

UV spectroscopic study and conformational analysis of domperidone

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Abstract

The UV absorption spectra of domperidone, 2-(3*H*)-benzimidazolone and 5-Cl-2-(3*H*)-benzimidazolone in CH₃CN have been studied both in the absence and in the presence of hard acids. A theoretical analysis of the electronic transitions of 2-(3*H*)-benzimidazolone has also been performed by means of quantum-mechanical methods.

Molecular mechanics (force field) calculations have been carried out to characterize the conformational space of domperidone. The results show a large number of conformers lying with 3 kcal mol⁻¹ with respect to the lowest energy structure.

1. Introduction

Understanding molecular recognition is of fundamental importance in the study of drug-receptor site interaction. Supramolecular systems are used to characterize intermolecular interactions which strongly depend on the electronic and conformational properties of the interacting molecules.

Domperidone, (I) (5-chloro-1-{1-[3-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)propyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one), potent *in vitro* antagonist of dopamine receptors, contains two 2-hydroxybenzimidazole moieties bound together through an aliphatic chain. It is sufficiently flexible to present quite a large conformational variability, while the basic benzimidazole groups are capable of interacting with hard acids.

We have therefore undertaken a study whose intent has been two-fold: first, to characterize the interaction between the above-mentioned moieties (O ligands) and magnesium ions (as hard acid and model of the cationic receptor sites) through an analysis of the electronic absorption spectra in an appropriate aprotic solvent (CH₃CN), and second, to investigate theoretically the conformational space of domperidone.

2. Experimental

2.1. Materials and methods

Domperidone (analytical grade) was kindly provided by Janssen and used without further purification. 2-(3*H*)-benzimidazolone and 5-Cl-2-(3*H*)-benzimidazolone were synthesized according to [1] and their identity was confirmed by ¹³C and ¹H NMR spectroscopy. Mg(ClO₄)₂ (analytical

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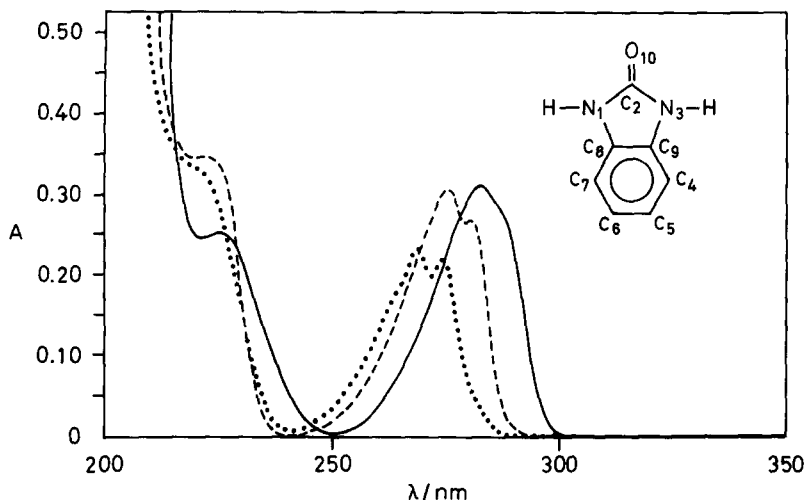


Fig. 1. UV absorption spectra of 2-(3H)-benzimidazolone (4.7×10^{-5} M): (—) in CH_3CN ; (---) in $\text{CH}_3\text{CN} + \text{Mg}(\text{ClO}_4)_2$ (1 M); (···) in $\text{CH}_3\text{CN} + \text{HClO}_4$ (1 M).

grade from Carlo Erba) was dried in an oven at 110°C for 2 h prior to its use to minimize the water content. CH_3CN (Fluka) was used for UV spectroscopy. UV spectra were recorded at 26°C on a Perkin–Elmer Lambda 16 spectrometer using 1 cm quartz cuvettes.

2.2. Computational procedures

All calculations have been run on an IBM RISC 6000 530H workstation using the GAUSSIAN 92

program package [2] to obtain accurate properties for the considered molecular systems in their excited states within the CI singles level of theory [3].

Conformational analysis of domperidone has been performed with the TRIPOS force field [4] within the SYBYL molecular modeling software package. The four relevant dihedral angles have been changed in 10° steps from 0 to 360° and the energy calculated for all the 1679616 conformers so generated. No electrostatic term was included in the energy evaluation.

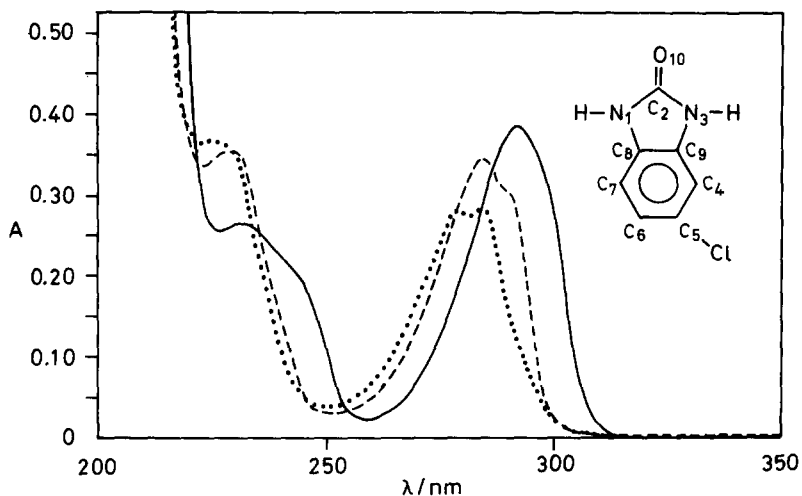


Fig. 2. UV absorption spectra of 5-Cl-2-(3H)-benzimidazolone (5.2×10^{-5} M): (—) in CH_3CN ; (---) in $\text{CH}_3\text{CN} + \text{Mg}(\text{ClO}_4)_2$ 1 M; (···) in $\text{CH}_3\text{CN} + \text{HClO}_4$ (1 M).

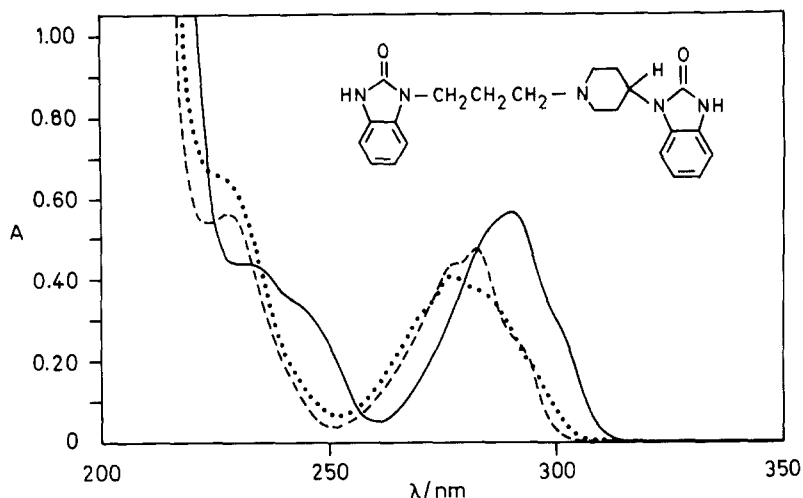


Fig. 3. UV absorption spectra of domperidone (4.62×10^{-5} M) (—) in CH_3CN ; (---) in $\text{CH}_3\text{CN} + \text{Mg}(\text{ClO}_4)_2$ (1 M); (···) in $\text{CH}_3\text{CN} + \text{HClO}_4$ (1 M).

3. Results and discussion

3.1. Electronic absorption spectra

3.1.1. 2-Hydroxybenzimidazole, II

The electronic absorption spectrum of I has been described only in connection with some analytical procedures [5,6]. In contrast, a comprehensive spectral study of the prototropic equilibria in the lowest excited singlet state of II (one chromophore of I) has been reported [7]. For such a molecule, which in solution exists mostly in the keto form (2-(3*H*)-benzimidazolone), a marked shift of its

electronic transition bands is observed on moving from organic solvents to water.

In aqueous solution, the keto form, stable in the 1–11 pH range, is protonated at the carbonyl group ($pK = -2.24$) whereas the mono anion is formed from deprotonation ($pK = 11.6$) at the NH group.

The absorption spectra of II in CH_3CN obtained in the present study are shown in Fig. 1. The large absorption band in the 250–300 nm range, characterized by a possible vibrational component, is presumably due to the overlapping of at least two electronic transitions. The presence of non-bonding electrons in the carbonyl oxygen suggests that one of these transitions has to be an $n-\pi^*$.

Table 1

Optimized (3-21G) bond lengths (Å) and angles (deg) of 2-(3*H*)-benzimidazolone (see Fig. 1)

Bond lengths		Bond angles	
C4–C9	1.370	C8–C9–C4	121.13
C8–C9	1.396	C9–C8–C7	121.13
C7–C8	1.370	C8–C7–C6	117.95
C6–C7	1.392	C5–C4–C9	117.95
C5–C4	1.393	N1–C8–C9	106.53
N1–C8	1.392	C2–N1–C8	111.25
C2–N1	1.384	N3–C2–N1	104.45
C2–N3	1.384	O10–C2–N1	127.77
O10–C2	1.210	H–N1–C8	126.60
H–N1	0.994	H–N3–C2	122.15
H–N3	0.994		

Table 2

Dihedral angles (deg) and energies (kcal mol^{-1}) for the four most stable conformers of domperidone

Conformer	$D1^a$	$D2^a$	$D3^a$	$D4^a$	E
Ia	220	70	290	300	60.26
Ib	280	290	70	250	61.00
Ic	210	80	300	290	61.13
Id	280	280	60	250	61.44

^a Dihedral angles $D1$, $D2$, $D3$ and $D4$ are defined as C15–N14–C13–C12, N14–C13–C12–C11, C13–C12–C11–N10 and C12–C11–N10–C8, respectively (see Fig. 4).

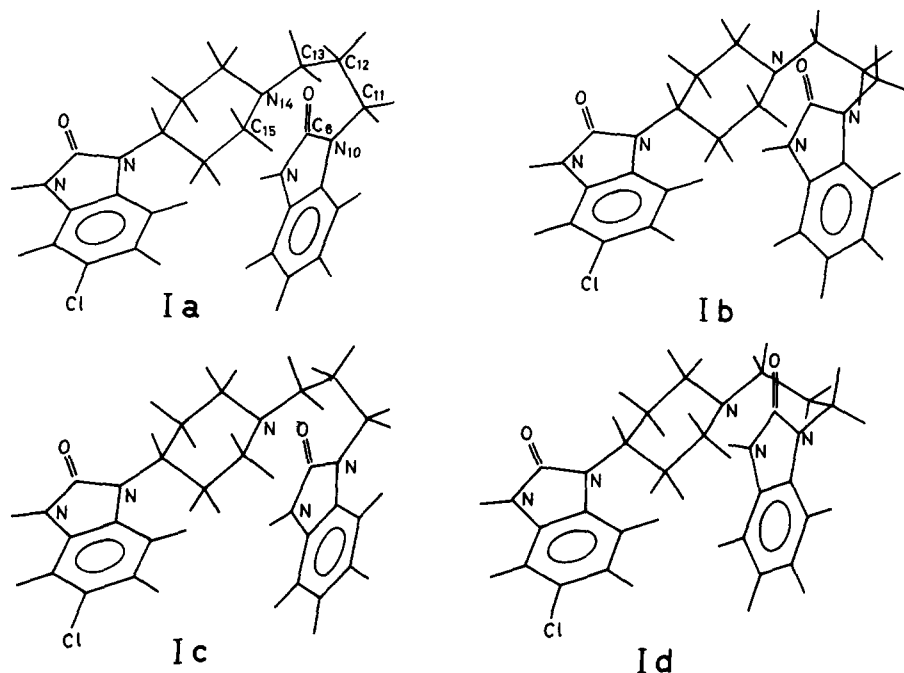


Fig. 4. The four most stable conformers of domperidone.

Such an assumption is supported by the spectral variations observed when II interacts with hard acids like Mg^{2+} ions; indeed, in addition to a better defined “structure” of the absorption band, an extra blue shift with respect to the situation observed in water is evident (see Fig. 1). These spectra perturbations arise from a solvated cation–base interaction whose associated energy is essentially due to a polarization term and which does not involve a significant charge transfer from the ligand to the cation: this last characteristic is indeed specific of a protonation process whose spectral features (an additional blue shift of the absorption bands) are also shown in Fig. 1.

It is important to underline that the chemical species present in a solution made with magnesium perchlorate and acetonitrile, both not perfectly dried, are many and are not very well defined. Quite recently [8], indications have been obtained pointing out that:

(i) the coordination number for ligands around the Mg^{2+} ion is approximately four;

(ii) ion pairing might be relatively strong ($Mg^{2+} \cdots ClO_4^-$);

(iii) the Mg^{2+} preferentially coordinates the water molecules.

3.1.2. 5-Cl-2(3H)-benzimidazolone, III

The absorption spectra of III in CH_3CN are shown in Fig. 2. The presence of a chlorine atom in the ring is responsible for the observed bathochromic shift of the 250–300 nm absorption band. The spectral variations induced by the interaction of III with Mg^{2+} in CH_3CN (see Fig. 2) are similar to those previously discussed for compound II.

3.1.3. Domperidone, I

The absorption spectra of I in CH_3CN (Fig. 3) overlaps that of an equimolar mixture of the two chromophores II and III; no dissimilar features are also observed in comparing the respective supramolecular systems “solvated magnesium cation–organic ligand”.

Such experimental results allow us to exclude, at least under our experimental conditions, an intramolecular stacking between the two benzimidazole

moieties which could take place in a “folded” conformation of the domperidone molecule.

3.2. Theoretical calculations

In order to provide theoretical support to the interpretation of the above-described absorption spectra and, in particular, to clarify the question regarding the location of the $n-\pi^*$ transition, we have performed, for compound II, ab initio “CI-singles” calculations, an adequate zeroth-order treatment for excited states. Although there appears to be deficiencies in the ability of CI-singles theory to predict accurate excitation energies, the order of states, within a given manifold, correlates with the experiment.

Vertical excitation energies have been obtained after a full geometry optimization (assuming the planarity of the ring system) of the ground state with the 3-21G basis set. Optimized bond distances and angles are listed in the Table 1. With respect to the singlet manifold, the two lowest predicted transitions have a $\pi-\pi^*$ character with a vertical excitation energy of 6.3 eV and 6.6 eV, respectively; an $n-\pi^*$ transition (7.8 eV) is predicted to give rise to the third singlet state.

The calculated energy value differences (38 nm between the first and the third transition) compare particularly well with the experimentally observed UV spectra and consequently support the presence of an $n-\pi^*$ transition in the 250–300 nm absorption band observed for compounds II and III.

3.3. Conformational analysis

The relative stabilities and dihedral angles of the most stable conformations obtained by means of force field calculations are presented in

Table 2; Fig. 4 shows the corresponding structures. The low energy conformers are “folded” and their energy differences are about 1 kcal mol⁻¹; this indicates the absence of a “dominant” conformation and a large conformational space available to domperidone. It is interesting to note that the most stable “unfolded” conformation of I ($D1 = -58^\circ$; $D2 = -166.7^\circ$; $D3 = -176.5^\circ$; $D4 = -6.1^\circ$) is predicted to have an energy value of 63.07 kcal mol⁻¹, i.e. only approx. 3 kcal mol⁻¹ more than the most stable “folded” conformer.

Such conformational mobility suggests the relevance of a possible dynamic (or induced fitting type) molecular recognition process where: (a) the role of the solvent is also determinant; (b) specific intermolecular interactions can dominate the formation of the domperidone–receptor complex.

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