A Molecular Orbital Study of the Conformational Properties of Tyramine and Phenethylamine

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The conformational behavior of tyramine and phenethylamine has been explored using a combination of MP2/6-31G(d,p) and CIS//MP2/6-31G(d,p) ab initio calculations. Seven stable conformer structures have been calculated for tyramine and four for phenethylamine. The increase in the number of conformers in going from phenethylamine to tyramine is due to syn and anti orientations of the hydroxyl and ethylamine substituents and can be related to an asymmetry in the electron density in the HOMO, similar to that found in phenol. In phenethylamine, the direction of the transition dipole moment (TDM) is predicted to vary significantly between different conformers, in agreement with experimental measurements. In both molecules, the electron density distribution in the frontier orbitals is sensitive to the orientation of the substituents and can be described by orbital mixing of the HOMO/HOMO-1 and the LUMO/LUMO+1. In phenethylamine, the electron density in the LUMO and LUMO+1 is particularly sensitive to the conformation of the alkylamine tail and this accounts for the change in the orientation of the TDM between different conformers. The presence of the hydroxyl group in tyramine is predicted to greatly reduce rotation of the TDM between different conformers. The OH group fixes the electron density distribution in the frontier orbitals into a phenol-like pattern. The effect of the OH group can be rationalized in terms of orbital mixing.

1. Introduction

Many biologically relevant molecules have as their basic skeleton an aromatic ring with a short alkyl or alkylamine side chain. The flexibility of the side chain allows such molecules to exhibit conformational isomerism and exist as mixtures of both folded (where the terminal atom of the side chain is located over the aromatic ring) and extended (with the side chain extending away from the ring) conformers.[1−7] Supersonic jet studies have shown that many amino acid analogues,[8,9] alkyl benzenes,[10−16] alkyl phenols,[17−19] and neurotransmitter[20−23] molecules display multiple stable molecular conformers. For certain *p*-alkyl substituted phenols (*p*-isopropylphenol, *p*-*sec*-butylphenol, and *p*-*tert*-butylphenol) a doubling of spectral features compared with those of the corresponding alkylbenzene has been observed.[11,17,18] In a previous paper, we interpreted this conformational doubling in terms of a symmetry-induced modification of the ground-state electron density coupled with favorable hyperconjugative interactions between the ring and alkyl tail sections of the molecule.[24]

Recent interest has focused on the observation that the orientation of the $S_1 \leftarrow S_0$ transition dipole moment (TDM) often changes between different conformer structures of the same molecule,[13,16,25,26] indicating a conformationally induced change in the electronic structure of the molecule in its ground and/or excited electronic states. Thus, different conformer structures may possess differences in their reactivity, an effect that could be highly significant if the molecule in question were biochemically active. Another interesting, related phenomenon revealed in the work of Simons et al. is that on introduction of a *p*-hydroxyl group (e.g., going from 2-phenylethanol to *p*-tyrosol and from phenylpropionic acid to 4-phenolpropionic acid), the rotation of the TDM between molecular conformers is greatly reduced.[27,28]

Phenethylamine and tyramine are two molecules of biological interest that display multiple molecular conformers. These molecules are structurally similar: both consist of a benzene ring with an ethylamine tail, but tyramine also possesses a hydroxyl group located para to the tail, as shown in Figure 1. Phenethylamine is the simplest of a family of aromatic neurotransmitter molecules, which includes dopamine and amphetamine, and as such has attracted much attention both computationally and experimentally.[9,29−33] Four origin bands are observed in the laser-induced fluorescence (LIF) excitation spectrum and these have been interpreted in terms of four different conformer structures of the molecule.[9] A possible fifth conformer band, observed by Sun and Bernstein,[33] has been recently reassigned as a phenethylamine−water complex, from its partially resolved rotational band contours and mass-selected R2PI spectrum.[29] Further rotational band contour analysis of the LIF excitation spectrum[32] has shown that two of the conformers have the amino group positioned above the ring, while the remaining two structures have the tail oriented away from the ring in an extended manner. The extended conformers display rotational contours corresponding to a transition dipole moment that is orientated along the short axis of the benzene ring. The folded conformers, in contrast, show hybrid rotational band contours, indicative of a transition dipole moment which is rotated toward the long molecular axis. Millimeter wave studies on the two most intense bands observed in the LIF

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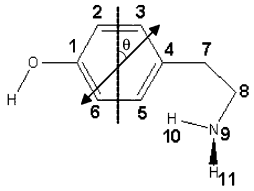

Figure 1. Atom numbering scheme and definition of the angle of rotation, θ, of the TDM for tyramine (and phenethylamine). Torsional angles are defined as follows: τ_1 (C3−C4−C7−C8), τ_2 (C4−C7−C8−N9), and τ_3 (C7−C8−N91−H10). H10 lies in the plane of the benzene ring when $\tau_3 = 0$. The structure shown has $\tau_1 = \tau_2 = \tau_3 = 0$.

spectrum have confirmed that they belong to the two folded conformations of the molecule.[21] Much of the computational work on the molecule has been published in tandem with the experimental studies, with several groups publishing ab initio structures which are consistent with available experimental evidence.[21,29,31,33]

Tyramine, a basic analogue of the amino acid tyrosine, has been much less thoroughly studied than phenethylamine. The LIF excitation spectrum displays six distinct conformer origin bands.[8,9] Unfortunately, the spectrum has not yet been recorded at rotational resolution. Relatively few computational studies have focused on this molecule. Levy et al. proposed three conformer structures, on the basis of semiempirical calculations, and suggested a further three could be generated by different, unspecified orientations of the amino group.[9] A molecular mechanics study[34] employing MM2 predicted 9 conformer bands, although no structures were published, while a Hartree−Fock ab initio study,[35] optimized at the HF/3-21G level, predicted only three stable conformer structures. Tyramine is closely related to the neurotransmitter molecule *p*-methoxyphenethylamine which shows seven conformer origin bands in its LIF spectrum,[22,36] and for which seven stable conformer structures have been calculated that are in good agreement with the high-resolution rotational structure of the origin bands.[36]

In this paper we report ab initio calculations, exploring the conformational properties of tyramine and phenethylamine, including the number, geometry and electronic structure of stable conformers, the conformer dependence of the TDM orientation, and the influence of the OH group on these properties.

2. Method

All calculations were carried out using the Gaussian 98 (G98)[37] software package, running under Linux on a PC. Initial geometry optimizations and ground-state electronic structure calculations (molecular orbitals) were conducted at the MP2/6-31G(d,p) level of theory. This combination of ab initio method and basis set has been shown to be successful in predicting the structures of similar molecules, with the optimized geometries agreeing well with those available from experiment.[38−40]

The four lowest energy structures of phenethylamine have been calculated previously using MP2 with a variety of basis sets.[21,28,31−33] Initial structures for optimization were based on these previously published structures, and the potential energy hypersurface was explored by sequential variation of the ethylamino torsional angles τ_1, τ_2, and τ_3, as defined in Figure 1. For tyramine, an additional degree of freedom was introduced with the hydroxyl torsion. Each optimized structure was verified to be a local minimum by the absence of any imaginary vibrational frequencies.

The excited state wave function for each conformer was evaluated using configuration interaction taking into account only single excitations (CIS). The CIS calculations were used to examine the electronic structure in S_1 and to determine the orientation of the electronic transition dipole moment (TDM) for the $S_1 \leftarrow S_0$ transition. Since the electronic transition is vertical, the TDM was calculated using the excited-state wave function derived from the MP2 optimized ground-state geometry. The orientation of the TDM is defined as the clockwise angle of rotation away from the short axis of the benzene ring, as shown in Figure 1.

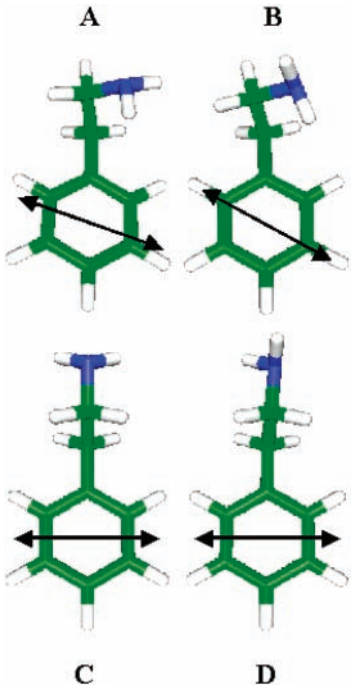

Figure 2. Structures of the four conformers of phenethylamine predicted by MP2/6-31G(d,p). The arrows indicate the predicted orientation of the TDM.

TABLE 1: Torsional Angles, Relative Energies, Orientation of TDM, and Distance of Amino Hydrogen above Ring (Folded Conformers), for the Four Conformers of Phenethylamine, Calculated from MP2/6-31G(d,p)

	A	B	C	D
τ_1/deg	79.7	85.1	89.7	88.9
τ_2/deg	61.1	66.4	179.9	180.9
τ_3/deg	60.8	175.3	58.1	177.7
E_{rel}/cm^{-1}	39.0	0.00	325.9	462.7
θ/deg	22	32	0	3
NH···C/Å	3.112	2.879		

3. Results and Discussion

3.1. Structures of Phenethylamine Conformers. With use of MP2/6-31G(d,p), four stable conformers are predicted for phenethylamine and are shown in Figure 2. The structures are in excellent agreement with those calculated by Dickinson et al.[29] and Sun and Bernstein.[33] The most stable calculated structure is that of conformer B, with the amino hydrogen located 2.879 Å above carbon 5 in the ring. The calculated geometrical parameters and relative energies of the four structures are summarized in Table 1.

CIS calculations showed that the geometry of the first excited state is not significantly different from that of the ground state for any of the conformers. The main change on excitation is a quinoidal-type distortion to the ring bonds. Experimentally, this is manifest in the appearance of only minimal vibronic structure in the LIF excitation spectrum.

The orientation of the $S_1 \leftarrow S_0$ TDM for each conformer, determined from CIS calculations, is shown in Figure 2 and

Table 1. The calculated orientation of the transition dipole moments for the various conformer structures are consistent with those determined experimentally.[29] For the extended conformers (C and D), the TDM is orientated almost parallel with the short axis of the benzene ring, whereas both the folded conformers (A and B) show a rotation in the orientation of the TDM toward the long axis of the benzene ring.

Conformer B is calculated to be the lowest energy conformer for this level of theory and basis set. However, the energies and energetic ordering of the conformers of phenethylamine and similar molecules are observed to be quite sensitive to the combination of computational method and basis set.[21,28,31−33] For MP2 calculations, a large difference in energy is observed between the folded and the extended molecular conformers. Such a difference is probably due to the problem of basis set superposition error, BSSE, to which MP2 calculations are know to be susceptible. In the folded conformations the tail section of the molecule also has access to the basis functions on the ring section of the molecule, and vice versa. This produces a large stabilizing interaction favoring the folded conformers over the extended. Estimates of the BSSE, using the counterpoise method, for phenethylamine[41] are on the order of 150% of the energy difference between conformer structures at the MP2/cc-pVTZ level of theory. Thus, conformer energies calculated in this way are tentative, at best.

A standard alternative to MP2 calculations is density functional theory (DFT). With use of the B3LYP functional, the conformer structures are essentially identical to those determined using MP2, with only slight differences in bond lengths and bond angles. The energy spread of the conformers is, however, much reduced (around 100 cm^{-1}) with the 6-31G(d,p) basis set. Conformer B is again calculated to be the most stable. The dependence of the energy on the electron density, instead of the wave function, as in MP2, means that DFT methods are generally much less susceptible to the size of the basis set used, and hence, to the problem of BSSE (which essentially stems from an effective increase in the quality of the basis set for folded conformers). However, DFT methods have been shown to struggle when dispersion interactions are taken into account.[42] In the case of phenethylamine, and tyramine, the positioning of the amine group over the ring at a distance of around 2.8 Å is certainly due to some type of van der Waals interaction. It is possible that the DFT calculations are underestimating this stabilizing interaction and hence B3LYP calculated energies are equally tentative.

In this work, our concern is not with the conformer energies but how the electronic structure affects conformational behavior. In this respect, both B3LYP and MP2 give essentially identical results for the electronic structure of the ground state for both phenethylamine and tyramine. Though the MP2 calculations are primarily discussed, the phenomenological observations were also reproduced using B3LYP electronic structure calculations.

3.2. Structures of Tyramine Conformers. For tyramine, seven stable conformer structures are predicted and these are shown in Figure 3. In all structures, the OH group lies in the plane of the ring, as in phenol.[24] The minimum energy structure is conformer A_1, with the NH_2 group located 2.98 Å above carbon 3 in the ring. Table 2 lists the energies, geometrical parameters, and TDM orientations for the seven conformers. The stable conformers of tyramine have very similar orientations of the alkylamine tail to the phenethylamine conformers. The extra conformers observed in tyramine are due to different relative orientations of the alkylamine chain and the hydroxyl group. Thus, conformers A, B, and D in phenethylamine are split into conformer pairs A_1 and A_2, B_1 and B_2, and D_1 and D_2, in tyramine. The members of each conformer pair are related by rotation of the in-plane OH group through 180°, as shown in Figure 3. Like phenethylamine, the folded conformers of tyramine show a significant rotation of the TDM from the short axis of the benzene ring. The angle of rotation is about 13° for each of the folded conformers, smaller than the maximum rotation of 32° for conformer B of phenethylamine.

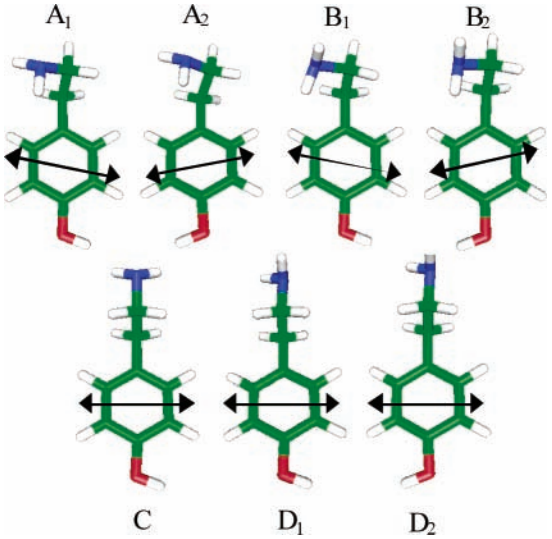

Figure 3. Conformers of tyramine predicted by MP2/6-31G(d,P). The arrows indicate the predicted orientation of the TDM.

TABLE 2: Torsional Angles, Relative Energies, Orientation of TDM, and Distance of Amino Hydrogen above Ring (Folded Conformers), for the Seven Conformers of Tyramine, Calculated from MP2/6-31G(d,p)

	A_1	A_2	B_1	B_2	C	D_1	D_2
τ_1/deg	79.7	108.9	85.0	103.2	90.1	91.9	89.9
τ_2/deg	61.6	66.1	62.1	68.2	180.6	181.4	183.3
τ_3/deg	56.6	59.9	171.5	174.6	59.3	178.2	171.8
E_{rel}/cm^{-1}	0.0	59.0	55.4	30.2	353.1	483.1	496.3
θ/deg	12.0	−13.5	13.0	−13.5	1.0	2.0	1.5
NH···C/Å	2.98	3.113	2.829	2.827			

Although seven stable conformer structures are predicted for tyramine, only six origin bands have been identified in the LIF excitation spectrum.[7,8] The clear relationship between the predicted conformer structures of tyramine and phenethylamine, taken together with the experimental confirmation of four phenethylamine conformers, lends veracity to the existence of seven tyramine conformers. Moreover, the closely related molecule, *p*-methoxyphenethylamine, shows seven identifiable conformers in its LIF excitation spectrum.[22,36] B3LYP/6-31G-(d,p) calculations predict that the pair of tyramine conformers D_1 and D_2 are almost degenerate, separated by only 1 cm^{-1} in the ground state. If these conformers possessed a similar small energy separation in the S_1 state, their origin bands would overlap and might be unresolved in the reported spectra. Indeed, the highest energy origin band (designated band E by Levy) appears to be significantly broader than the others and may be due to the overlapping 0−0 transitions of these two conformers.

Although seven bands are observed in the LIF excitation spectrum of *p*-methoxyphenethylamine, nine conformer structures have been calculated,[22,36] similarly to the nine conformer structures calculated using MM2 for tyramine.[34] Seven of the calculated conformers are structurally equivalent to those presented here for tyramine; the additional two conformers are similar to conformer pairs A and B, but have the amino lone

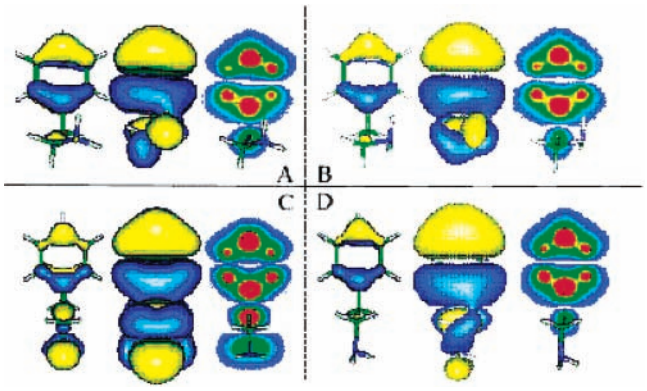

Figure 4. HOMO of the four conformers of phenethylamine, at an isosurface value of 0.06 e/Å^3 (left) and 0.01 e/Å^3 (middle) and a slice through the molecular orbital taken at 0.3 Å above the ring plane (right.) Red shading shows regions of high electron density, while blue shows regions that are electron-deficient.

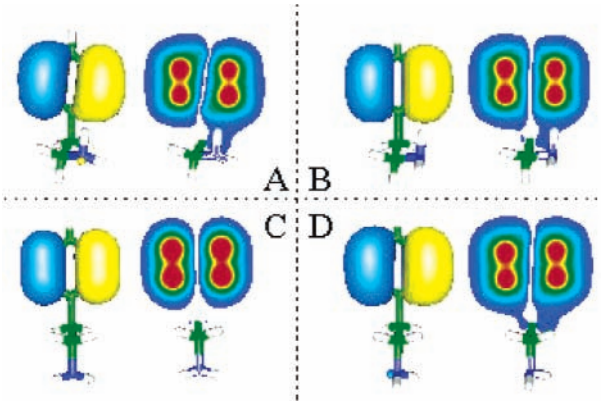

Figure 5. HOMO-1 of the four conformers of phenethylamine at an isosurface value of 0.01 e/Å^3 (left) and a slice through the molecular orbital taken at 0.3 Å above the ring plane (right.)

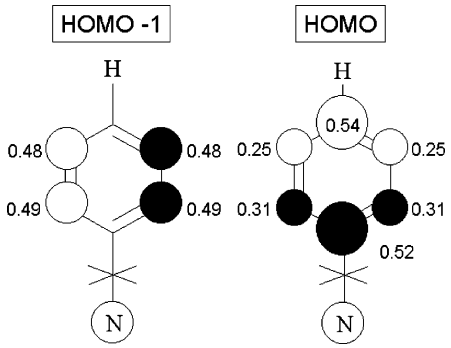

Figure 6. Orbital coefficients for the HOMO and HOMO-1 of phenethylamine conformer C, obtained from CIS//MP2/6-31G(d,p) calculations.

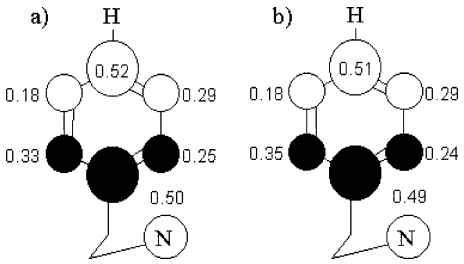

Figure 7. HOMO orbital coefficients for phenethylamine conformer A from (a) MP2/6-31G(d,p) calculation and (b) from a linear combination of conformer C orbitals.

pair oriented toward the ring. We found that such a structure is a stationary point in the geometry optimization for tyramine, but has several imaginary frequencies, indicating that it is not a global minimum.

The increase in the number of conformers in going from phenethylamine to tyramine implies an interaction between the hydroxyl group and the alkylamine group that is analogous to that observed between the hydroxyl group and alkyl group in *p*-alkyl phenols.[11,17,18] Other authors have suggested that this remote effect may be due to the oxygen lone pair electrons interacting differently with either side of the ring.[36] However, in our previous study of conformational behavior in alkyl benzenes and alkyl phenols, we showed that the OH group produces an asymmetric electron distribution in the HOMO that can be accounted for by a symmetry-induced orbital mixing of the π orbitals and does not appear to be due to specific electronic interactions of the substituent. As we will now show, the electronic structure of the conformers of phenethylamine and tyramine and effects such as conformer doubling and TDM rotation can be rationalized in similar terms.

3.3. Ground-State Electronic Structure of Phenethylamine Conformers. The HOMO of the conformers of phenethylamine are shown in Figure 4. In each case the HOMO is shown at a high isosurface value (0.06 e/Å^3) to emphasize regions of high electron density and at a low isosurface value (0.01 e/Å^3) to indicate the full extent of the molecular orbital. A slice through the HOMO, taken at 0.3 Å above the molecular plane, is also shown to better illustrate the π electron density in the HOMO. The HOMO-1 for each conformer is shown in Figure 5, at an isosurface value of 0.01 e/Å^3, along with a slice through the molecular orbital, taken at 0.3 Å above the molecular plane. It is clear that the electron density in both the HOMO and HOMO-1 is sensitive to the orientation of the tail section of the molecule with respect to the ring. This might be expected in the folded conformers, where the position of the NH_2 group over the ring might lead to a perturbation of the ring electron density. However, a distortion to the HOMO and HOMO-1 electron density is also observed in conformer D, where the amino group is orientated away from the benzene ring. The asymmetric electron density in the HOMO and HOMO-1 of phenethylamine can be explained in terms of orbital mixing, as follows.

The conformers of phenethylamine fall into two symmetry classes. Conformer C, with the extended tail, has C_s symmetry, with a mirror plane running through the long axis of the benzene ring, perpendicular to the ring plane. In the other conformers, A, B, and D, reorientation of the alkylamine tail lowers the symmetry to C_1. Under C_s symmetry, the HOMO and HOMO-1 are of symmetry species A′ and A″, respectively, and mixing is prohibited. However, under the C_1 symmetry of conformers A, B, and D, both orbitals are of symmetry species A and mixing is allowed.

Figure 6 shows the orbital coefficients of the HOMO and HOMO-1 of phenethylamine conformer C; the coefficients are symmetric across the long molecular axis of the benzene ring. The asymmetric pattern of orbital coefficients in the HOMO (and the HOMO-1) of conformers A, B, and D can be described by a linear combination of the HOMO and HOMO-1 of the symmetric conformer C, with appropriate mixing coefficients. For example, Figure 7a shows the orbital coefficients obtained directly from the MP2/6-31G(d,p) calculation for conformer A, and Figure 7b shows a calculated linear combination of the HOMO and HOMO-1 of conformer C, with contributions of 89.9% and 10.1%, respectively. (The orbital density on the nitrogen is taken as the reference for the addition, to ensure

TABLE 3: Percentage Contribution of the Unperturbed (Conformer C) HOMO and HOMO-1 to the HOMO and HOMO-1 of the Conformers of Phenethylamine

	HOMO		HOMO-1	
	%HOMO	%HOMO-1	%HOMO-1	%HOMO
A	89.9	10.1	89.4	10.6
B	95.8	4.2	96.9	3.1
C	100	0	100	0
D	96.1	3.9	96.2	3.8

correct phase matching between the molecular orbitals.) The two are in excellent agreement. Table 3 gives the percentage contributions of the HOMO and HOMO-1 of the unperturbed conformer C, to the HOMO and the HOMO-1 of each of the phenethylamine conformers.

3.4. Ground-State Electronic Structure of Tyramine Conformers. The members of each pair of tyramine conformers can be considered to be related by rotation of the OH group through 180° with the orientation of the alkylamine tail fixed or, equivalently, reflection of the alkylamine tail in the vertical plane through the long axis of the ring, with the OH orientation fixed. Figure 8 shows slices through the HOMO of conformers A_1 and A_2, using these two alternative representations of the conformer pair. As shown in Figure 8a, rotation of the OH group is accompanied by a shift in the asymmetric electron density distribution on the ring. Figure 8b shows that reorientation of the tail, with the OH group fixed, has little effect on the electron density distribution in the ring. Thus, there is an asymmetric electron distribution in the HOMO (and HOMO-1), related to the position of the OH group, and the NH_2 group of the tail experiences a different electronic distribution on the proximate ring carbons (3 and 5) between conformers A_1 and A_2.

The origin of the asymmetric electronic distribution in tyramine is the same as that for phenol and phenethylamine, that is, symmetry-induced orbital mixing. All the conformers of tyramine have C_1 symmetry and thus the HOMO and HOMO-1 are of symmetry A and mixing is allowed. To generate unperturbed (symmetric) tyramine orbitals, we can fix the OH group to lie perpendicular to the ring plane and constrain the tail to its position in conformer C. Figure 9 shows the orbital coefficients for this hypothetical symmetric (C_s) conformer of tyramine, determined from an MP2/6-31G(d,p) calculation; this structure is not a stable molecular conformer. Figure 10 compares the calculated orbital coefficients for the HOMO of tyramine conformer A_1 and the orbital coefficients generated from a linear combination of the unperturbed tyramine HOMO and HOMO-1 with contributions of 86.2% and 13.8%, respectively. (The phase of the molecular orbitals on the hydroxyl hydrogen is taken as the reference for the orbital mixing.) The two are in reasonable agreement, the main difference occurs on carbon 6, and may be due to an additional electronic influence of the OH group. The orbital patterns of the other tyramine conformers (vide infra) can be reproduced by similar linear combinations; the mixing coefficients are given in Table 4.

The influence of the orientation of the OH group on the electron density pattern in the ring can be understood in terms of the change in phase pattern of the HOMO and HOMO-1 when the OH group is rotated through 180°. This is illustrated for the conformer pair A_1/A_2 in Figure 11. In the HOMO, there is a nodal plane between the OH and the ring. In the HOMO-1, the phenolic hydrogen has the same phase as the carbons on that side of the ring. When the OH group rotates through 180°, the phase on the OH group is reversed, and the phase pattern on the ring changes to maintain the correct phase relationship with the OH. Now consider interconversion of conformers A_1-

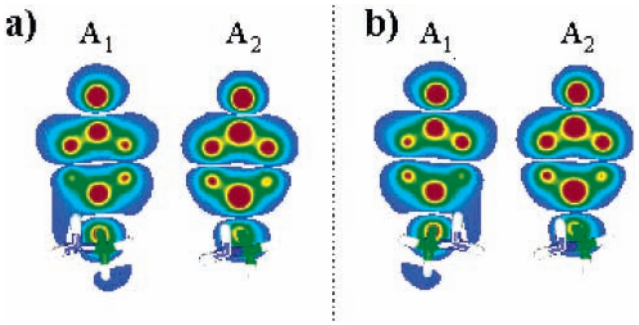

Figure 8. Slices through the HOMO of conformers A_1 and A_2 of tyramine taken at 0.3 Å above the ring plane, showing (a) the effect of rotation of the OH group with tail fixed and (b) the effect of reorientation of the tail with the OH group fixed.

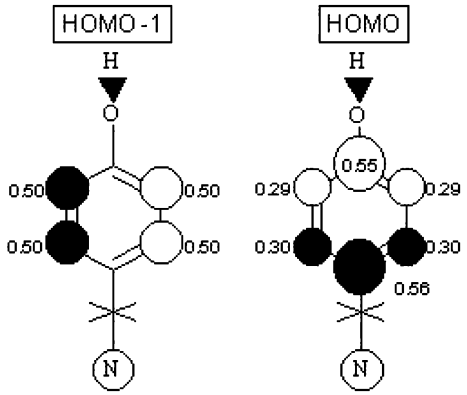

Figure 9. HOMO and HOMO-1 orbital coefficients of the hypothetical symmetric (C_s) tyramine conformer from an MP2/6-31G(d,p) calculation.

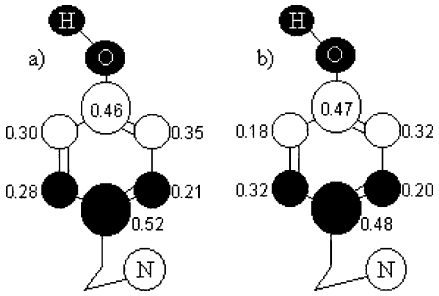

Figure 10. HOMO orbital coefficients for tyramine conformer A_1 from (a) an MP2/6-31G(d,p) calculation and (b) a linear combination of the HOMO and HOMO-1 of the C_s conformer.

TABLE 4: Percentage Contribution of the HOMO and HOMO-1 of the Hypothetical Symmetric (C_s) Conformer to the HOMO and HOMO-1 of the Conformers of Tyramine

	HOMO		HOMO-1	
	%HOMO	%HOMO-1	%HOMO	%HOMO-1
A_1	86.2	13.8	5.5	94.5
B_1	86.4	13.6	3.7	96.3
C	89.2	10.8	1.7	98.3
D_1	88.4	11.6	3.4	96.6

and A_2 via reorientation of the alkylamine tail, with the OH group fixed. This corresponds (in all conformer pairs) to reflection of the tail in the vertical plane through the long axis of the ring. This transformation leaves the phase on the nitrogen unchanged and hence the phase pattern in the ring unchanged. Thus, the phase pattern in the HOMO and HOMO-1, and consequently the electron distribution in the linear combination, is dictated by the orientation of the OH group.

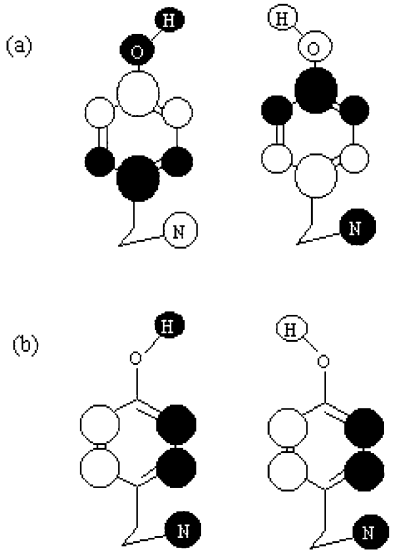

Figure 11. Change in the phase pattern of (a) the HOMO and (b) the HOMO-1 of tyramine when the OH group is rotated through 180°.

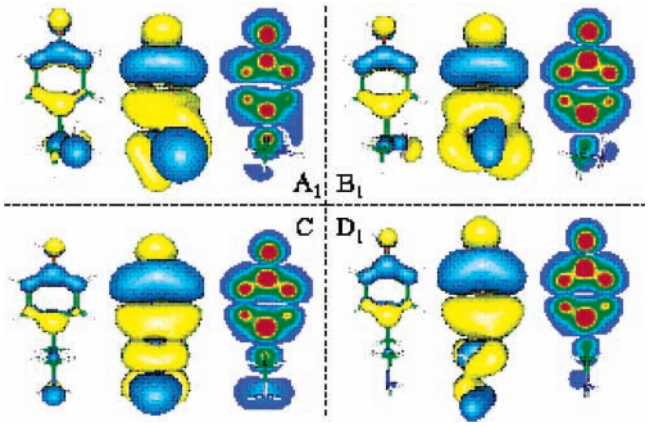

Figure 12. HOMO of four conformers of tyramine, shown at an isosurface value of 0.06 and 0.01 e/Å^3 and a slice through the molecular orbital taken at 0.3 Å above the ring plane. Red shading shows regions of high electron density, while blue shows regions that are electron-deficient.

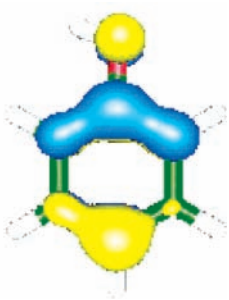

Figure 13. HOMO of phenol, shown at an isosurface value of 0.06 e/Å^3.

Figure 12 shows the HOMO of the four tyramine conformers A_1, B_1, C, and D_1, that is, those with different conformations of the tail but the same orientation of the OH group. The HOMO electron density distribution of all of the tyramine conformers is very similar and resembles that of phenol, shown in Figure 13. For each conformer, carbon 3 is observed to have a much lower electron density than carbon 5; and carbon 6 has a lower electron density than carbon 2. The electron density pattern differs significantly from that of the phenethylamine conformers: the pair of ring carbon atoms proximal to the tail (C3 and C5) have lower electron density than those distal from the tail (C2 and C6) in tyramine, whereas the converse applies in phenethylamine. Although there is some variation between conformers, the HOMO electron density is influenced much less by the position of the tail than that in phenethylamine. The presence of the OH group locks the electron density into a phenol-like pattern.

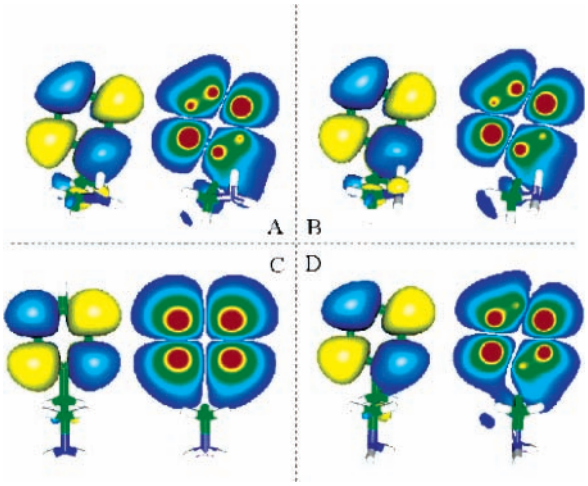

Figure 14. LUMO of the four conformers of phenethylamine, shown at an isosurface value of 0.02 e/Å^3, and a slice through the LUMO taken at 0.3 Å above the molecular plane.

TABLE 5: CIS Expansion Coefficients for the $S_1 \leftarrow S_0$ Transition of the Four Conformers of Phenethylamine

conformer	H → L	H-1 → L+1	H → L+1	H-1 → L
A	0.43906	0.36518	0.29497	0.27531
B	−0.42921	−0.37517	0.29943	−0.27731
C	0.51628	0.45097		
D	0.49	0.43090	0.17983	−0.16506

The stable conformers of tyramine and phenethylamine are structurally similar with respect to the orientation of the alkylamine chain. In each case the tail adopts a staggered structure, consistent with the presence of a stabilizing hyperconjugative interaction between each section.[43,44] In the HOMO of every conformer, the π orbital extends from the ring over tail sections of the molecule, increasing the extent of electron delocalization.

For both tyramine and phenethylamine, the changes in ground state electron density between the different conformer structures of each molecule are relatively small and in themselves do not account for the differences in the TDM orientation between different conformers. We now go on to examine the electronic structure of the excited state.

3.5. Excited-State Electronic Structure of Phenethylamine Conformers. The $S_1 \leftarrow S_0$ transition of phenethylamine involves the HOMO, HOMO-1, LUMO, and LUMO+1 orbitals. Table 5 gives the CIS expansion coefficients for the orbital transitions that make up the overall $S_1 \leftarrow S_0$ excitation in the different conformers. The HOMO → LUMO transition makes the largest contribution to the excitation for each conformer, but for conformers A, B, and D transitions between the other pairs of orbitals also make a significant contribution. For the symmetric conformer C (with benzene-like π-orbitals), only the HOMO → LUMO and HOMO-1 → LUMO+1 are involved.

The LUMO of each conformer is shown in Figure 14. The electron density pattern in this molecular orbital is much more sensitive to the orientation of the tail than was observed in the HOMO. In conformers A, B, and D, the degree of deviation from the symmetric orbital pattern of conformer C increases

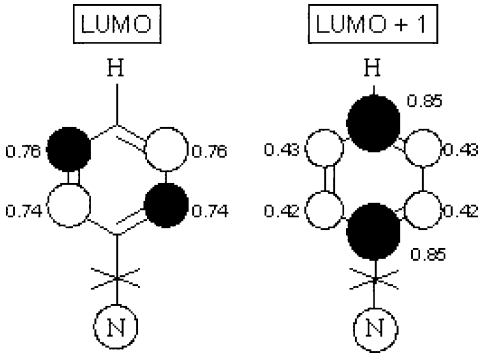

Figure 15. Orbital coefficients of the LUMO and LUMO+1 of phenethylamine conformer C, obtained from CIS//MP2/6-31G(d,p) calculations.

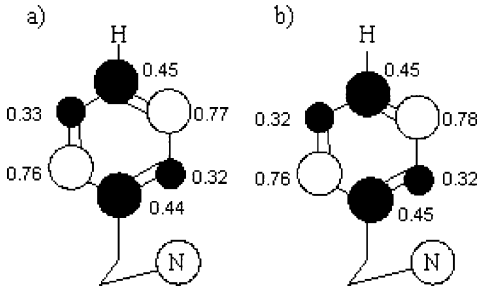

Figure 16. LUMO orbital coefficients for phenethylamine conformer A from (a) CIS//MP2/6-31G(d,p) calculations and (b) a linear combination of the LUMO and LUMO+1 of conformer C.

TABLE 6: Percentage Contribution of the Symmetric (Conformer C) LUMO and LUMO+1 to the LUMO and LUMO+1 of the Conformers of Phenethylamine

	LUMO		LUMO+1	
	%LUMO	%LUMO+1	%LUMO	%LUMO+1
A	60.3	39.7	40.6	59.4
B	57.3	42.7	42.6	57.4
C	100	0	0	100
D	73.6	26.4	26.4	73.6

with the degree of folding of the alkyl tail. The migration of electron density accompanying the change in orbital shape correlates well with the predicted rotation of the TDM away from the short axis of the benzene ring.

As with the HOMO, the LUMO electron distribution in the asymmetric conformers can be explained in terms of mixing of the symmetric LUMO and LUMO+1 orbitals of conformer C. Figure 15 shows the orbital coefficients for the LUMO and LUMO+1 of phenethylamine conformer C obtained directly from an CIS//MP2/6-31G(d,p) calculation.

Figure 16a shows that a linear combination of these orbitals, with contributions of 60.3% and 39.7% from the LUMO and LUMO+1, respectively, reproduces the observed orbital pattern in conformer A. The orbital coefficients for the LUMO of conformer A obtained directly from the CIS calculation are shown in Figure 16b. Similar linear combinations can be generated which reproduce the observed orbital pattern for conformers B and D; the mixing coefficients are given in Table 6.

As in the LUMO, the orbital density in the LUMO+1 shows a significant dependence on the orientation of the tail, as shown in Figure 17. Again, linear combinations of the conformer C LUMO and LUMO+1 reproduce the observed electron density in the LUMO+1 of A, B, and D; the mixing coefficients are given in Table 6.

As can be seen from Table 6, the degree of mixing between the LUMO and LUMO+1 correlates well with the observed

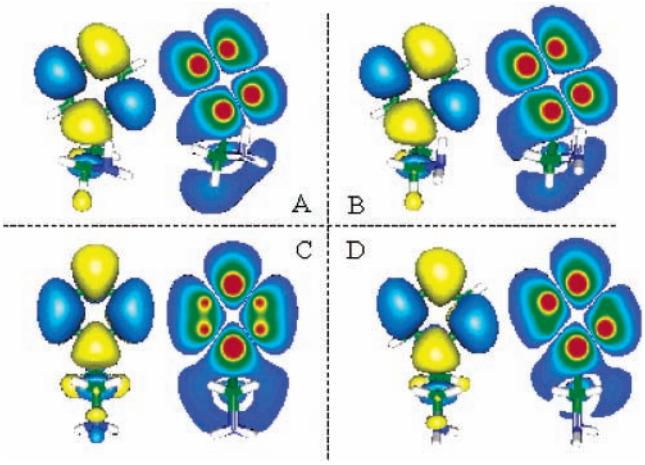

Figure 17. LUMO+1 of the four conformers of phenethylamine, shown at an isosurface value of 0.02 e/Å^3, and a slice through the molecular orbital at 0.3 Å above the molecular plane.

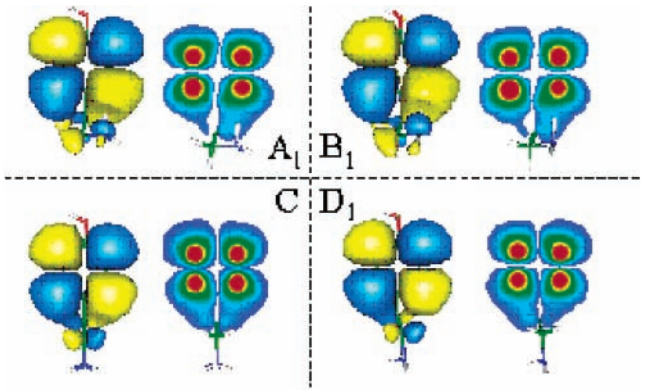

Figure 18. LUMO of four conformers of tyramine, shown at an isosurface value of 0.02 e/Å^3, and a slice through the molecular orbital at 0.3 Å above the molecular plane.

TABLE 7: The CIS Expansion Coefficients for the $S_1 \leftarrow S_0$ Transition of the Seven Conformers of Tyramine

conformer	H → L	H-1 → L+1
A_1	0.60769	0.33992
A_2	0.61417	0.33687
B_1	0.62452	0.31294
B_2	0.60849	−0.34578
C	0.61191	0.33687
D_1	0.61358	0.33782
D_2	0.61411	−0.33855

change in orientation of the TDM. The degree of rotation of the TDM increases in the order conformer C < D < A < B, and the degree of orbital mixing also follows this trend. In conformer C, unmixed, the TDM lies along the short axis, while in conformer B, with almost equal contributions from the LUMO and LUMO+1, the TDM is rotated through 32°.

3.6. Excited-State Electronic Structure of Tyramine Conformers. For tyramine, only the HOMO → LUMO and HOMO-1 → LUMO+1 transitions make significant contributions to the overall $S_1 \leftarrow S_0$ electronic transition. Table 7 gives the expansion coefficients for the transitions that make up the overall $S_1 \leftarrow S_0$ excitation in the different conformers.

The LUMO of the four tyramine conformers with different tail conformations are shown in Figure 18. As observed for the HOMO, the presence of the hydroxyl group in tyramine greatly reduces the sensitivity of the LUMO electron density to the orientation of the alkylamine chain, compared with phenethylamine. In the folded conformers, A_1/A_2 and B_1/B_2, a slight

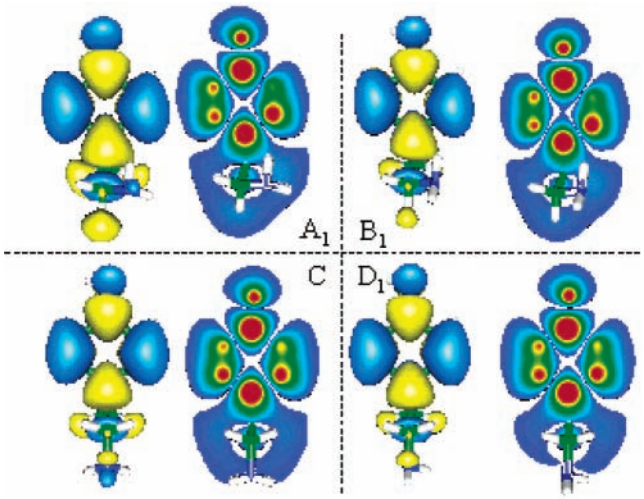

Figure 19. LUMO+1 of four conformers of tyramine, shown at an isosurface value of 0.02 e/Å^3, and a slice through the molecular orbital at 0.3 Å above the molecular plane.

TABLE 8: Percentage Contribution of the LUMO and LUMO+1 of the Hypothetical Symmetric (C_s) Conformer to the LUMO and LUMO+1 of the Conformers of Tyramine

	LUMO		LUMO+1	
	%LUMO	%LUMO+1	%LUMO	%LUMO+1
A_1	96.1	3.9	9.2	90.8
B_1	85.3	14.7	5.6	94.4
C	99.6	0.4	4.5	95.5
D_1	98.4	1.6	7.8	92.2

rotation of the nodal plane that passes along the long axis of the molecule can be discerned. The rotation in nodal plane of the LUMO correlates with the TDM orientation for each conformer. Thus, conformers A_1 and B_1, which show a positive rotation of the TDM from the short axis, show a positive rotation of the nodal plane, and conformers A_2 and B_2 show negative rotation of the TDM and the LUMO nodal plane.

The influence of the OH group is further apparent in the LUMO+1, where the electron density is largely unchanged between the different conformers, as shown in Figure 19.

As in phenethylamine, the electron density in the LUMO and the LUMO+1 of the asymmetric conformers of tyramine can be described by linear combinations of the (hypothetical) symmetric tyramine LUMO and LUMO+1. The mixing coefficients are given in Table 8. It can be seen that the degree of orbital mixing of the LUMO and LUMO+1 in tyramine is very small compared with that in phenethylamine (Table 6).

4. Conclusion

Four stable conformer structures are predicted for phenethylamine, in good agreement with previous experimental and computational studies. Introduction of the para hyroxyl group in tyramine leads to an increase in the number of conformers and seven stable structures are predicted, although only six origin bands have been identified so far in the LIF spectrum. For both molecules, the orientation of the TDM is predicted to depend on the conformation of the alkylamine tail, but this effect is much more pronounced in phenethylamine than in tyramine. The effect of the OH group on the number of conformers and the conformer dependence of TDM orientation can be rationalized in terms of symmetry-induced mixing of the frontier orbitals.

Some general conclusions can be drawn on the conformational properties of substituted benzenes. In molecules of the form benzene ring plus alkyl (or substituted alkyl) tail, conformers which are asymmetric with respect to the vertical plane through the long axis show symmetry-induced mixing of the HOMO and HOMO-1 and of the LUMO and LUMO+1, leading to an asymmetric electron density distribution in the frontier orbitals. The electron density distribution in these orbitals is sensitive to the orientation of the alkyl tail and this is manifested as a variation in the direction of the transition moment between different conformers. In phenethylamine, we find that the conformer dependence of the electron density distribution is particularly marked for the LUMO and LUMO+1 and this largely accounts for the experimentally observed variation in the direction of the TDM. This is in agreement with the previous observation of Kroemer et al.[30] that conformationally induced changes in the TDM of 3-phenylpropionic acid are primarily caused by changes in the nodal structure of the LUMO and LUMO+1. The change in orientation of the TDM between the different conformers of phenethylamine correlates well with the extent of mixing between the LUMO and LUMO+1.

In analogous phenolic molecules, the introduction of a para hydroxyl substituent transforms each phenyl conformer with an asymmetric tail into a nondegenerate pair of conformers with syn and anti orientations of the hydroxyl group and tail. This conformational doubling arises from an asymmetric electron density distribution in the HOMO that is controlled by the orientation of the OH group and is insensitive to the orientation of the alkyl tail. The controlling influence of the OH is also apparent in the LUMO and LUMO+1 and results in a much smaller variation in TDM direction between conformers than in the corresponding substituted benzenes. The OH group effectively locks the electron density in the frontier orbitals into a phenol-like pattern.

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