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Density functional molecular computations on protonated serotonin in the gas phase and various solvent media

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Abstract

5-Hydroxytryptamine (serotonin) was geometry optimized at the B3YP/6-31G(d) level of theory to determine the energetically most favourable conformations of the aromatic hydroxyl group and the protonated ethylamine side chain. The hydroxyl group was found to be most stable at *anti* for all conformations, and the two lowest energy gas phase conformers found were: $\chi_2 = g^+, \chi_3 = g^-$ and $\chi_2 = g^-, \chi_3 = g^+$. The protonated amino group was found equally stable at g^+, g^- and *anti*. The transition structures linking each gas phase minimum were also computed. Minima found were subjected to solvation calculations in chloroform, DMSO, ethanol and water, which shifted their relative stabilities.

1. Biological background

Serotonin (5-hydroxytryptamine) is a chemical messenger distributed widely throughout the body, and is formed by the hydroxylation and decarboxylation of tryptophan [1,2]. The highest concentration is found in the blood platelets and other granulated white blood cells [3,4]. Aside from acting as a chemical messenger, serotonin may also elicit a cardiovascular response. Upon platelet aggregation, sufficient amounts of serotonin are released to cause the contraction of vascular smooth muscle cells [5]. Uptake (storage) of serotonin by blood cells increases the viscosity of blood, and decreases platelet deformability [6], resulting in a restricted capillary flow. Conse-

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quently, these effects act to increase the total peripheral resistance in the cardiovascular system, possibly leading to hypertension [6]. Despite these findings, serotonin has also been shown to elicit a vasodilatory response [7,8]. Agonists such as ketanserin block the response of serotonergic receptors responsible for vasoconstriction. When this occurs, vasodilatation is the response exhibited.

Serotonin is also found in the hypothalamus, the limbic system, the cerebellum, the spinal cord and the retina. Its exact function at each site depends specifically on which receptors are present, and these neurochemical interactions are quite complex. When an electrical signal is propagated between neurons, a chemical messenger is released into the gap between adjacent neural cells, the synapse. Serotonin acts as one of these chemical messengers. Upon crossing the synapse, serotonin reacts with the 5-hydroxytryptamine receptor (5-HT) located on the post-synaptic membrane [9]. Currently, seven different receptor groups are known: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 [5]. Within each receptor group, there are several subtypes which each specify a distinct function. Most receptors have similar functions, others, however, produce entirely different responses: the 5-HT_3 receptors are ion channels and in the gastrointestinal tract, the 5-HT_4 receptors facilitate secretion and peristalsis [9].

The aromatic indole structure composed of a benzene ring fused to a pyrrole ring occurs as two isomeric forms: either indole or isoindole. Serotonin, 5-hydroxytryptamine, is a relatively simple substituted indole; it does not contain a stereocenter and is therefore achiral.

A specific geometry of serotonin is recognized at 5-HT receptor sites and knowledge of this interaction is important in drug design. There are two methods that have emerged as treatment for the neurophysiological disorders caused by serotonin imbalances. The first method involves the use of a receptor agonist for the 5-HT_1 receptor [10], where the synthesized agonists show a high affinity and selectivity for this specific receptor. The second method involves the use of ligands to inhibit transporters that remove serotonin from the synapse [11]. Once a ligand binds to a receptor, it induces a conformational change which allows for signal transduction. Certain 5-HT receptors are capable of accommodating bivalent agonists, suggesting that there are other ligands that are capable of eliciting effects with varying affinities and efficacies. It has been proposed that the high affinity binding site on the 5-HT receptor for serotonin (and similar biogenic amines) consists of an interaction between the positively charged amino group of the alkylamine side chain and a matching recognition site [12]. Herein lies the importance of conformational studies. Knowing the physiologically most favourable conformation provides a clue as to how the ligand–receptor interaction works, and how the signal transduction is carried out.

After the ligand–receptor interaction has diminished, serotonin is cleared from the synapse by reuptake molecules and broken down in the pre-synaptic neuron by monoamine oxidase B (MAOB). This is useful in treating depression as, an increased (or maintained) level of serotonin in the synapse has been found effective in alleviating depression. These two pathways of serotonin removal have been exploited with the successful development of selective reuptake inhibitors such as fluoxetine (Prozac), as well as selective MAOB inhibitors such as selegiline (deprenyl).

2. Computational method

Fully relaxed scans were performed (data not shown) on all four torsions, allowing for the deduction of the conformers that comprise this study. The torsional angles that were optimized consisted of the hydroxy group, which extends from carbon 6 and the protonated ethylamine substituent, which extends from the carbon in position 3 (Fig. 1A). Note that all numbering which describes the location of ring substituents (that is, the hydroxyl group and the protonated ethylamino group) are referred to under IUPAC rules and in the indicated figures are located next outside the ring system. Other numbering (regarding model assembly) refers to the internal

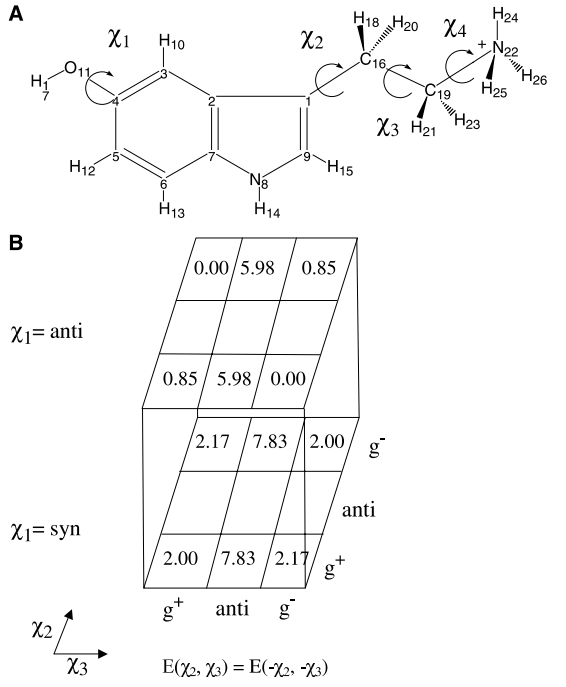


Fig. 1. (A) IUPAC numbering vs internal coordinate numbering system and defined torsional angles of Serotonin. Bold numbers outside the ring indicate IUPAC numbering and numbering in place of atoms indicates the internal numbering system. The torsions are defined: χ_1: H_{17}–O_{11}–C_4–C_3; χ_2: C_{19}–C_{16}–C_1–C_2; χ_3: N_{22}–C_{19}–C_{16}–C_1; χ_4: H_{24}–N_{22}–C_{19}–C_{16}. (B) Potential energy hypersurface. All figures reported in kcal/mol.

coordinate numbering system, and is located in the place of atoms.

Serotonin was exclusively defined using the *z*-matrix internal coordinate system to define its molecular structure, stereochemistry and geometry. The GAUSSIAN 98 [13] program was been used to optimize the geometrical parameters of serotonin. Density functional calculations were carried out at the B3LYP/6-31G(d) level of theory to optimize geometrical parameters. The above basis set was used for full optimizations of the minima found on conformational potential energy curves (PEC) (data not shown) and potential energy surfaces (PES). These are the deduced minima that comprise the potential energy hypersurface (PEHS) [14]. In order to characterize each minimum found, frequencies were computed on each supposed minimum at B3LYP/6-31G(d).

In order to further investigate the influence of the conjugated π-system on the protonated amino group in the gas phase, solvation calculations were performed. The self-consistent reaction field (SCRF) method was employed, with Tomasi's polarized continuum model (PCM) [15,16] defining the solvent cavities surrounding serotonin. Two classes of solvents were used: polar protic (ethanol and water) and polar aprotic (chloroform and dimethylsulfoxide or DMSO).

In order to deduce the transition structures, the potential energy surface was used to generate probable guesses for each structure. These guesses were inputted and the quadratic synchronous transit (QST3) [17] method was used to further optimize the guesses to a first-order saddle point. The transition structure optimizations, as well as the solvation calculations, were also carried out at B3LYP/6-31G(d).

3. Results and discussion

Serotonin was numbered in a way to allow for the modular substitution of the ring with the appropriate substituents (Fig. 1A). Scans were carried out on each of the torsions while the remaining variables remain unconstrained (data not shown). Throughout all of the scans, the orientation of χ_1 in the *anti*(180.0°) position was more energetically favourable than the syn(0.0°) position.

3.1. Potential energy surface

The potential energy surface (PES) with respect to χ_2 and χ_3 was examined (Fig. 2). Data collected is in quite good agreement with the data collected from the potential energy hypersurface. The PES, which was calculated at RHF/3-21G, was a sufficiently good indicator of the location of minima and transition structures. On the surface, there are deep minima at both the γ_D (g^+, g^-) and γ_L (g^-, g^+) positions, which were confirmed to be the global minima when χ_1 is at 180.0°, and both α_D (g^+, g^+) and α_L (g^-, g^-) the next nearest local minima. None of the supposed minima located using the PES vanished at B3LYP/6-31G(d).

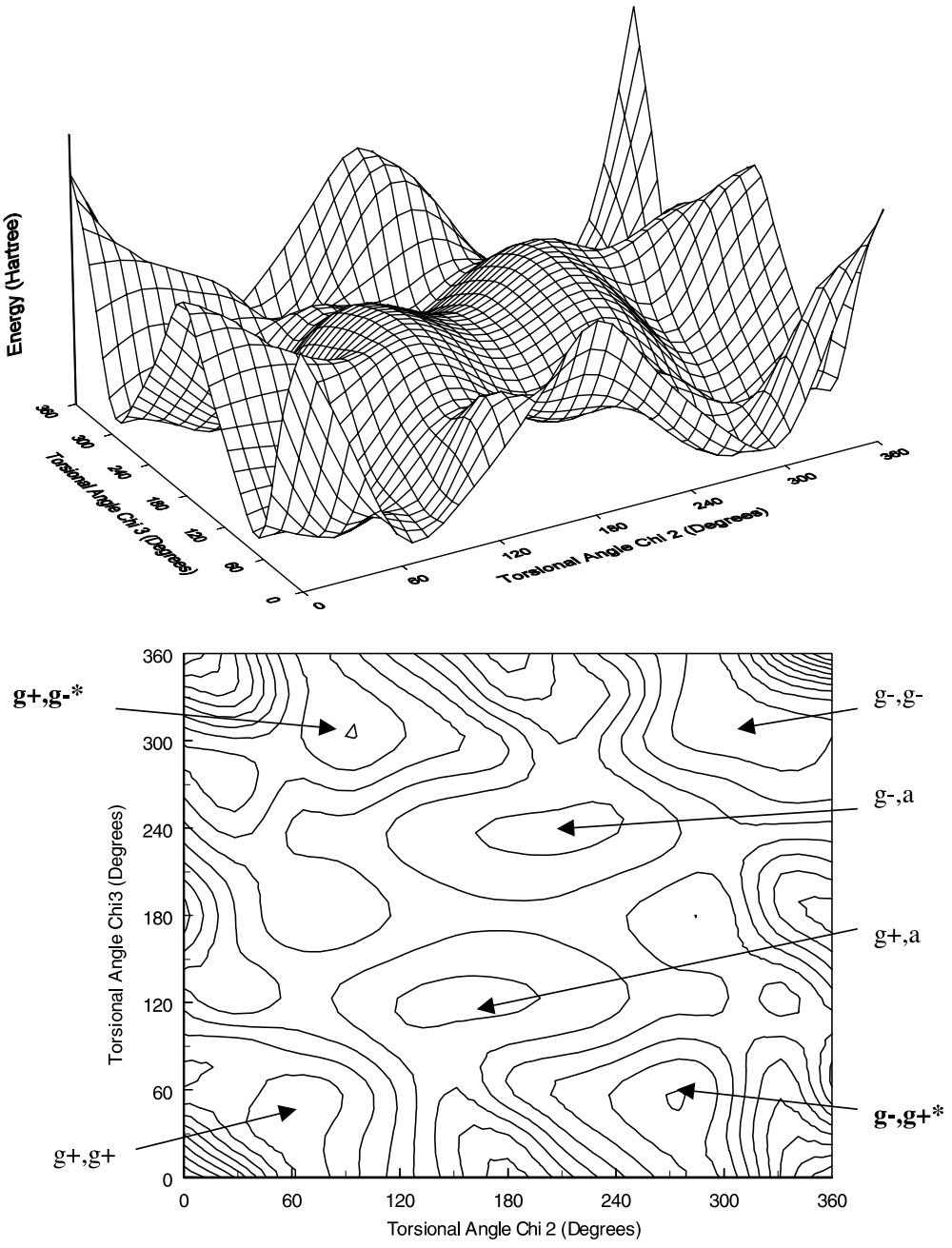


Fig. 2. Potential energy surface for $\chi_1 = \text{anti}$, $E = f(\chi_2, \chi_3)$ (global minima denoted by *).

3.2. Potential energy hypersurface (PEHS)

In order to attempt to completely explore the lowest energy conformation of serotonin, a potential energy hypersurface was constructed. For this scheme, 12 optimizations were done allowing for a full elucidation of the structure. The three torsions involved were: χ_1 on the central indole

Table 1
Optimized structures of serotonin obtained at B3LYP/6-31G(d) level of theory

Conformers			Optimized values			Energy hartree	Rel. energy kcal/mol
χ_1	χ_2	χ_3	χ_1	χ_2	χ_3		
syn	g^+	g^+	4.0	71.7	52.9	−573.386105351	2.00
syn	g^+	*anti*	4.0	76.2	−176.3	−573.376803063	7.83
syn	g^+	g^-	9.4	86.4	−52.3	−573.385832464	2.17
syn	g^-	g^+	−9.4	−86.4	52.3	−573.385832423	2.17
syn	g^-	*anti*	−4.1	−76.3	176.3	−573.376802935	7.83
syn	g^-	g^-	−4.0	−71.6	−52.3	−573.386105372	2.00
anti	g^+	g^+	177.1	68.7	52.3	−573.387929999	0.85
anti	g^+	*anti*	177.9	70.9	−172.9	−573.379761112	5.98
anti	g^+	g^-	174.9	81.1	−57.6	−573.389286362	0.00
anti	g^-	g^+	−174.9	−81.1	57.6	−573.389286362	0.00
anti	g^-	*anti*	−177.9	−70.7	172.8	−573.379760977	5.98
anti	g^-	g^-	−177.1	−68.7	−52.3	−573.387929986	0.85

moiety, and χ_2 and χ_3 on the protonated side chain. The last torsion χ_4 was not included because it is a free rotor and is subject to free rotational movement. The geometry of conformers examined in the twelve optimizations was based upon the scans (data not shown), but more heavily on the PES: six minima were found for various combinations of χ_2 and χ_3, however χ_1 exists only in the *anti* or *syn* conformation, for a total of 12 minima (at 180.0°, χ_3 was found to be a transition structure). Both the data obtained from the scans (not shown) and the PES are in very good agreement. Two energetically degenerate global minima were found: $\chi_1 = anti(174.9°)$, $\chi_2 = g + (81.1°)$ and $\chi_3 = g^-(-57.6°)$, and $\chi_1 = anti(185.1°)$, $\chi_2 = g^-(-81.1°)$ and $\chi_3 = g^+(57.6°)$ (Table 1). The next nearest energetically favourable conformers were both 0.85 kcal/mol less stable, and they were located at $\chi_1 = anti(177.1°)$, $\chi_2 = g^+(68.7°)$ and $\chi_3 = g^+(52.3°)$, and $\chi_1 = anti(182.9°)$, $\chi_2 = g^-(-68.7°)$ and $\chi_3 = g^-(-52.3°)$ (Table 1, Fig. 4). The fact that they are genuine minima was confirmed by frequency data obtained (Table 2). Each point found as a sum of the scans, PES and PEHS was characterized as a minimum-no imaginary frequencies were observed for any of the conformers.

It can be seen in Fig. 4 that the global minima have a folded conformation, which bends towards the π-system of the pyrrole segment of the indole moiety. Since the nearest amino hydrogen is over 3.5 Å away from carbon 9 (Fig. 1B), there appears to be an electrostatic interaction between the positively charged amino moiety and the aromatic π-system. It is quite probable that this interaction is responsible for the energetically preferred conformations in the gas phase.

Table 2
Low lying frequency data for optimized serotonin at B3LYP/6-31G(d) level of theory

Input torsions			Vibrational frequencies (cm^{-1})[a]
χ_1	χ_2	χ_3	
syn	g^+	g^+	45.9, 87.9, 133.1, 154.9, 183.8, 245.2
syn	g^+	*anti*	44.3, 74.8, 88.6, 154.4, 192.6, 203.1
syn	g^+	g^-	48.3, 90.5, 113.2, 155.1, 199.0, 211.8
syn	g^-	g^+	48.2, 90.5, 112.9, 155.1, 198.9, 211.7
syn	g^-	*anti*	44.3, 74.8, 88.6, 154.4, 192.6, 203.1
syn	g^-	g^-	45.9, 87.9, 133.1, 154.9, 183.8, 245.2
anti	g^+	g^+	43.1, 88.0, 134.5, 154.3, 83.2, 241.9
anti	g^+	*anti*	53.1, 74.2, 88.4, 153.9, 193.1, 210.3
anti	g^+	g^-	57.1, 95.9, 121.9, 157.2, 195.5, 225.3
anti	g^-	g^+	57.1, 95.9, 121.9, 157.2, 195.5, 225.4
anti	g^-	*anti*	53.5, 74.2, 88.5, 154.0 193.2, 210.2
anti	g^-	g^-	43.6, 88.0, 134.5, 154.3, 183.2, 241.9

[a] First six vibrational frequencies shown.

In order to illustrate the potential energy hypersurface, Fig. 1B was generated. Fig. 1B expresses the energetic relationship between different conformers and the two equivalent global minima. The relationship between the enantiomeric pairs may be expressed by the function

Table 3
Solvation data for serotonin in various polar protic and aprotic media

Conformers			Energy in solvent medium (hartree)				
χ_1	χ_2	χ_3	Gas phase (SCF)	Chloroform	DMSO	Ethanol	Water
syn	g^+	g^+	−573.386105351	−573.483753715	−573.483753715	−573.483753715	−573.483753715
syn	g^+	anti	−573.376803063	−573.461927868	−573.461927868	−573.461927868	−573.461927868
syn	g^+	g^-	−573.385832464	−573.486016418	−573.486016418	−573.486016418	−573.486016418
syn	g^-	g^+	−573.385832423	−573.486034724	−573.486034724	−573.486034724	−573.486034724
syn	g^-	anti	−573.376802935	−573.461927868	−573.461927868	−573.461927868	−573.461927868
syn	g^-	g^-	−573.386105372	−573.483742234	−573.483742234	−573.483742234	−573.483742234
anti	g^+	g^+	−573.387929999	−573.490761446	−573.490761446	−573.490761446	−573.490761446
anti	g^+	anti	−573.379761112	−573.467624575	−573.467624575	−573.467624575	−573.467624575
anti	g^+	g^-	−573.389286362	−573.497286550	−573.497286550	−573.497286550	−573.497286550
anti	g^-	g^+	−573.389286362	−573.497367670	−573.497367670	−573.497367670	−573.497367670
anti	g^-	anti	−573.379760977	−573.467593537	−573.467593537	−573.467593537	−573.467593537
anti	g^-	g^-	−573.387929986	−573.490756677	−573.490756677	−573.490756677	−573.490756677

$$E(\chi_2, \chi_3) = E(-\chi_2, -\chi_3),$$

where, on the two potential energy surface cross-sections of Fig. 1B. The pairs are related by their identical energy differences from the global minima. The next most energetically stable pairs for $\chi_1 = \text{anti}$: $[\chi_2 = g^+, \chi_3 = g^+]$ and $[\chi_2 = g^-, \chi_3 = g^-]$, which are both less stable by 0.85 kcal/mol (Table 1). The following pair reside on the lower cross-section for $\chi_1 = \text{syn}$: $[\chi_2 = g^+, \chi_3 = g^+]$ and $[\chi_2 = g^-, \chi_3 = g^-]$. This pair is less stable by 2.00 kcal/mol.

3.3. SCRF solvations

Each observed minimum was also subjected to a solvated environment, which varied from polar protic solvents to polar aprotic solvents (Table 3). The protic solvents employed were water and ethanol, with dielectric constants of 78.39 and 24.55, respectively. The aprotic solvents employed were chloroform and dimethylsulfoxide, which have dielectric constants of 46.70 and 4.9, respectively. The SCF energies of all four solvating environments were plotted against their respective gas phase energies (Fig. 3). Curves A–D are plots of the relative energies of the solvated conformers against $y = x$, where x is the relative energy in the gas phase. Graphs A and B (polar aprotic solvents chloroform and DMSO, respectively) show a decrease in the observed energy difference between conformers in the gas phase. When serotonin is solvated by chloroform (Fig. 3, Graph A) the largest energy difference between the gas phase global minimum ($\chi_1 = anti$, $\chi_2 = g^+$, $\chi_3 = g^-$ or $\chi_1 = anti$, $\chi_2 = g^-$, $\chi_3 = g^+$) and the least energetically favourable minimum found ($\chi_1 = syn$, $\chi_2 = g^+$, $\chi_3 = anti$ or $\chi_1 = syn$, $\chi_2 = g^-$, $\chi_3 = anti$) is reduced from 7.83 kcal/mol to approximately 2 kcal/mol. As well, two conformers become slightly more stable than the global minimum. Upon solvation by DMSO (Fig. 3, Graph B), there is a drastic reduction in the overall energy difference as, four conformers actually become more energetically favourable than the gas phase global minimum. This trend continues with the polar protic solvents ethanol and water (Fig. 3, Graphs C and D, respectively). In both solvents, the same seven conformers emerge as being more energetically favourable than the gas phase global minimum however; the solvation effects are of a slightly greater magnitude in water, owing to its greater polarity. Of these seven conformers, the most stable is $\chi_1 = anti$, $\chi_2 = g^-$, $\chi_3 = anti$, which is 1.90 kcal/mol more energetically favourable. Although these solvation effects do change the relative stabilities of conformers, they do not do so drastically. A similar trend is seen in the $\Delta G_{\text{Solvation}}$ values (Table 4, Fig. 3, Graph F), as the less energetically favourable minima have much greater (negative) values than the more favourable minima. These observed effects are conserved through

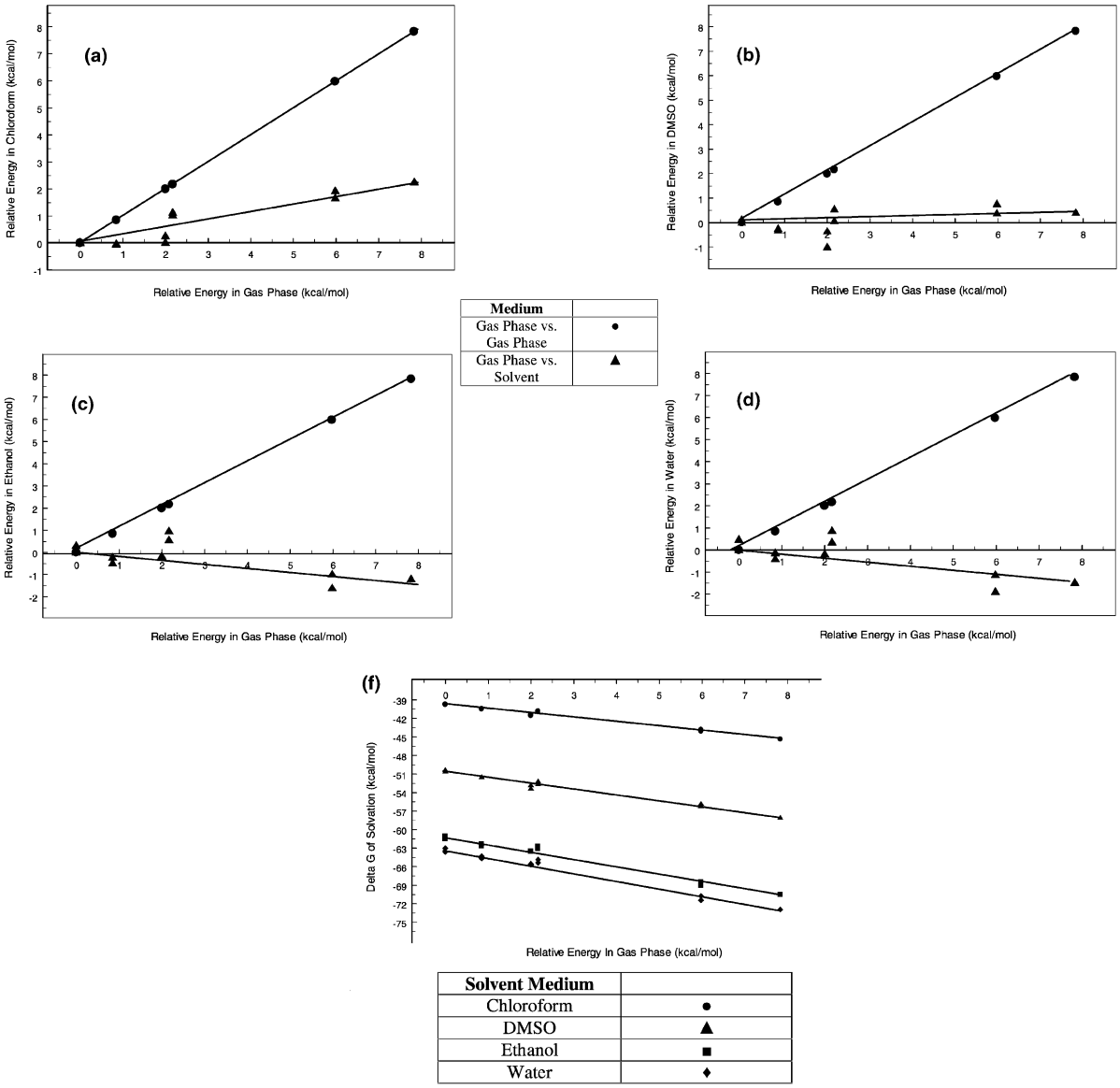


Fig. 3. Schematic diagram of minima and adjoining transition structures.

both protic and aprotic solvents, as they exhibit near parallel slopes. The cause of this shift in relative conformational stability is due to an increased solvent interaction with conformers that have an outstretched ethylamine side chain ($\chi_1 = anti,\ \chi_2 = g^-,\ \chi_3 = anti$) in comparison to those that are curved towards central indole moiety ($\chi_1 = anti, \chi_2 = g^+, \chi_3 = g^-$ or $\chi_1 = anti, \chi_2 = g^-, \chi_3 = g^+$). The polarized continuum model defines the solvent cavities as interlocking atomic spheres, which are better suited to establishing more solvating spheres on an outstretched structure as opposed to one that is more compact. Therefore, in a physiological scenario (solvated by water) one may assume that serotonin may exist as one of the outstretched conformers, possibly interacting with the 5-HT receptor in this conformation as well.

Table 4
ΔG of solvation for serotonin various polar protic and aprotic media

Conformers			$\Delta G_{Solvation}$ (kcal/mol)			
χ_1	χ_2	χ_3	Chloroform	DMSO	Ethanol	Water
syn	g^+	g^+	−41.40	−52.83	−63.58	−65.66
syn	g^+	anti	−45.37	−58.08	−70.54	−72.93
syn	g^+	g^-	−40.83	−52.17	−63.10	−65.35
syn	g^-	g^+	−40.92	−52.67	−62.69	−64.85
syn	g^-	anti	−45.37	−58.08	−70.54	−72.93
syn	g^-	g^-	−41.58	−53.37	−63.52	−65.56
anti	g^+	g^+	−40.52	−51.53	−62.70	−64.66
anti	g^+	anti	−43.82	−55.85	−68.49	−70.75
anti	g^+	g^-	−39.77	−50.58	−61.49	−63.59
anti	g^-	g^+	−39.71	−50.39	−61.11	−63.03
anti	g^-	anti	−44.10	−56.21	−69.07	−71.44
anti	g^-	g^-	−40.46	−51.49	−62.38	−64.31

Table 5
Torsional angles of transition structures linking minima

Minimum 1		Transition structure		Minimum 2	
χ_2	χ_3	χ_2	χ_3	χ_2	χ_3
81.1	−57.6	**82.76**	**−45.75**	−70.7	172.8
−70.172	172.8	**−52.95**	**−40.02**	−68.7	−52.3
−68.7	−52.3	**−70.99**	**−186.89**	−81.1	57.6
−81.1	57.6	**−82.76**	**45.79**	70.9	−172.9
70.9	−172.9	**144.12**	**74.03**	68.7	52.3
68.7	52.3	**71.01**	**−173.10**	81.1	−57.6
−70.7	172.8	**179.8**	**179.9**	70.9	−172.9

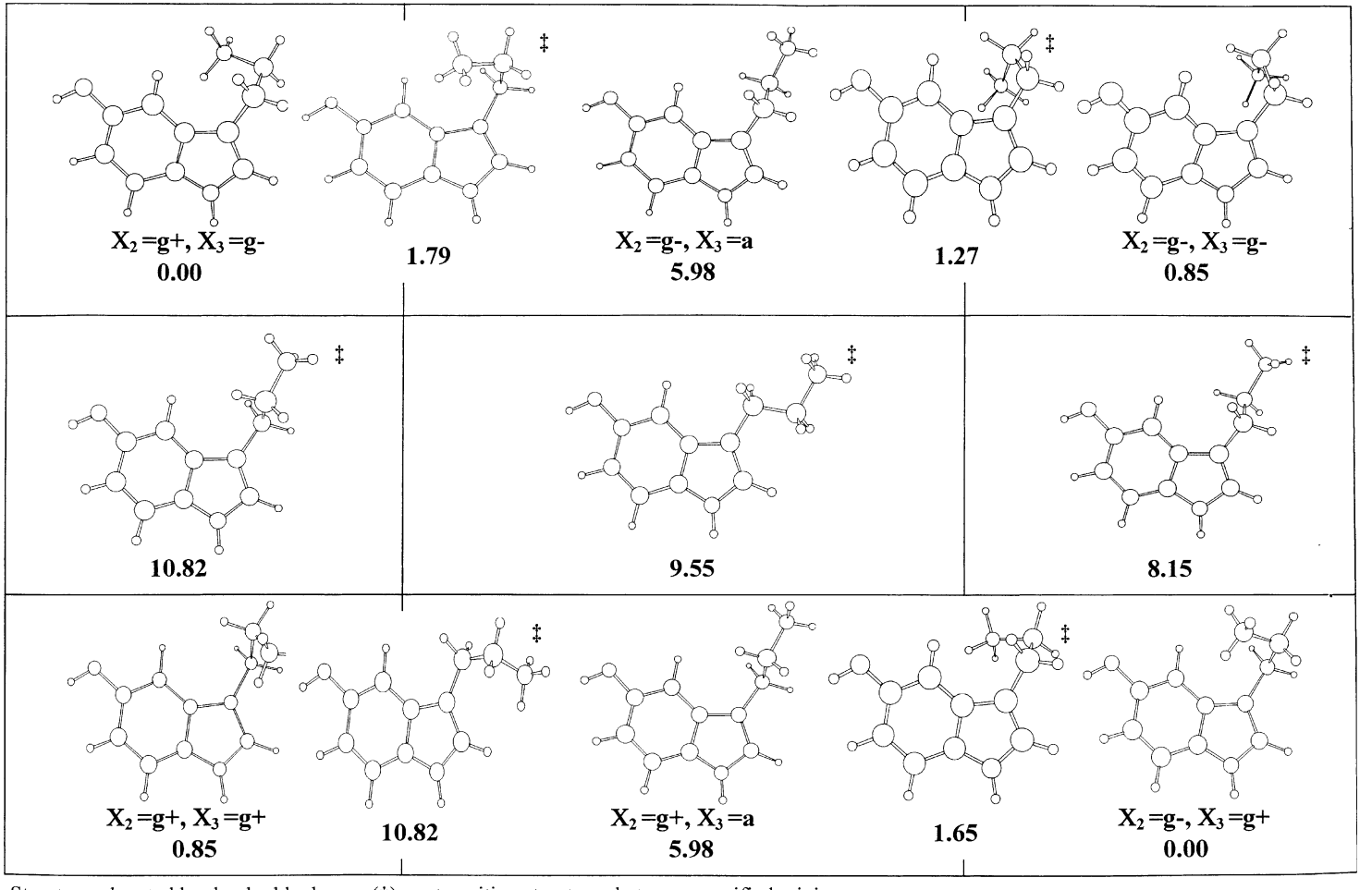
3.4. Conformational reaction-pathways

Using the PES, the reaction intermediates between conformers were calculated. Initial guesses used in the QST3 calculations came from the supposed saddle points on the surface. The torsional angles of the transition structures are listed in Table 5. In addition, a schematic diagram (Fig. 4) shows all of the structures found in this study, where $\chi_1 = anti$ (minima and transition structures), as well as their respective gas phase energies and placement.

4. Conclusions

Protonated serotonin was subjected to conformational analysis at the DFT level in the gas phase. The global minimum corresponded to two equivalent side chain orientations: g^+, g^- as well as g^-, g^+. The aromatic hydroxyl group was coplanar, with a small energy difference for the two orientations. The protonated ethylamine group oriented itself nearly perpendicular to the aromatic ring, energetically degenerate in the two equivalent orientations. Conformational transition states were also determined by the use of quadratic synchronous transit between each pair of minimum energy points.

A solvation study was carried out on all conformers using four solvents (chloroform, dimethylsulfoxide, ethanol and water). It was found that the relative conformational stability increased with solvent polarity and, correspondingly, the free energy of solvation was the greatest for water.



Structures denoted by the double dagger (‡) are transition structures between specified minima.

Fig. 4. Schematic diagram representing the set of transition states between global minima. All figures reported in kcal/mol.

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