of the broad band envelope centered at 13.32 eV in the photoelectron spectrum [4].

The electronic structure of the frontier DOs suggests that the redox properties of compounds **2** and **5** can be varied by substitution at the benzene ring.

Compounds 3 (medazepam) and 6 (nordazepam)

The outermost DOs of medazepam and nordazepam are shown in Fig. 6. The corresponding ionization energies are assigned and correlated in Fig. 7, where available experimental data are also reported for comparison. As observed in the previous compounds, **3** and **6** show the same succession of cationic states, with IE values of the carbonilic compound **6** higher than in **3** by 0.2–1 eV. The first four ionizations are of π type and are localized in the benzene rings. An *n*N^4 ionization interposes between the third and fourth π levels. The ionization with high $\pi_{C=N}$ character is calculated at 10.38 eV in **3** and at 10.97 eV in **6**. The latter value is in agreement with the experimental IE at 11.2 eV in the PE spectrum [4], while we associate the former value with the experimental band at 10.49–10.6 eV [3, 4], in agreement with the assignment of Andreocci et al. [3], but in disagreement with that of Khvostenko et al. [4] (Fig. 7). To compare theoretical and experimental data, we consider a one-to-one correlation between theoretical and experimental values. The very good correlations obtained, Fig. 8,

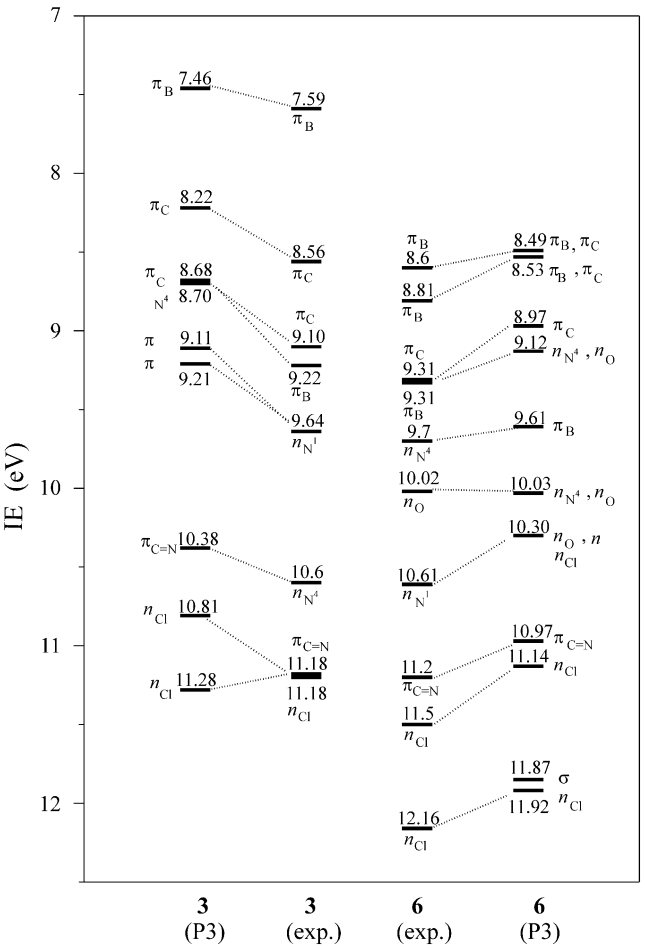

Fig. 7 Correlation diagram for compounds **3** and **6**, and comparison with experimental data

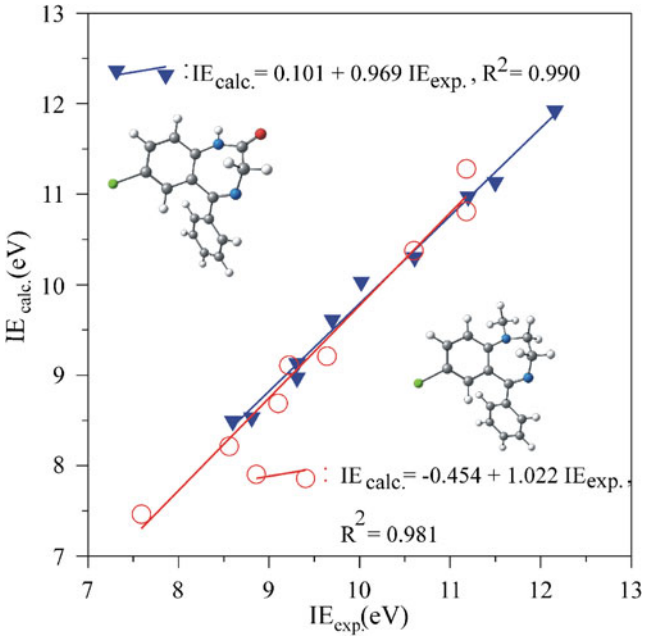

Fig. 8 IE_{calc} vs. IE_{exp} for medazepam and nordazepam

give valuable support to our assignments of the ionization processes of both benzodiazepines. The PE spectrum of medazepam was reported by Khvostenko et al. [4] and by Andreocci et al. [3]. The assignments of the ionization bands proposed by the two research groups differ noticeably from each other. The first ionization energy, at 7.7 eV in [3] and 7.59 eV in [4], was assigned to a $n\mathrm{N}^1$ lone pair ionization by Andreocci et al. and to a $\pi_B(b_1)$ ionization by Khvostenko et al. Our P3 results assign the first calculated ionization at 7.46 eV to a π_B (b_1) level, in agreement with Khvostenko et al. The band in the 8.2–10.2 eV range in the PE spectrum of **3** was associated with four ionizations by Khvostenko et al., with the energy levels $\pi_C(b_1) < \pi_C(a_2) < \pi_A(a_2) < n\mathrm{N}^4$, on the basis of the ratio area of this band envelope and the first one-electron band. On the contrary, Andreocci et al. [3] associate this multiprocess band with

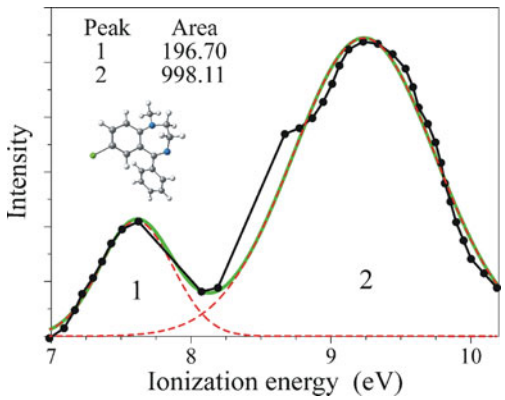

Fig. 9 Deconvolution of the 8.2–10.2 eV experimental ionization energy envelope of medazepam [4]

Table 1 Values (in eV) of vertical electron affinity VEA, vertical ionization energy VIE, hardness η = (VIE − VEA)/2, and experimental first singlet transition energy S_1 for diazepines

Compound	1	2	3	4	5	6
VIE	7.48	7.35	8.22	8.81	8.46	8.49
VEA	−0.78	−0.38	0.23	−0.14	0.13	0.60
η	4.13	3.86	3.99	4.48	4.16	3.94
S_1 [a]			3.47		4.14	3.92

[a] From [4]

five final states, in the order $n\mathrm{N}_4 < \pi_B < \pi_B < \pi_C < \pi_C$. P3 calculations associate the band with five ionizations: $\pi_C(b_1) < \pi_C(a_2) < n\mathrm{N}^4 < \pi_B(a_2) < \pi$, on the basis of the same area ratio approach as mentioned previously. This is in agreement with the results for the deconvolution of the first two ionization bands in the PE spectrum of **3** (Fig. 9), which gives an area ratio of 5.07.

In the case of compound **6**, we only notice one discrepancy from the assignment proposed by Khvostenko et al. These authors assign the third band in the spectrum at 9.7 eV to an $n\mathrm{N}^4$ ionization, while we assign it to a π_B ionization calculated at 9.61 eV and put the $n\mathrm{N}^4$ ionization (IE_{calc}=9.12 eV) in the experimental band centered at 9.31 eV. Our assignment of the ionization processes for nordazepam does not confirm the one reported by Andreocci et al. for diazepam (N^1-methylnordazepam) [3], which associates the first two IEs with $n\mathrm{N}^1$ and $n\mathrm{N}^4$ ionizations, respectively.

Vertical electron affinities

B3LYP/6-31+G* VEA values are reported in Table 1, and the electronic structures of the lowest unoccupied molecular

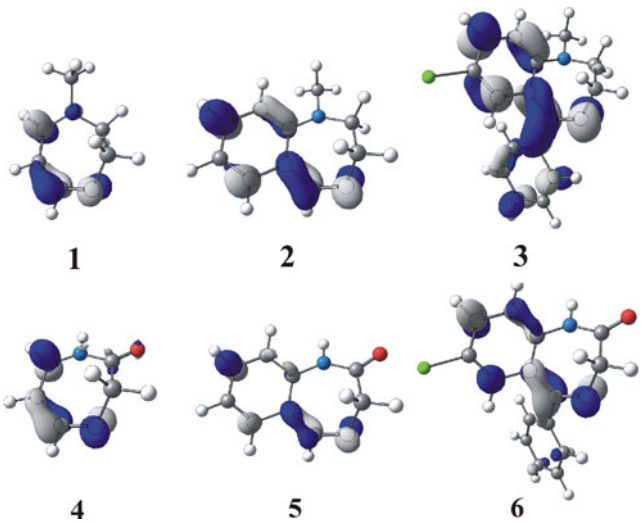

Fig. 10 Lowest unoccupied molecular orbitals of the investigated compounds

orbitals (LUMO) of the fully optimized neutral initial state, the extra electron site, are shown in Fig. 10. It can be seen that the extra charge in **3** is localized in both the benzene rings, while it is localized in **6** largely in the B ring. Therefore, the VEA of nordazepam can be varied by appropriate substitution on the benzene B ring, and by substitution on both rings in medazepam. Data in Table 1 indicate that the IEs of the seven-membered rings of diazepine are predicted to be negative; the fusion of a benzene ring and the C=O group, however, produces a significant increase in EA, so both of the benzodiazepines show positive VEA values. The IE and EA values determine the redox properties of a molecule. The values obtained indicate that medazepam is more easily oxidized (lower IE) and less easily reduced (lower EA) than nordazepam. The (IE − EA) energy gap, which determines the hardness value of a molecule, expressed as η = (IE − EA)/2, decreases along the series as: $\eta(\mathbf{1}) > \eta(\mathbf{2}) > \eta(\mathbf{3})$ and $\eta(\mathbf{4}) > \eta(\mathbf{5}) > \eta(\mathbf{6})$, with medazepam being less hard (i.e., less stable) than nordazepam. Interestingly, the computed hardness values of **3**, **5** and **6** closely follow the trend in the available experimental singlet UV transition energies [4], which seems to indicate that, in the present compounds, the hardness value follows the HOMO and LUMO positions, and configuration interaction effects during the excitation process are comparatively similar.

Summary and conclusions

The ab initio electron propagator theory in the P3/CEP-31G* approximation has been used to calculate vertical ionization energies of medazepam, nordazepam, and their molecular subunits. Vertical electron affinities were obtained by a ΔSCF procedure from the total energies of the anions and neutral compounds using the B3LYP/6-31+G* method. The electronic character of the ionization process was established by analyzing the Dyson orbitals and comparing the calculated results with available experimental and theoretical data. A comparison with previous estimates shows significant divergences in many cases. Our assignment is supported by the very good correlation we obtain between theoretical and experimental IE values. The outermost cationic states and the lowest anionic states of the investigated compounds have π character. The electron affinity of the medazepam and the ionization potential of nordazepam can be varied by substitution at both the benzene rings, while the EA of nordazepam and the IE of medazepam can be varied by substitution at the benzene B ring. Owing to the strong electron-withdrawing power of the C=O group, nordazepam has a higher EA and IE than medazepam; as a result, medazepam is a less hard (i.e., less stable) compound than nordazepam. Interestingly, the hardness values of the investigated compounds follow the trend observed for the experimental singlet UV transition energies.

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