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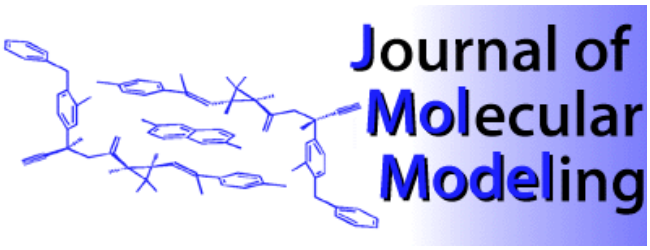

FULL PAPER

Solvation and Conformational Properties of Melatonin: a Computational Study

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Abstract The conformational space of melatonin, as defined by dihedral angles representing different orientations of the carboxamido ethyl side chain, was calculated in vacuum and aqueous solution, using the AM1 semiempirical methodology, and the AM1-SM2.2 solvation model, respectively. The effects of conformation and aqueous solvation on several molecular properties typically used as descriptors in structure-activity relationship studies, such as Mulliken charges and the HOMO-LUMO gap, were considered. In the case of the charges on the O(3) and N(4) atoms, the effects of conformation were shown to be larger than those due to structural changes, while the charge on O(16) was greatly affected by structural and very little by conformational changes. Based on the computed values for this charge in analogs with different binding affinities, we suggest that the electrostatic features of the 5-methoxy moiety do not modulate binding affinity. Taken together, our results suggest that conformational and solvation effects should be considered in order to obtain realistic structure-activity relationships of the melatonin system.

Keywords Melatonin, Conformation, Solvation

Introduction

The hormone melatonin (N-acetyl-5-methoxytryptamine) which is synthesized principally in the pineal gland, has been involved in several physiological functions, including the entrainment of seasonal and circadian rhythms.[1] In humans, melatonin is thought to be involved in the regulation of sleep, seasonal disorders, depression and aging.[2] Besides, antitumoral properties of melatonin [3], as well as the involvement of this hormone in the responsiveness of the immune system have been described.[4] The effects of melatonin seem to be mediated through membrane receptors located in different regions of the brain, in particular in the suprachiasmatic nuclei of the hypothalamus and the pars tuberalis. In some species melatonin is also synthesized by retinal photoreceptors, where it probably acts locally to regulate various aspects of retinal physiology.[5] On the other hand, recent evidence suggests that melatonin, being a highly lipophilic molecule, has pleiotropic non-receptor-mediated functions that may influence also peripheral tissues as direct targets. In this context, there has been experimental

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Table 1 *Relative energies (respect to global minimum) in kcal mol^{-1} of six conformations of melatonin and selected analogs*

	Conf.1	**Conf.2**	**Conf.3**	**Conf.4**	**Conf.5**	**Conf.6**
θ1	**180**	**180**	**90**	**50**	**-70**	**-170**
θ2	**180**	**-80**	**140**	**90**	**-40**	**150**
θ3	**0**	**60**	**0**	**0**	**0**	**60**
(1) (vacuum)	1.7	2.5	3.0	3.6	5.2	2.5
(1) (H_2O)	0.5	1.4	1.3	2.5	3.7	0.9
(2) (vacuum)	0.0	2.3	4.1	4.8	7.8	1.7
(2) (H_2O)	0.0	0.0	1.5	2.4	3.8	0.8
(3) (vacuum)	0.0	0.1	1.8	3.0	4.8	0.8
(3) (H_2O)	0.0	0.0	1.5	2.4	3.8	0.8
(4) (vacuum)	0.0	4.1	4.6	5.9	10.1	2.9
(4) (H_2O)	0.0	3.1	4.0	4.7	8.2	2.4
(5) (vacuum)	0.0	1.3	1.6	3.0	4.8	0.7
(5) (H_2O)	0.0	0.9	1.5	2.5	3.7	0.7
(6) (vacuum)	0.0	1.7	1.6	2.5	4.2	3.4
(6) (H_2O)	0.0	1.5	1.7	2.0	4.1	0.8
(7) (vacuum)	0.0	1.7	1.7	3.1	4.9	0.8
(7) (H_2O)	0.0	1.0	1.5	2.4	3.7	0.7

evidence supporting that melatonin, as an antioxidant, can protect against damage caused by free radicals.[6] In relation to this, we have recently confirmed the thermodynamical feasibility of melatonin reaction with the hydroxyl radical.[7] Newly designed potent and specific melatonin agonists and antagonists could lead to new insights into the physiological roles of melatonin. These compounds could also be applied in the treatment of disturbances of the circadian rhythms, such as those caused by transmeridional flights (jet lag) and shift work, as well as in some forms of depression and anxiety.

Quantitative structure-activity relationships studies (QSAR) have been shown to be of great importance as useful tools for the development of new drugs. They allow researchers to obtain structural information about specific receptors, and on the other hand, once a correlation between structure and activity is found, any number of related compounds can be readily screened to select molecules with the desired activity. Hitherto, the most used strategy in the search for new melatonergic drugs consisted in the synthesis of structurally-related compounds and their examination by a limited number of *in vivo* or *in vitro* biological tests. In this sense, several attempts have been performed with moderate success. Based on the bioisosteric properties of the naphtalenic ring with respect to the indolic ring and the structural similarity between melatonin and serotonin, several melatonin receptor agonists were described.[8] One alternative strategy to improve the understanding of the relationship between melatonin activity and structure may involve the comparative study of the molecular characteristics of melatonin with those of its related compounds. From this theoretical standpoint, it is important to use appropriate molecular descriptors in order to obtain a significant structure-activity correlation. Quantum chemical techniques provide a valuable tool to define a large number of molecular and local quantities characterizing the reactivity, shape and binding properties of a given molecular system that may be used as molecular descriptors. The most frequently used quantum-chemical descriptors are: net atomic charges, net group charges, orbital energies of the highest occupied molecular orbital ε(HOMO) and lowest unoccupied molecular orbital ε(LUMO), LUMO-HOMO energy gap, as well as dipole moment and polarizability.[9]

In the case of melatonin, QSAR analysis have been reported using, as molecular descriptors, the polarizability, the HOMO orbital energy, the net charge on the nitrogen of the N-acetyl group,[10] the LUMO-HOMO energy gap and the electron density in the HOMO on the side-chain nitrogen atom,[11] computed at one optimized geometry of melatonin and analogs. Frontier orbitals and polarizability are thought to be related to charge transfer and hydrophobic interactions, respectively, and it has been reported that the 5-methoxy and N-acetyl moieties are important for both ligand binding and biological activity.[10,12-14] The above mentioned QSAR studies are limited by the electronic structure calculations being performed in gas phase and on only one conformation of the molecule. Since melatonin and most of its bioisosteric analogs have been reported to be highly flexible molecules,[15] more sophisticated three-dimensional QSAR stud-

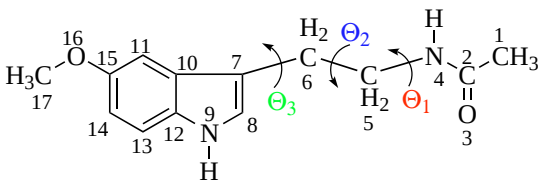


Figure 1 *Structure of melatonin*

ies have been performed in order to obtain a better insight into the structural requirements of the melatonin pharmacophore.[16-18] However, a systematic investigation of conformation effects on the molecular properties of melatonin and its analogs is still lacking, with the exception of a recent report for melatonin by Vasilescu and Broch.[19] Since in that study the solvation/conformation interplay was neglected, we considered worthwhile to carry out a systematic study taking into account both conformational freedom and solvation effects for melatonin and six bioisosteric analogs. The organization of this work is as follows: in section two we present the computational methodology, in section three we show potential energy surfaces in vacuum and in aqueous solution for melatonin and we also discuss the dependence of selected quantum-mechanically derived molecular descriptors on conformation and solvation for melatonin and the selected analogs, and finally, we present our conclusions in section four.

Methods

Calculations were performed at the AM1 semiempirical level [20] for the isolated species and using the AM1-SM2.2 model of solvation [21] for the hydrated species. This model has been successfully employed in incorporating solvent effects in related systems.[22]

Potential energy surfaces were obtained by rotating the θ1, θ2 and θ3 dihedral angles, as shown in Figure 1. Dihedral θ1 is defined as C2-N4-C5-C6, θ2 is N4-C5-C6-C7, and θ3 is C5-C6-C7-C8. Potential energy surfaces were obtained on a 36x36x4 grid generated by rotating θ1 and θ2 in 10º-increments from 0º to 360º, with θ3 taking values of 0º, 60º, 90º, and 120º. At each point of the grid the structure of the isolated systems was fully optimized with θ1, θ2 and θ3 fixed at their respective values.

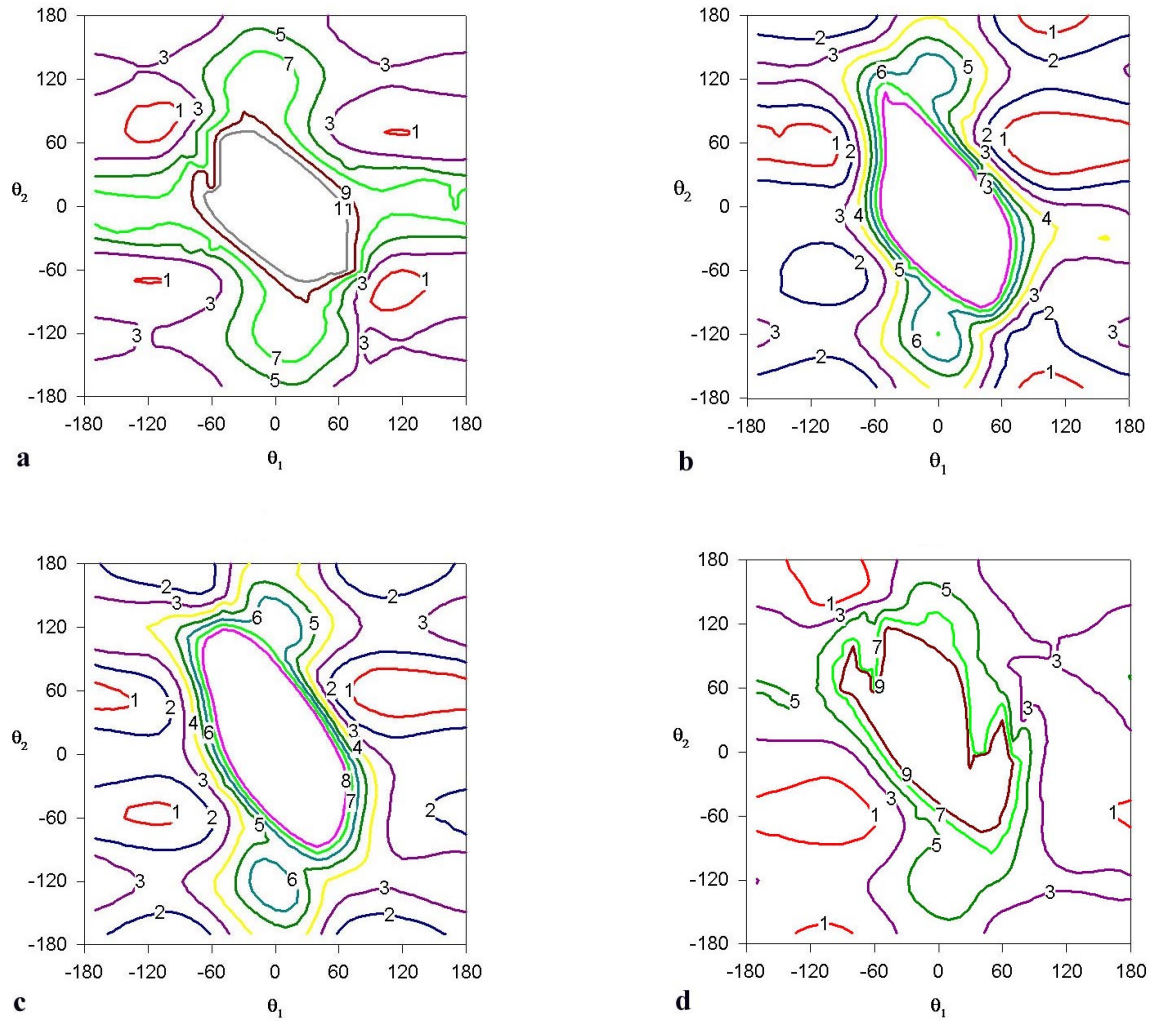


Figure 2 *Conformational energy surfaces contour plots of melatonin in vacuum with respect to the global minimum (kcal·mol^{-1}). In panels a, b, c, and d plots are shown for θ3: 0º, 60°, 90°, and 120°, respectively*

Table 2 *Charge on O(3) in (*e*) evaluated at six different conformations for Melatonin and six analogs in vacuum*

O(3)	Conf. 1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	-0.3731	-0.3690	-0.3628	-0.3590	-0.3580	-0.3699
(2)	-0.3697	-0.3737	-0.3640	-0.3645	-0.3667	-0.3700
(3)	-0.3725	-0.3678	-0.3624	-0.3595	-0.3572	-0.3691
(4)	-0.3673	-0.3741	-0.3649	-0.3666	-0.3680	-0.3659
(5)	-0.3724	-0.3691	-0.3632	-0.3605	-0.3585	-0.3696
(6)	-0.3697	-0.3691	-0.3633	-0.3629	-0.3611	-0.3682
(7)	-0.3732	-0.3693	-0.3630	-0.3595	-0.3580	-0.3700

Table 3 *Charge on N(4) in (*e*) evaluated at six different conformations for Melatonin and six analogs in vacuum*

N(4)	Conf. 1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	-0.3915	-0.3925	-0.3726	-0.3583	-0.3704	-0.3940
(2)	-0.3934	-0.3902	-0.3711	-0.3563	-0.3734	-0.3923
(3)	-0.3922	-0.3937	-0.3734	-0.3602	-0.3696	-0.3949
(4)	-0.3934	-0.3918	-0.3727	-0.3596	-0.3771	-0.3823
(5)	-0.3921	-0.3927	-0.3731	-0.3592	-0.3685	-0.3945
(6)	-0.3937	-0.3927	-0.3746	-0.3594	-0.3692	-0.3951
(7)	-0.3916	-0.3923	-0.3726	-0.3587	-0.3681	-0.3942

Table 4 *Charge on O(16) in (*e*) evaluated at six different conformations for Melatonin and six analogs in vacuum*

O(16)	Conf. 1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	-0.2135	-0.2136	-0.2140	-0.2146	-0.2140	-0.2137
(2)	-0.2120	-0.2121	-0.2125	-0.2132	-0.2126	-0.2122
(3)	-0.1996	-0.1997	-0.2000	-0.2007	-0.2001	-0.1992
(4)	-0.2119	-0.2120	-0.2126	-0.2133	-0.2126	-0.2123
(5)	-0.2349	-0.2351	-0.2354	-0.2361	-0.2355	-0.2351
(6)	-0.2096	-0.2099	-0.2102	-0.2108	-0.2102	-0.2098
(7)	-0.1891	-0.1891	-0.1897	-0.1904	-0.1898	-0.1893

Potential energy surfaces in aqueous solution were obtained by performing single-point calculations with the AM1-SM2.2 Hamiltonian at the gas phase optimized geometries. These calculations included the relaxation of the electronic structure of the solute due to solvation. All the calculations were performed using the AMSOL package.[23]

Results and discussion

The gas phase θ1, θ2 contour plots of melatonin for several values of θ3 are shown in Figure 2. Low energy regions occur between θ1 and θ2 in the intervals [–180º, –60º] and [60º, 180º] for θ3 = 0º, while for the other values of θ3, the intervals get narrower for θ2. In all cases, a very pronounced maximum occurs at θ1 = θ2 = 0º. The whole surface for θ3 = 180º (not shown) is considerably higher than the others, due to steric repulsions between the side chain and the aromatic ring, whereas the other investigated surfaces (θ3 = 0º, 60º, 90º, and 120º) lie almost at the same energy values. Our potential energy surfaces are consistent with results previously reported by Jansen et al.,[15] since all the local minima found using molecular mechanics techniques reported in that study lie at low energy regions. The conformational energy maps acquainted in this work are similar to those reported by Vasilescu and Broch, [19] who performed AM1 and *ab initio* computations to explore the conformational space of isolated melatonin. These authors reported four minima characterized by a folded ethylamido side chain (θ3 similar to 90º), which are located in low energy regions of our map. As in all cases these regions are very flat and separated by low energy

Table 5 *HOMO-LUMO difference in (eV) evaluated at six different conformations for Melatonin and six analogs in vacuum*

Homo-Lumo	Conf. 1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	8.218	8.299	8.165	8.125	8.158	8.237
(2)	8.288	8.296	8.276	8.269	8.265	8.294
(3)	8.264	8.260	8.248	8.230	8.235	8.268
(4)	8.215	8.241	8.267	8.189	8.141	8.212
(5)	7.886	7.964	7.847	7.801	7.872	7.910
(6)	7.976	7.965	7.959	7.938	7.945	7.967
(7)	7.766	7.850	7.737	7.699	7.764	7.796

Table 6 *Charge on O(3) in (*e*) evaluated at six different conformations for Melatonin and six analogs in aqueous solution*

O(3)	Conf.1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	-0.4427	-0.4465	-0.4334	-0.4224	-0.4296	-0.4471
(2)	-0.4429	-0.4477	-0.4337	-0.4236	-0.4352	-0.4463
(3)	-0.4419	-0.4462	-0.4332	-0.4229	-0.4290	-0.4466
(4)	-0.4330	-0.4525	-0.4349	-0.4309	-0.4440	-0.4419
(5)	-0.4424	-0.4467	-0.4339	-0.4233	-0.4296	-0.4470
(6)	-0.4398	-0.4488	-0.4367	-0.4304	-0.4390	-0.4456
(7)	-0.4429	-0.4465	-0.4335	-0.4224	-0.4291	-0.4471

Table 7 *Charge on N(4) in (*e*) evaluated at six different conformations for Melatonin and six analogs in aqueous solution*

N(4)	Conf.1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	-0.4024	-0.3992	-0.3907	-0.3773	-0.3868	-0.4006
(2)	-0.4038	-0.4011	-0.3910	-0.3784	-0.3929	-0.4002
(3)	-0.4035	-0.4004	-0.3915	-0.3794	-0.3866	-0.4014
(4)	-0.4075	-0.4025	-0.3914	-0.3799	-0.3958	-0.3910
(5)	-0.4030	-0.3996	-0.3911	-0.3784	-0.3853	-0.4011
(6)	-0.4064	-0.3941	-0.3925	-0.3755	-0.3806	-0.4024
(7)	-0.4026	-0.3995	-0.3906	-0.3779	-0.3849	-0.4009

barriers, their characterization is more relevant than the identification of local minima. Moreover, it is likely that the active conformations are influenced not only by the potential energy surface of the isolated molecule but also by specific interactions with the receptor that may cause the active conformation to be different from local minima.

The AM1 optimized geometry reported herein, shows a very good agreement with the X-ray structure reported for melatonin.[24] Regarding bond distances, the mean quadratic deviation is 0.0387 Å. The X-ray structure presents dihedral angles of $\theta 1 = 168.9^{o}$, $\theta 2 = 169.6^{o}$, and $\theta 3 = 6.5^{o}$, corresponding to an extended structure. The energy computed for this conformation turned out to be 5 kcal mol^{-1} above the computed global minimum. This is probably due to specific interactions in the crystal, not present in the isolated system situation, and points out to the relevance of the environmental effects in these highly flexible systems.

In order to assess the influence of solvation on melatonin conformation, we have computed the conformational contour plots for melatonin in aqueous solution, shown in Figure 3. Even if melatonin presents polar moieties, solvation does not significantly affect the features of the potential energy surfaces.

The influence of conformation on four typical molecular descriptors was investigated by computing their values in the about 6000 configurations of melatonin used in the mapping of the potential energy surfaces, both in vacuum and in aqueous solution. For sake of simplicity, we chose six selected conformations (depicted in Table 1), for which, the Mulliken charges [25] on O(3), N(4), and O(16), and the LUMO-HOMO orbital energy gap under vacuum an aqueous solution , are

Table 8 *Charge on O(16) in (e) evaluated at six different conformations for Melatonin and six analogs in aqueous solution*

O(16)	Conf.1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	-0.2242	-0.2243	-0.2237	-0.2234	-0.2234	-0.2243
(2)	-0.2211	-0.2211	-0.2206	-0.2202	-0.2203	-0.2211
(3)	-0.2220	-0.2222	-0.2216	-0.2212	-0.2212	-0.2217
(4)	-0.2186	-0.2185	-0.2181	-0.2178	-0.2178	-0.2186
(5)	-0.2417	-0.2419	-0.2413	-0.2409	-0.2409	-0.2418
(6)	-0.2260	-0.2258	-0.2253	-0.2248	-0.2245	-0.2258
(7)	-0.2107	-0.2108	-0.2104	-0.2101	-0.2101	-0.2109

Table 9 *HOMO-LUMO difference in (eV) evaluated at six different conformations for Melatonin and six analogs in aqueous solution*

Homo-Lumo	Conf.1	Conf. 2	Conf. 3	Conf. 4	Conf. 5	Conf. 6
(1)	8.438	8.449	8.429	8.417	8.416	8.452
(2)	8.368	8.375	8.361	8.350	8.342	8.378
(3)	8.272	8.286	8.263	8.250	8.259	8.292
(4)	8.318	8.309	8.310	8.297	8.273	8.319
(5)	8.327	8.330	8.328	8.328	8.352	8.320
(6)	7.606	7.624	7.595	7.596	7.612	7.617
(7)	8.327	8.325	8.330	8.331	8.353	8.316

shown in Tables 2-9, respectively. We have selected these Mulliken charges, because they can provide information about electrostatic characteristics of the N-acetyl and 5-methoxy moieties that have been proposed as relevant in the binding properties and biological activity of melatonin and some bioisosteric analogs.[12-14] All of the selected conformations were within a range of 5 kcal mol^{-1} relative to the global minimum for melatonin. The same holds for the selected analogs, with the exception of conformation five of 8-Chloro and 8-Iodo melatonin, which turned out to lie higher in energy due to steric repulsion between the halides and the ethylamide chain (Table 1). Since, as mentioned above, constraints due to the receptor structure may cause the active conformation of melatonin to have a potential energy considerably larger than in the isolated system; it is relevant to monitor how changes in conformation affect the values of the descriptors. Significant changes in the values of the O(3) and the N(4) charges with conformation were observed, while the charge on O(16) showed less sensitivity. The same trend is observed in the calculations performed in aqueous solution. The main difference consisted in the fact that in the latter case, the Mulliken charges were enhanced with respect to vacuum, as expected.

Tables 2-9 also show the values of the same descriptors evaluated at the six selected conformations for the analogs depicted in Table 10. The variations in O(3) and N(4) charges due to conformational changes turned out to be greater than those due to structural changes. This is consistent with the fact that the conformational changes considered involve the N-acetyl moiety in which the O(3) and N(4) are located. On the other hand, as discussed above, the influence of conformational changes on the O(16) charge is comparatively much smaller, while the presence of substituent groups considerably affected the electrostatic characteristics of the 5-methoxy group. However, these variations do not correlate with the binding affinities (Table 11) experimentally evaluated.[10-14] Considering as an example, the values of this parameter in conformation one of melatonin, and its 14-OCH_3 and 14-OH derivatives were -0.2135, -0.1891, and -0.2349 *e*, while their relative binding affinities were 1, 8, and 200, respectively.[10-14] Based on these results, it seems likely that the electrostatic features of the 5-methoxy moiety do not modulate the binding to the receptor. Taking together our results and the experimental evidence that replacement of the 5-methoxy group by an hydrogen or an hydroxyl group almost abolishes binding ability,[10-14] we suggest that the 5-methoxy group influences binding in a yes/no manner, probably related to the steric, besides the electrostatic features of this moiety.

In melatonin and all the analogs considered, both HOMO and LUMO are mainly localized to the indolic moiety; therefore, this descriptor may be related to stacking interactions with aromatic receptor residues.[26] In fact, there seems to be a correlation between binding affinities and this descriptor (e. g. compounds five, six, and seven that show a poor affinity, present lower values). However, consideration of solvent effect significantly modified this picture. In the latter case, the less active compound (i.e. compound six), is the only one

Table 10 *Structure of melatonin and six melatonin analogs*

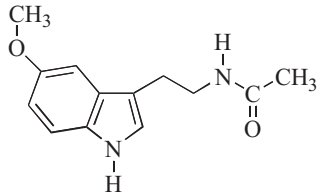
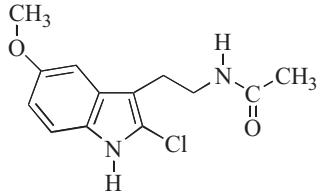
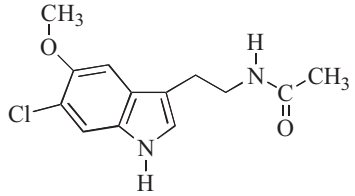
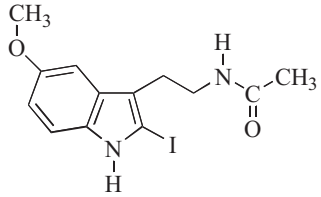
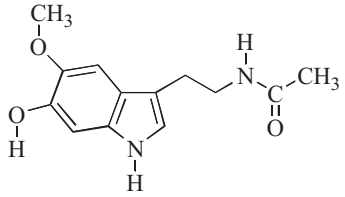
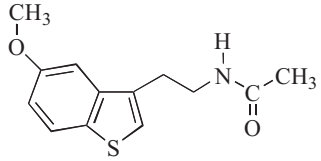
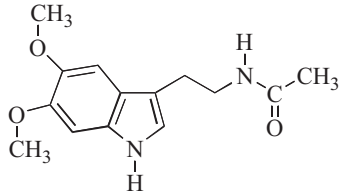
Compound	Name	Structure
(1)	Melatonin	
(2)	8-ChloroMelatonin	
(3)	14-CholoroMelatonin	
(4)	8-IodoMelatonin	
(5)	14-HydroxyMelatonin	
(6)	N-acetyl 15-methoxy benzothiophene	
(7)	14-MethoxyMelatonin	

Table 11 *Relative binding affinities for Melatonin and six analogs.[10,14]*

	Ki
(1)	1.00
(2)	0.06
(3)	1.30
(4)	0.10
(5)	8.80
(6)	200.00
(7)	7.00

presenting a significantly lower value of the HOMO-LUMO gap. As in O(16) charge in the case of this descriptor in vacuum, changes due to conformation are much smaller than those due to structural modifications.

Regarding the charges on O(3), and N(4) atoms, the situation is still less clear since there seems to be a complex interplay between conformation and magnitude of charge. For some conformations, substitution may lead to a decrease, while for others it may lead to an increase of the descriptor values. In this context, these results suggest that the explicit consideration of conformational effects is necessary when

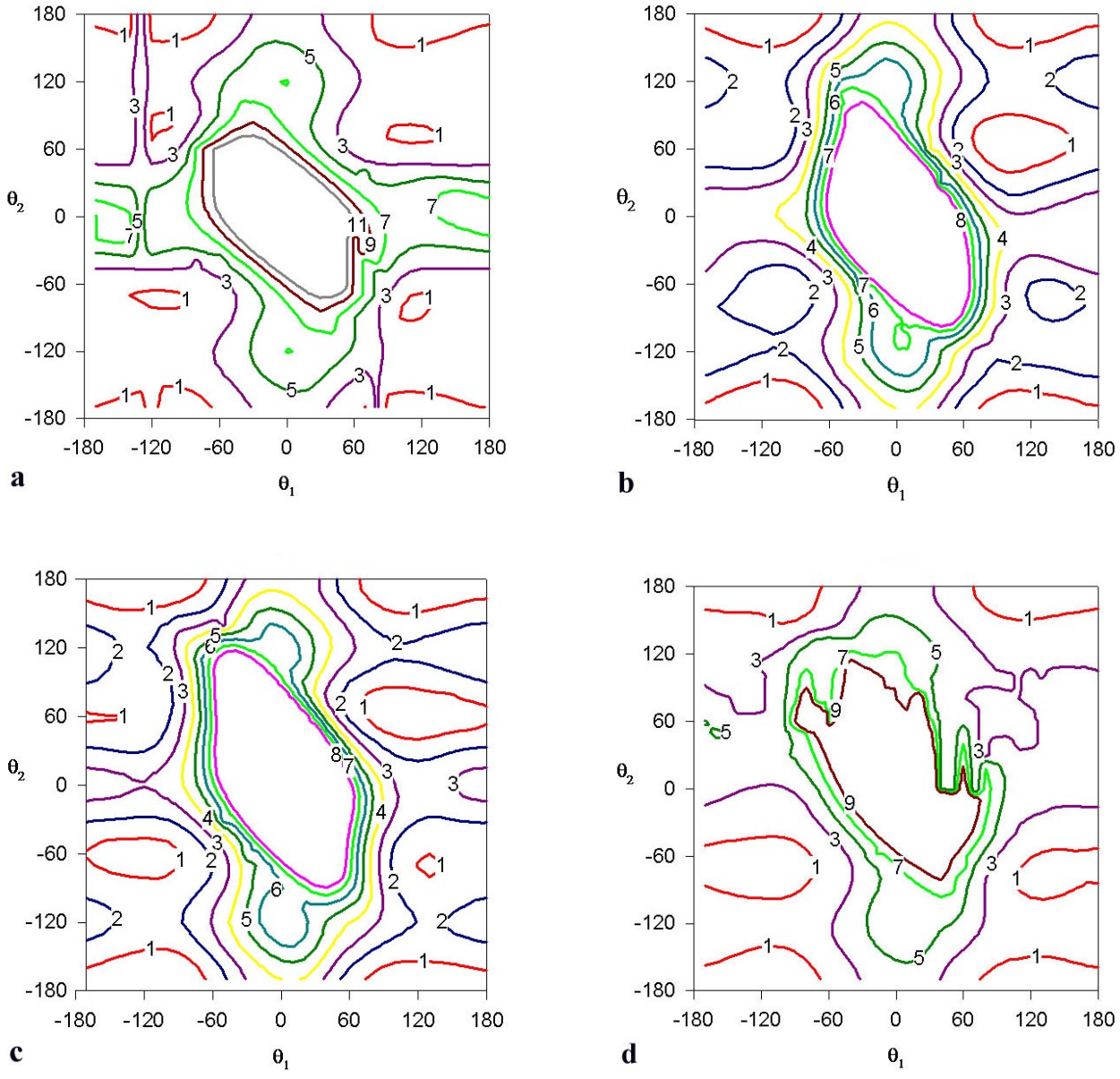


Figure 3 *Conformational energy surfaces contour plots of melatonin in aqueous solution with respect to the global minimum (kcal·mol^{-1}). In panels a, b, c, and d plots are shown for θ3: 0°, 60°, 90°, and 120°, respectively.*

accounting for the electrostatic characteristics of the N-acetyl moiety.

In going from vacuum to water solution (Tables 2-9) it can be noted that all charges get enhanced, as expected. This enhancement is larger in the case of the O(3) charge (about 21 %), than in the N(4) (about 2 %) and O(16) (about 7%). The enhancement of Mulliken charges is not always of the same magnitude, in such a way that changes due to solvation are of the same order of magnitude to those due to structural changes. As an illustrative example, we can consider the case of the O(16) charge: in vacuum, the values are –0.1996 and –0.2120 *e* for the 14-chloro and 8-chloro derivatives at conformation one, respectively, while in water solution the order is reversed, being the values (–0.2220 and –0.2211 *e*, respectively). This shows that neglecting the environment effects may lead to significant errors at trying to elucidate structure-activity relationships in these systems.

Conclusions

In the present study we show the conformational potential energy surfaces for melatonin in vacuum and in aqueous solution. We have confirmed previous results about the highly flexible nature of melatonin structure, since extense low energy regions connected by low energy barriers were found. Although the influence of aqueous solvation on the computed surfaces turned out to be minor, the electronic structure of melatonin undergoes a significant change in some cases, as reflected by the values of the molecular descriptors. We also report results for molecular descriptors of six related analogs, both in vacuum and in aqueous solution. In the case of the charges on the O(3) and N(4) atoms, the effects of conformation were shown to be greater than those due to structural changes. On the other hand, the charge on O(16) and the HOMO-LUMO energy gaps are very much affected by structural changes but very little by conformational changes. Based on the computed values for the O(16) charge in analogs with very different binding affinities, we can suggest that the relevance of the 5-methoxy moiety in binding may be related to steric, besides the electrostatic effects. Taken together, our results suggest that both conformational and solvation effects should be considered in order to obtain realistic structure-activity relationships of the melatonin system.

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Supplementary Material Available The cartesian coordinates of compounds 1-7 (conformation one) are available as separate files.

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