Conformational Preferences of 2-Phenethylamines. A Computational Study of Substituent and Solvent Effects on the Intramolecular Amine−Aryl Interactions in Charged and Neutral 2-Phenethylamines

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Abstract: A computational investigation of the conformational preferences of 2-phenethylamine has been carried out with a variety of techniques. To determine the intrinsic (in the absence of a solvent medium) conformational preferences of the 2-phenethylamine system, ab initio calculations at various levels of theory up to the MP2/6-311+G(d,p)//MP2/6-31G(d,p) level were carried out. This is the most sophisticated level of theory that has been applied to this biologically important system to date. In the absence of a solvent medium, phenethylamines prefer a folded gauche conformation for both the charged and neutral amines, indicating a favorable interaction between the amino group and the aromatic ring. To probe the nature of this intramolecular interaction further the effects of ring substituents on the conformational preferences were studied. The results have been compared to those obtained with semiempirical and molecular mechanics force field methods. The molecular mechanics force fields employing default parameters typically performed poorly for this system, but the results were improved significantly if the electrostatic charges were replaced. The effects of aqueous solvation have also been investigated with the GB/SA and the SM2 continuum solvation models. The best agreement with experiment is obtained when the MP2/6-311+G-(d,p)//MP2/6-31G(d,p) results are combined with the SM2-calculated solvent effect. Results of nearly the same quality can be obtained if the solvent effect is calculated with the GB/SA solvation model using AM1-CM1A charges.

Introduction

2-Phenethylamine is the parent structure for a variety of biologically important compounds including dopamine, tyrosine, amphetamine, and adrenaline (Figure 1). These compounds are flexible and can potentially assume a number of conformations. We have previously reported a study of the effects of aqueous solvation on the conformational properties of the neurotransmitter dopamine.[1] In the aqueous phase at neutral pH, experiments indicate that dopamine exists in a nearly equal mixture of the extended (anti) and folded (gauche) forms.[2] Our calculations in the aqueous phase were in general agreement with this finding. In addition, the calculations revealed that, in the absence of solvent, the intrinsic preference for protonated dopamine is for the folded form and that the equal population of the anti and gauche forms in solution results from preferential solvation of the anti form. It is not surprising that the gauche structure would be favored in the gas phase as it allows for a favorable interaction between the positively charged ammonium group and the π cloud of the aromatic ring. This type of interaction is reminiscent of the *intermolecular* π-cation interactions that have been identified as being important in the area of molecular recognition with synthetic hosts[3,4] and enzymes.[5]

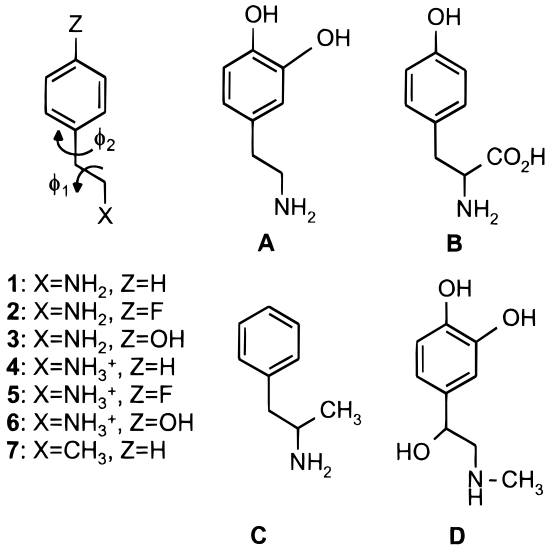

Figure 1. Compounds **1**−**7** studied in this work. Compounds **A** through **D** are representative bioactive compounds containing the phenethylamine molecular framework: (**A**) dopamine, (**B**) tyrosine, (**C**) amphetamine, and (**D**) adrenaline.

The 2-phenethylamine system has been the subject of several theoretical and experimental studies. Martinez et al. observed at least four conformations (two anti and two gauche) in the

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gas phase with fluorescence excitation.[6] Many of the theoretical studies that have been reported have employed semiempirical methods or ab initio methods with small basis sets at the Hartree−Fock level.[7−9] At the time we began this work, the most recent computational study of 2-phenethylamine had been carried out at the HF/3-21G level.[10] It appeared, therefore, that an ab initio molecular orbital investigation with larger basis sets and including electron correlation of this important biochemical structure was warranted. While our work was in progress, two important articles were published which employed a combination of both experimental and theoretical methods to study the conformational preferences of 2-phenethylamine.[11,12] The Godfrey et al.[11] study employed microwave spectroscopy as the experimental technique, and Bernstein and Sun[12] performed fluorescence excitation, dispersed emission, hole burning, and mass resolved excitation spectroscopy. The Godfrey et al. study also included ab initio calculations up to the MP2/6-31G(d,p)//MP2/6-31G(d,p) level. In the current study we report ab initio calculations at several levels of theory up to MP2/6-311+G(d,p)//MP2/6-31G(d,p) thereby enabling a study of the effects of basis set size and electron correlation on the conformational energies of 2-phenethylamine. In Godfrey et al. and Sun and Bernstein studies a total of five conformations have been observed for 2-phenethylamine. Three of these conformations are in the gauche family (with respect to the ϕ_1 dihedral angle, see Figure 1) and two are anti. The members of the anti or gauche sets differ in their C−N dihedral angles. In this study we will consider the four most important conformations of 2-phenethylamine which are depicted in Figure 2. Two of these are anti (A1 and A2) and two are gauche (G1 and G2). There is a fifth conformation that has been considered in previous studies[11,12] that is significantly higher in energy and is not expected to be populated at room temperature.

To expand on the foundations of the 2-phenethylamine system laid down by Godfrey et al. and Sun and Bernstein, we have chosen to also study the model compounds **1**−**6**. We have looked at both the neutral amines and the protonated amines to explore whether the intrinsic preference for the gauche conformation requires the presence of the positively charged ammonium group. To learn something of the nature of this interaction we have also examined the effect of modulating the aromatic electron density via substitution in the para ring position by both an electron withdrawing and electron donating group. Ultimately, one would like to also have an understanding of the conformational preferences of biologically active molecules in the aqueous phase. We have therefore also performed calculations with the GB/SA[13] and SM2[14] continuum aqueous solvation models to examine the effects of solvation on the conformational equilibrium.

An additional purpose of this work is to determine if less computationally demanding methods can be used to approximate the results obtained with ab initio molecular orbital methods. High level ab initio methods provide accurate results but are not computationally efficient for the rapid screening of a large number of conformations. We have also performed calculations with several molecular mechanics force fields and with the AM1 semiempirical Hamiltonian. We are particularly interested in determining if classical force field calculations, which are the method typically employed for conformational searching, can provide reasonable results for these systems which involve very subtle electronic effects. The ab initio calculations can provide an accurate reference system for evaluation of the molecular mechanics calculations and provide the data needed for the accurate parametrization of force fields.

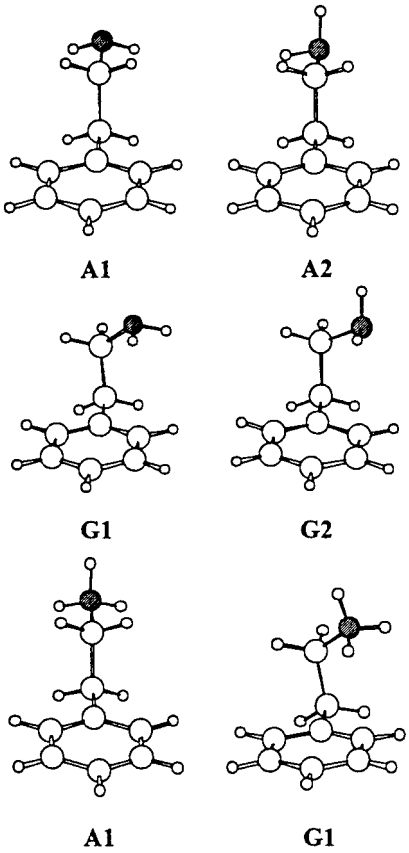

Figure 2. MP2/6-31G(d,p)-optimized structures for **1** and **4**. The top row contains the A1 (left) and A2 (right) conformations of **1**. The middle row contains the G1 (left) and G2 (right) conformations of **1**. The bottom row contains the A1(left) and G1 (right) conformations of **4**.

Methods

Ab initio calculations were carried out with the Gaussian92[15] and Gaussian94[16] program packages running on a Convex 3480, an IBM RS6000-560, an SGI PowerIndigo2 (R8000), an SGI PowerChallenge L (R10000), a Cray Y-MP, or a Cray C-90. Geometry optimizations were carried out at the HF/6-31G(d,p)[17] level as well as the MP2/6-31G(d,p) level. Input structures with anti and gauche conformations about dihedral angle ϕ_1 (Figure 1) were investigated for the charged systems. Four conformations (A1, A2, G1, G2) were examined for

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the neutral systems and two (A1, G1) were studied for the charged systems (Figure 2). For the gauche rotamers, complete geometry optimizations were carried out. For some of the calculations on the anti rotamers (**1**, **2**, **4**, **5**), geometry optimizations were performed under the constraint of C_s symmetry. For those cases that were tested (**1**, **4**), changes in results upon reoptimization without the symmetry constraint were negligible. Vibrational frequency calculations were carried out at the HF/6-31G(d,p)//HF/6-31G(d,p) level to confirm that the optimized structures were true minima. Single point calculations were also performed on the HF/6-31G(d,p) and MP2/6-31G(d,p) optimized geometries at the MP2/6-31+G(d,p) and MP2/6-311+G(d,p) levels.

Semiempirical calculations with the AM1 Hamiltonian were carried out with the AMPAC 2.1[18] program as implemented in AMSOL 4.5.[19] Molecular mechanics calculations were carried out with the MM2*, MM3*, and AMBER* force fields as implemented in the MACROMODEL 5.5/BATCHMIN suite of programs.[20] In this work we are evaluating the performance of these force fields, as they are distributed, for this class of compounds by a direct comparison to ab intio results. In those cases where the distributed version of the force field does not perform adequately, we have chosen to investigate if the force field results could be significantly improved simply by supplying a set of alternative charges. The benefit of using a molecular mechanics force field, as opposed to an ab initio or semiempirical molecular orbital method, is the great speed with which relative conformational energies can be evaluated. This allows for the comprehensive searching of the potential energy surfaces for molecules with many conformational degrees of freedom and allows force field calculations to be extended to Monte Carlo and molecular dynamics simulations. To preserve this inherent benefit of molecular mechanics calculations, we were interested in keeping reparametrization efforts to a minimum in terms of CPU requirements. This will allow for the extension of the methods to larger systems with many more conformational degrees of freedom which have the potential for aryl−amine interactions. For this reason, we have employed the class IV charge model, AM1-CM1A, of Cramer and Truhlar and co-workers.[21] These charges were calculated with use of the AMSOL 4.5 program.[19] For phenethylamines **1**−**6**, the determination of AM1-CM1A charges required only 1 to 3 CPU *minutes* on an R4000 Silicon Graphics Indigo2 workstation.

The effects of aqueous solvation were included via three computational protocols. The first, labeled GB/SA, refers to use of the GB/SA water model as implemented in MACROMODEL/BATCHMIN 5.5 with the AMBER* force field, using default parameters. CM1-GB/SA refers to GB/SA calculations, using the AMBER* force field with the electrostatic charges replaced by AM1-CM1A charges (provided as Supporting Information). The third, labeled SM2, refers to use of the SM2 solvation model and AM1 gas phase Hamiltonian as implemented in the AMSOL4.5[19] program.

Results and Discussion

Gas Phase Conformational Energies. (a) Neutral Phenethylamines. Table 1 provides a summary of the conformational energy differences calculated with AM1 and various levels of ab initio theory. There is reasonable agreement between the AM1 results and HF/6-31G(d,p) results for the A1 and G1 relative energies. This is consistent with our earlier studies of dopamine.[1,22] For example, both AM1 and HF/6-31G(d,p) predict conformation G1 to be slightly more stable than A1 for neutral 2-phenethylamine (by 1.03 and 0.39 kJ/mol, respectively) and the stability of G1 relative to A1 to increase substantially for the protonated 2-phenethylamine (see below). However, for the neutral phenethylamines, AM1 severely overestimates the relative energy of the A2 and G2 conformations which involve twisting of the carbon−nitrogen bond.

Table 1. Relative Conformational Energies[a] from Semiempirical and ab Initio Calculations

		conformation			
molecule	method	A1	A2	G1	G2
1	AM1	1.03	8.13	0.00	5.74
	HF/6-31G(d,p)	1.34	1.12	0.95	0.00
	MP2/6-31G(d,p)	3.27[b]	4.68	0.31	0.00
		(3.97)[c]	(5.58)	(0.46)	(0.00)
	MP2/6-31+G(d,p)	4.49	4.47	1.74	0.00
		(5.41)	(5.20)	(2.47)	(0.00)
	MP2/6-311+G(d,p)	4.50	4.52	0.96	0.00
		(5.39)	(5.29)	(1.50)	(0.00)
2	AM1	0.76	7.64	0.00	5.38
	HF/6-31G(d,p)	1.68	1.14	1.67	0.00
	MP2/6-31G(d,p)	3.36	4.67	0.98	0.00
		(4.22)	(5.53)	(1.09)	(0.00)
	MP2/6-31+G(d,p)	4.87	4.51	2.37	0.00
		(5.70)	(5.15)	(3.07)	(0.00)
	MP2/6-311+G(d,p)	4.85	4.54	1.56	0.00
		(5.63)	(5.22)	(2.03)	(0.00)
3	AM1	0.90	7.90	0.00	5.67
	HF/6-31G(d,p)	1.71	1.38	1.39	0.00
	MP2/6-31G(d,p)	3.36	4.87	0.63	0.00
		(4.04)	(5.59)	(0.52)	(0.00)
	MP2/6-31+G(d,p)	4.94	4.81	2.09	0.00
		(5.30)	(4.99)	(2.27)	(0.00)
	MP2/6-311+G(d,p)	4.94	4.85	1.27	0.00
		(5.26)	(5.06)	(1.26)	(0.00)
4	AM1	12.72		0.00	
	HF/6-31G(d,p)	14.35		0.00	
	MP2/6-31G(d,p)	18.87		0.00	
		(20.67)		(0.00)	
	MP2/6-31+G(d,p)	19.40		0.00	
		(20.46)		(0.00)	
	MP2/6-311+G(d,p)	20.79		0.00	
		(22.13)		(0.00)	
5	AM1	10.79		0.00	
	HF/6-31G(d,p)	11.97		0.00	
	MP2/6-31G(d,p)	16.53		0.00	
		(18.20)		(0.00)	
	MP2/6-31+G(d,p)	16.82		0.00	
		(17.70)		(0.00)	
	MP2/6-311+G(d,p)	18.16		0.00	
		(19.57)		(0.00)	
6	AM1	12.97		0.00	
	HF/6-31G(d,p)	14.23		0.00	
	MP2/6-31G(d,p)	19.66		0.00	
		(21.63)		(0.00)	
	MP2/6-31+G(d,p)	19.92		0.00	
		(21.06)		(0.00)	
	MP2/6-311+G(d,p)	21.34		0.00	
		(22.91)		(0.00)	
7	AM1	1.13		0.00	
	HF/6-31G(d,p)	0.00		2.51	
	MP2/6-31G(d,p)	0.38		0.00	
	MP2/6-31+G(d,p)	0.00		0.33	
	MP2/6-311+G(d,p)	0.79		0.00	

[a] In kJ/mol. [b] Relative energies for the top row of values are for HF/6-31G(d,p)-optimized geometries. [c] Relative energies for the bottom of values (given in parentheses) are for MP2/6-31G(d,p)-optimized geometries.

For the neutral phenethylamines, there is a very small energy difference between the most stable anti and gauche conformations at the HF/6-31G(d,p)//HF/6-31G(d,p) level ranging from 1.12 to 1.38 kJ/mol. The preference for the gauche conformation increases substantially, however, when electron correlation is included at the MP2/6-31G(d,p)//HF/6-31G(d,p) level and again when the basis set is enlarged to the MP2/6-311+G**//HF/6-31G(d,p) level. This preference is enhanced even further when correlation is included in the geometry optimization (values in parentheses in Table 1). The MP2/6-311+G(d,p)//MP2/6-31G(d,p) results show a preference for the most-stable gauche rotamer (G2) that is as large as 5.29 kJ/mol compared to the most stable anti rotamer, A1 (and 5.39 kJ/mol compared

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to the less stable anti rotamer, A1). This preference for the gauche rotamer of 2-phenethylamine is larger than the *penalty* that is often used as an estimate for gauche interactions in alkanes (0.8 kcal/mol = 3.3 kJ/mol).[23] The magnitude of this appreciable preference for the gauche rotamers of compounds **1**−**3** is underestimated in the AM1 and HF/6-31G(d,p) results.

Inspection of Table 1 reveals that as Godfrey et al. suggest,[11] the MP2/6-31G(d,p)//MP2/6-31G(d,p) calculations capture the salient energetic relationships between the conformations which are not entirely represented by the HF/6-31G(d,p)//HF/6-31G-(d,p) calculations nor by the MP2/6-31G(d,p)//HF6-31G(d,p) calculations. However, there are some details that are revealed only with larger basis sets. Most notably, the relative energy of conformation A1 increases from 3.97 kJ/mol at the MP2/6-31G(d,p)//MP2/6-31G(d,p) level to 5.39 kJ/mol at the MP2/6-311+G(d,p)//MP2/6-31G(d,p) level. The G1 conformation also increases in relative energy slightly (ca. 1 kJ/mol).

The present study sets the highest level of theory thus far applied to 2-phenethylamine at MP2/6-311+G(d,p)//MP2/6-31G(d,p). With respect to basis set, there is a larger increase in the preference for gauche in going from MP2/6-31G(d,p) energies to MP2/6-31+G(d,p) energies than from MP2/6-31+G-(d,p) to MP2/6-311+G(d,p) for both the HF and MP2 geometries. In either case, the effect of increasing basis set is not as dramatic as the effect due to correlation. There appears to be reasonable convergence in the conformational relative energy differences with respect to basis set, indicating that larger basis sets presumably would not result in substantial changes. For example, the difference in the relative energy of the A1 and A2 conformations changes by only 0.02 to 0.09 kJ/mol in going from MP2/6-31+G(d,p)//MP2/6-31G(d,p) to MP2/6-311+G-(d,p)//MP2/6-31G(d,p). It is not clear from the present work if more sophisticated treatments of electron correlation would result in even greater preferences for the gauche rotamers. There is an upper limit to the relative energy of the anti rotamers because both anti and gauche rotamers are observed experimentally. However, it is not entirely clear what the energetic value of this upper limit is because the supersonic jet may represent a nonequilibrium mixture of conformers that results from the trapping of conformers at a relatively high temperature early in the expansion cooling process.[12]

Compound **7**, propylbenzene, is included to provide a comparison with a system lacking the aryl−amine interactions but possessing similar steric requirements. HF/6-31G(d,p)//HF/6-31G(d,p) results for **7** predict a preference for the anti rotamer of 2.51 kJ/mol. Once again, this is similar to the 3.3 kJ/mol penalty for gauche interactions that is often used as an estimate for simple alkanes. The preference for the anti rotamer disappears, however, when larger basis sets are employed and electron correlation is included in the calculation. At the highest level of theory considered in this work, there is a slight preference for the gauche rotamer. Both the gauche and anti conformations of propylbenzene are observed in the gas phase by jet expansion fluorescence excitation spectroscopy.[24−26] There have been reports in the literature that CH/π interactions influence the conformational properties of compounds that involve close approach of aryl and alkyl groups[27] and that such interactions warrant further investigation.[28]

(b) Protonated Phenethylamines. As would be expected, much larger energy differences are seen for the N-protonated phenethylamines **4**−**6**. Once again, the AM1 results are very similar to the HF/6-31G(d,p)//HF/6-31G(d,p) results with a 12.72 kJ/mol preference for gauche for AM1 and 14.35 kJ/mol for HF/6-31G(d,p). As is seen for the neutrals, the preference for the gauche rotamers increases when electron correlation is included and larger basis sets are used. At the MP2/6-311+G-(d,p)//MP2/6-31G(d,p) level, the preference for gauche conformations is as high as 22.91 kJ/mol. This is a very substantial energetic preference for folded conformations that is consistent with a favorable interaction between the NH_3^+ group and the aromatic ring. An energy difference of this magnitude was reported by Nagy et al. for the gauche versus anti conformations of the H1 tautomer of histamine with the side chain nitrogen protonated.[29]

Substituent Effects

It is reasonable to assume that the strength of the π- - -H_3N^+ interaction (and presumably the π- - -H_2N interaction) should depend upon the availability of electron density above the aromatic ring. The conformational energy differences should, therefore, be affected by electron donating or withdrawing substituents on the ring. Such a substituent effect has been reported in the literature for side chains to aromatic rings containing oxygen or halogens, where C(aryl)−H- - -O hydrogen bonding, n_O- - -π^* orbital interactions, and an aryl gauche effect were raised as possible explanations.[30] The results in Table 1 indicate that such a substituent effect also exists for the 2-phenethylamines but is most pronounced for the charged series **4**−**6**. The general trend for this series is that introduction of an electron withdrawing fluorine on the ring diminishes the preference for the gauche rotamer and the introduction of an electron donating OH group increases it. This is consistent with an N−H- - -π type of interaction where the approach of the positively charged NH_3^+ group to the π system is favored in the case of an electron-rich aromatic ring. The direction of this substituent effect is opposite to that seen for aromatic rings bearing oxygen-containing side chains where electron withdrawing groups were found to favor the gauche rotamers.[30]

For the neutrals, the presence of the lone pair on the nitrogen complicates the picture. It becomes instructive to segregate the relative energies in Table 1 into a comparison of A1 and G1 and a comparison of A2 and G2. This corresponds to rotating about the sp^3 C−sp^3 C bond, bringing the amino group from an anti to a gauche relationship with the aromatic ring in each of the two NH_2 rotamer orientations. The A1−G1 energy differences are 3.89, 3.60, and 4.00 kJ/mol, respectively, for the para ring substituents, H, F, and OH. The A2−G2 energy difference is 5.29, 5.22, and 5.06 kJ/mol for the same series. Thus, the amino group orientation with the NH bond vectors pointing to the ring and the lone pair pointing away from the ring follows the same trend that is observed for the symmetric NH_3^+ rotor and can be explained on the basis of electrostatics assuming an N−H- - -π type of interaction. For the A2, G2 pair of rotamers, the introduction of both a fluorine and a hydroxy ring substituent acts to decrease the preference for the gauche rotamer, indicating that there are a combination of effects taking place when the nitrogen lone pair is oriented toward the aromatic ring. At the highest levels of theory, the preference for G2 over G1 increases with the introduction of a fluoro substituent (from 1.50 to 2.03 kJ/mol) and decreases with the

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Table 2. Relative Gas Phase Conformational Energies[a] from Molecular Mechanics Calculations

		conformation			
molecule	method	A1	A2	G1	G2
1	MM2* [b]	1.51	0.00	1.05	0.13
	MM3* [c]	2.85	0.38	1.46	0.00
	AMBER* [d]	0.59	0.00	2.09	4.39
	AMBER*/CM1A[e]	7.87	5.98	1.17	0.00
2	MM2*	1.72	0.00	2.01	0.54
	MM3*	2.76	0.01	2.13	0.00
	AMBER*	1.09	0.00	3.31	0.38
	AMBER*/CM1A	9.29	6.99	1.97	0.00
3	MM2*	1.51	0.08	1.38	0.00
	MM3*	2.93	0.46	1.76	0.00
	AMBER*	0.75	0.25	2.64	0.00
	AMBER*/CM1A	10.00	8.24	1.88	0.00
4	MM2*	2.89		0.00	
	MM3*	16.36		0.00	
	AMBER*	5.32		0.00	
	AMBER*/CM1A	22.31		0.00	
5	MM2*	0.00		0.42	
	MM3*	11.58		0.00	
	AMBER*	0.00		0.00	
	AMBER*/CM1A	21.14		0.00	
6	MM2*	0.47		0.00	
	MM3*	15.57		0.00	
	AMBER*	0.00		1.36	
	AMBER*/CM1A	23.40		0.00	

[a] In kJ/mol. [b] MM2 force field as implemented in MacroModel 5.5, using default electrostatic parameters and a constant dielectric. [c] MM3 force field as implemented in MacroModel 5.5, using default electrostatic parameters and a constant dielectric. [d] Amber force field as implemented in MacroModel 5.5, using default electrostatic parameters and a constant dielectric. [e] Amber force field as implemented in MacroModel 5.5, using a constant dielectric and CM1A charges.

introduction of an hydroxy substituent (from 1.50 to 1.26 kJ/mol).

Molecular Mechanics Energetic Results. The molecular mechanics energetic data in the absence of solvent is presented in Table 2. When compared to the ab initio results, the force fields using default parameters substantially underestimate the effect of N-protonation on the conformational equilibria. A similar result was seen in earlier molecular mechanics investigations.[31] However, all of the molecular orbital methods indicate a strong perturbation in the anti-gauche equilibria from protonation that favors the gauche rotamers in the absence of solvent. Compared to the ab initio data in Table 1, the MM2* and AMBER* force fields significantly underestimate the preferences for the gauche rotamers for the charged compounds. This is somewhat corrected in the MM3* results. MM3* as implemented in MACROMODEL is able to reproduce the salient effects of protonation and even some degree of the ring substituent effect that were observed in the ab initio studies. A dramatic effect due to N-protonation is seen in the MM3* results. The correct trend is seen in both cases for fluoro substitution (**2** and **5**). MM3* predicts a slight decrease in the ΔE values upon OH substitution. The MM3* agreement with MP2/6-311+G(d,p)//HF/6-31G(d,p) is far from quantitative, but most of the important trends are seen and there is reasonable agreement with the HF/6-31G(d,p)//HF/6-31G(d,p) results.

Of the three force field protocols that employed default parameters, MM3* certainly performs the best for this system. However, much better performance is obtained if the default charges in AMBER* are replaced with AM1-CM1A charges. These charges were calculated for the A1 conformation of **1**−**6**. The electron distribution and, therefore, the atomic charges are dependent upon conformation.[22,32,33] However, a very common approximation made in molecular mechanics force field parametrization is that charges derived by quantum mechanical calculations of a single conformation may be used in force field calculations of all regions of the conformational hypersurface. For dopamine, we have observed that this approximation affects gas phase molecular mechanics calculations that employ charges derived from fits to the electrostatic potential calculated for a single conformation. There was far less dependence on the conformation used to derive the charges when an aqueous continuum solvent model was used.[22] Methods of charge derivation which include multiple conformations have been reported in the literature.[34,35] However, in this study we have chosen to examine if acceptable results can be obtained by employing charges derived from a quantum mechanical calculation of a single conformation.

The AMBER*/CM1A results in Table 2 show a significant overestimation of the preference for gauche rotamers for the neutral compounds, but indicate much better agreement with the ab initio data for the charged 2-phenethylamines. Even with the overestimation of the ΔE's for the neutrals, the AMBER*/CM1A approach does the best job of describing the important features of this system. The dramatic increase in ΔE values upon N-protonation is observed, and the correct susbtituent effect trends are calculated for both the neutral and charged 2-phenethylamines. Given the minimal cpu time required to calculate the AM1-CM1A charges, it is very encouraging to see such a substantial improvement in the agreement between the force field results and the ab initio results.

Gas Phase Structures. Selected structural features from the ab initio optimized geometries are shown for **1** and **4** in Table 3, and the MP2/6-31G(d,p) optimized structures for **1** are shown in Figure 2. In general these data indicate that there is little change in the phenethylamine structures when electron correlation is included in the calculations. There are some slight changes in the calculated bond distances. For example, the N−C bond for **1** is longer in the MP2/6-31G(d,p) optimized structures for both rotamers and the Cβ−C(Ar) bond is noticeably shorter. The bond angles reported in Table 3 show little difference between the Hartree−Fock and MP2 optimizations. Also, there is only a ca. 4° difference for the ϕ_1 dihedral angle for the gauche rotamers of **1** and **4**. The changes in the ϕ_1 and ϕ_2 dihedral angles upon inclusion of electron correlation act to bring the amine group closer to the aromatic ring. The N−H- - -C(Ar) data in Table 3 are the distances between the amino hydrogen atom that is facing the aromatic ring and two closest aryl ring carbon atoms. These distances are expected to be shortened upon inclusion of electron correlation given the increase in the gauche preference that is seen for the MP2 results in Table 1. The Hartree−Fock and MP2 results provided in Table 3 indicate that protonation of the amine results in a tightening of the folded structures. This is evidenced by the fact that the ϕ_1 values are smaller for gauche rotamers of **4** compared to **1** and ϕ_2 values are larger, which results in reduced amino hydrogen to ring carbon distances.

Aqueous Phase Calculations. Tables 4, 5, and 6 contain the energetic data as calculated with the GB/SA[13] and SM2[14,36] solvation models. Both of these solvation models describe the solvent as a continuum dielectric and employ the combination of a generalized Born term for the electrostatic component of the hydration free energy and a solvent-accessible surface area

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Table 3. Selected Calculated Structural Features for Phenethylamines **1** and **4**

Phenethylamine (**1**)

	anti				gauche			
	HF/6-31G(d,p)		MP2/6-31G(d,p)		HF/6-31G(d,p)		MP2/6-31G(d,p)	
structural feature[a]	A1	A2	A1	A2	G1	G2	G1	G2
N−Cα	1.451	1.454	1.461	1.464	1.449	1.453	1.459	1.462
Cα−Cβ	1.538	1.531	1.537	1.528	1.540	1.532	1.539	1.530
Cβ−C(Ar)	1.514	1.513	1.461	1.504	1.514	1.515	1.459	1.506
N−Cα−Cβ	115.2	110.3	115.9	110.1	116.3	111.2	115.8	109.8
Cα−Cβ−C(Ar)	112.8	112.7	111.8	111.6	113.6	113.6	111.8	111.7
ϕ_1	180.0	178.6	180.0	177.8	62.2	64.7	60.3	62.1
ϕ_2	−89.0	−88.9	−88.1	−88.1	−99.2	−95.0	−94.5	−92.2
N−H- - -C(Ar)					2.823	2.687	2.638	2.638
					3.021	2.779	2.889	2.687

Phenethylammonium (**4**)

	anti		gauche	
	HF/6-31G(d,p)	MP2/6-31G(d,p)	HF/6-31G(d,p)	MP2/6-31G(d,p)
N−Cα	1.521	1.522	1.513	1.512
Cα−Cβ	1.526	1.520	1.529	1.527
Cβ−C(Ar)	1.515	1.509	1.515	1.509
N−Cα−Cβ	110.6	111.0	109.9	108.5
Cα−Cβ−C(Ar)	109.9	108.3	112.3	110.2
ϕ_1	180.0	180.0	56.0	54.7
ϕ_2	−89.0	−88.4	−104.6	−98.8
N−H- - -C(Ar)			2.497	2.323
			2.731	2.412

[a] Distances are in Å. Bond and dihedral angles are in deg. Cα is the carbon bearing the amino group. Cβ is the carbon attached to the aromatic ring. C(Ar) is the aromatic ring carbon bearing the ethylamine side chain. ϕ_1 is the dihedral angle corresponding to rotation about the Cα−Cβ bond. ϕ_2 is the dihedral angle corresponding to rotation about the Cβ−C(Ar) bond. The N−H- - -C(Ar) values are the distances between the amino hydrogen and the two closest carbons of the aromatic ring, which in all cases are the C(Ar) carbon and the ring carbon ortho to C(Ar).

Table 4. Conformational Energy Differences in Aqueous Solution and Solvent Effects on Phenethylamine Conformations As Calculated with the GB/SA Method

		conformation			
compd		A1	A2	G1	G2
1	ΔG(aq)[a,b]	2.38	0.00	7.03	4.64
	ΔG(Hyd)[c]	−16.73	−18.51	−13.60	−18.28
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$[d]	6.95	5.07	6.19	0.00
2	ΔG(aq)	2.34	0.00	6.65	4.184
	ΔG(Hyd)	−16.68	−17.96	−14.63	−14.13
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	3.08	1.39	1.53	0.00
3	ΔG(aq)	2.38	0.00	6.95	4.56
	ΔG(Hyd)	−27.50	−29.35	−24.80	−24.55
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	2.31	0.26	1.01	0.00
4	ΔG(aq)	0.00		3.18	
	ΔG(Hyd)	−300.00		−290.23	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	12.36		0.00	
5	ΔG(aq)	0.00		3.78	
	ΔG(Hyd)	−312.25		−307.78	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	15.10		0.00	
6	ΔG(aq)	0.00		3.34	
	ΔG(Hyd)	−317.61		−315.64	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	20.94		0.00	

[a] All values are in kJ/mol. [b] ΔG(aq) values are the differences in the free energies in aqueous solution as calculated with Amber*-GB/SA for each of the conformations. [c] ΔG(Hyd) is the free energy of hydration for each conformation, which is calculated by subtraction of the Amber* gas phase energy from the the Amber*-GB/SA solution phase energy. [d] $\Delta\Delta G$(Hyd) is the relative free energy of hydration for the each of the conformations (i.e. differences in ΔG(Hyd) values). $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$ is the relative energy ordering of the combination of the MP2/6-311+G(d,p)//MP2/6-31G(d,p) relative energies and the GB/SA relative hydration free energies. This quantity represents the energy rankings of the conformations based on the highest quality ab initio results, including a correction for the GB/SA-calculated solvent effect.

Table 5. Conformational Energy Differences in Aqueous Solution and Solvent Effects on Phenethylamine Conformations As Calculated with the CM1-GB/SA Method

		conformation			
compd		A1	A2	G1	G2
1	ΔG(aq)[a,b]	5.10	1.76	2.22	0.00
	ΔG(Hyd)[c]	−15.11	−16.6	−11.31	−12.34
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$[d]	3.09	1.50	0.00	0.47
2	ΔG(aq)	6.23	2.85	2.34	0.00
	ΔG(Hyd)	−12.48	−13.56	−9.05	−9.42
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	2.57	1.08	2.40	0.00
3	ΔG(aq)	10.00	8.24	1.88	0.00
	ΔG(Hyd)	−29.66	−31.15	−26.02	−26.27
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	1.87	0.18	1.51	0.00
4	ΔG(aq)	7.03		0.00	
	ΔG(Hyd)	−288.49		−272.50	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	6.14		0.00	
5	ΔG(aq)	8.23		0.00	
	ΔG(Hyd)	−274.22		−260.71	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	6.06		0.00	
6	ΔG(aq)	8.99		0.00	
	ΔG(Hyd)	−284.47		−269.24	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	7.68		0.00	

[a] All values are in kJ/mol. [b] ΔG(aq) values are the differences in the free energies in aqueous solution as calculated with Amber*-CM1A-GB/SA for each of the conformations. [c] ΔG(Hyd) is the free energy of hydration for each conformation, which is calculated by subtraction of the Amber*-CM1A gas phase energy from the the Amber*-CM1A-GB/SA solution phase energy. [d] $\Delta\Delta G$(Hyd) is the relative free energy of hydration for the each of the conformations. $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$ is the relative energy ordering of the combination of the MP2/6-311+G(d,p)//MP2/6-31G(d,p) relative energies and the GB/SA (with CM1A charges) relative hydration free energies. This quantity represents the energy rankings of the conformations based on the highest quality ab initio results, including a correction for the GB/SA (with CM1A charges)-calculated solvent effect.

dependent term for the description of first-shell solvent effects. They differ, however, in many ways, including most notably their underlying treatment of the solute. The GB/SA solvation model of MACROMODEL employs a molecular mechanics description of the solute, and the SM2 solvation model employs a quantum mechanical (AM1) description of the solute. There are also other differences especially in the surface tension parameters used in the solvent-accessible surface area dependent

Table 6. Conformational Energy Differences in Aqueous Solution and Solvent Effects on Phenethylamine Conformations As Calculated with the SM2 Method

compd		conformation A1	A2	G1	G2
1	ΔG(aq)[a,b]	0.00	8.21	0.67	8.33
	ΔG(Hyd)[c]	−24.83	−23.72	−23.13	−21.21
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$[d]	1.77	2.78	−0.42	0.00
2	ΔG(aq)	0.00	8.16	1.12	8.28
	ΔG(Hyd)	−22.88	−21.56	−21.00	−19.22
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	1.97	2.87	0.25	0.00
3	ΔG(aq)	0.00	8.46	1.58	8.94
	ΔG(Hyd)	−47.09	−45.63	−44.61	−42.92
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	1.49	2.75	0.00	0.40
4	ΔG(aq)	0.00		5.66	
	ΔG(Hyd)	−284.39		−266.02	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	3.76		0.00	
5	ΔG(aq)	0.00		8.68	
	ΔG(Hyd)	−293.68		−274.29	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	0.18		0.00	
6	ΔG(aq)	0.00		4.28	
	ΔG(Hyd)	−306.60		−290.20	
	$\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$	6.51		0.00	

[a] All values are in kJ/mol. [b] ΔG(aq) values are the differences in the free energies in aqueous solution as calculated with AM1-SM2 for each of the conformations. [c] ΔG(Hyd) is the free energy of hydration for each conformation, which is calculated by subtraction of the AM1 gas phase energy from the AM1-SM2 solution phase energy. [d] $\Delta\Delta G$(Hyd) is the relative solvation free energy for the each of the conformations. $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$ is the relative energy ordering of the combination of the MP2/6-311+G(d,p)//MP2/6-31G(d,p) relative energies and the SM2 relative hydration free energies. This quantity represents the energy rankings of the conformations based on the highest quality ab initio results, including a correction for the SM2-calculated solvent effect.

term. Both of these solvation models rely on the partial atomic charges for the electrostatic component of the hydration free energy. In GB/SA, these charges are supplied as parameters to the molecular mechanics force field. In SM2 these charges are calculated via a Mulliken population analysis of the SCF wave function. For this reason, the SM2 solvation model accounts for solvent-induced charge redistribution.[14]

In Tables 4, 5, and 6, the ΔG(aq) term refers to the conformational energy differences in solution as calculated directly with the solvent model, including the corresponding underlying gas phase Hamiltonian (AMBER* force field for GB/SA calculations, AM1 for SM2 calculations). ΔG(hyd) is the free energy change associated with the transfer of a substance from the gas phase to the aqueous phase (with the standard states being one molar ideal gas and one molar ideal solution). Experimental values for this quantity are typically used to parametrize solvation models.[37] For each rotamer, a ΔG(hyd) value can be obtained by subtracting the gas phase energy (AMBER*, AMBER*/CM1, or AM1) from the aqueous phase energy value (GB/SA, CM1-GB/SA, or SM2). The difference between the hydration free energies for the anti and gauche rotamers represents the solvent effect on the conformational equilibrium and is reported in Tables 4, 5, and 6 as $\Delta\Delta G$(hyd). This quantity allows for a comparison of the three solvent model implementations after removing any errors in their respective underlying gas phase descriptions. The negative values for $\Delta\Delta G$(hyd) indicate the amount by which a particular rotamer is solvated preferentially over the least-well-solvated rotamer of the set that was assigned the 0.00 value. Finally, the $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{hyd}))$ quantity represents an estimate of the differences in free energy in aqueous solution among the four conformers and is obtained by combining the MP2/6-311+G(d,p)//MP2/6-31G(d,p) gas phase energy differences with the solvent effect on conformational equilibrium, $\Delta\Delta G$(hyd). This amounts to replacing the AMBER*, AMBER*/CM1, or AM1 solute descriptions that are built into the ΔG(aq) values with high-level ab initio descriptions of the solute and then again ranking the conformations according to energy.

Analysis of the results in Tables 4, 5, and 6 indicates that there is a great deal of variation in the ΔG(aq) values as calculated with the three methods. This is to be expected on the basis of the differences between the gas phase AM1, AMBER*, and AMBER*/CM1 results reported in Tables 1 and 2. Most of the available experimental data on conformer distributions are for the protonated amines. However, for amphetamine, which differs from **1** only by a methyl group on the α-carbon, Makriyannis and Knittel reported a 36% population of the anti rotamer for the free base in D_2O based on vicinal $^1H-^1H$ NMR coupling constants.[38] Only the CM1-GB/SA ΔG(aq) values indicate a gauche rotamer of **1** as the lowest-energy conformation in aqueous solution. However, when the underlying gas phase description is replaced by high-level ab initio results (the $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{Hyd}))$ values), all three solvent model implementations result in a gauche rotamer predicted to be the lowest-energy conformation. Both CM1-GB/SA and SM2 result in $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{hyd}))$ values that indicate a small preference for a gauche conformation in aqueous solution and are in general agreement with the experimental amphetamine data. The GB/SA results show a larger preference for the G2 conformation in aqueous solution with all others 5 to 6 kJ/mol higher in energy. All of the solvent model calculations predict the best solvated conformation of **1** to be one of the anti conformations, A1 or A2, although the GB/SA results predict the G2 conformation to be nearly as well solvated as the A2 conformation and better solvated than the A1 conformation. All of the solvation models predict **3** to be the neutral 2-phenethylamine with the most favorable interactions with the solvent (most negative ΔG(Hyd) values). None of the solvation models indicate that there is a large change in the relative solvation of the four conformers ($\Delta\Delta G$(Hyd) values for **1**−**3**) with ring substitution.

Martin et al. reported that equal populations of the anti and gauche rotamers exist in aqueous solution for both 2-phenethylamine hydrochloride (trans = 49%) and *p*-chlorophenethylamine hydrochloride (trans = 52%).[39] For amphetamine hydrochloride, Makriyannis and Knittel reported a value of 45% trans in D_2O.[38] Given the large preferences for the gauche conformation in the absence of solvent reported in Table 1, the experimental result in aqueous solution of near 1:1 population of anti and gauche conformers indicates that the anti conformation is preferentially solvated in an aqueous medium. This is to be expected since the charged NH_3^+ group is more available for interactions with surrounding water molecules in the anti conformation than in the gauche where it is partially shielded by the aromatic ring.

Once again, there is significant variation in the ΔG(aq) values as calculated with the three methods reported in Tables 4, 5, and 6. Analysis of the $\Delta\Delta G$(hyd) values indicates that all of the methods correctly predict the anti conformation to be preferentially solvated over the gauche. The CM1-GB/SA and SM2 calculations predict the magnitude of the solvent effect to be larger than that predicted by GB/SA. Given the available experimental data, it appears that the combination of the MP2/6-311+G(d,p)//MP2/6-31G(d,p) and SM2-calculated solvent effect provides the best estimate of the conformational energy differences in aqueous solution for **1** followed by CM1-GB/

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Table 7. Breakdown of SM2 Hydration Free Energies into Relative ΔG_{ENP} and ΔG_{CDS} Terms[a]

compd		conformation A1	A2	G1	G2
1	$\Delta\Delta G_{ENP}$	−1.03	0.00	−1.91	−0.51
	$\Delta\Delta G_{CDS}$	−3.16	−3.02	−0.53	0.00
2	$\Delta\Delta G_{ENP}$	−1.14	0.00	−1.94	−0.65
	$\Delta\Delta G_{CDS}$	−3.18	−3.00	−0.50	0.00
3	$\Delta\Delta G_{ENP}$	−1.34	0.00	−1.43	−0.46
	$\Delta\Delta G_{CDS}$	−3.31	−3.18	−0.76	0.00
4	$\Delta\Delta G_{ENP}$	−27.83		0.00	
	$\Delta\Delta G_{CDS}$	−3.51		0.00	
5	$\Delta\Delta G_{ENP}$	−17.02		0.00	
	$\Delta\Delta G_{CDS}$	−2.38		0.00	
6	$\Delta\Delta G_{ENP}$	−14.19		0.00	
	$\Delta\Delta G_{CDS}$	−2.22		0.00	

[a] In kJ/mol. See text for a description of terms.

SA and finally GB/SA. Inspection of the $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{hyd}))$ values for **4**, **5**, and **6** indicates that the direction of the substituent effect is the same in aqueous solution as in the gas phase if CM1-GB/SA or SM2 calculations are used. Fluorine substitution favors population of the anti rotamer and hydroxy substitution favors increased population of the gauche rotamer. This trend is not preserved in the GB/SA calculations where **5** has a more positive value of $\Delta(E(\text{MP2}) + \Delta\Delta G(\text{hyd}))$ than **4**. In general, the CM1-GB/SA results more closely resemble the SM2 results than the GB/SA results.

It is possible to break the SM2 hydration free energies ($\Delta G(\text{hyd})$) into two components: ΔG_{ENP} and ΔG_{CDS}. ΔG_{ENP} represents the solute electronic and nuclear contribution to the hydration free energy as well as the polarization free energy, which arises from the interaction of the network of atom-centered charges with the surrounding dielectric medium. The ΔG_{CDS} term represents all other contributions to the hydration free energy which pertain to local first-shell effects, such as cavity formation, solute−solvent dispersive interactions, local hydrogen bonding effects with specific functional groups, and any structural rearrangements of the solvent to accommodate the presence of the solute. While the SM2 solvation model was parametrized against intact $\Delta G(\text{hyd})$ values and not the component ΔG_{ENP} and ΔG_{CDS} terms, Cramer and Truhlar have reported that they were able to largely separate the optimization of the parameters which contribute predominantly to the G_{ENP} term from that of the solvent-accessible surface tensions which contribute mainly to the G_{CDS} term, allowing for an interpretation of the solvation free energies.[14,37]

The SM2-calculated hydration free energies were broken down into the component ΔG_{ENP} and ΔG_{CDS} values for each of the conformations. Table 7 includes a breakdown of the relative component ΔG_{ENP}'s and ΔG_{CDS}'s for the set of conformations. They have been normalized in such a way that the conformation with the least favorable ΔG_{ENP} or ΔG_{CDS} is assigned the zero value. In general, the AMSOL-calculated solvent-accessible surface areas are 2−3% larger for the anti rotamer than the gauche rotamer. For the neutrals, much of the favored solvation of the anti conformations over the gauche arises from increased solvent accessible surface area of the NH_2 group, allowing for increased local interaction with water which appears in the changes in the ΔG_{CDS} term. For the charged phenethylamines, however, the ΔG_{CDS} terms are very similar in the anti and gauche conformations. Most of the preferential solvation of the anti conformations arises from increases in the polarization free energy (which will produce changes in the ΔG_{ENP} term). In the gauche conformations, the charged NH_3^+ group is partially shielded from the high dielectric medium by the aryl group, and in the anti conformations this charged group is more available for solvation.

Conclusions

The work presented here indicates that intramolecular aryl−amine interactions can greatly influence the conformational preferences of the biologically important class of phenethylamine compounds. The ab initio calculations reported here are the most sophisticated to date on this important system. The results indicate that there is an intrinsic preference for the gauche rotamers for both the neutral and charged species. The preferences for the gauche rotamers are in agreement with the results of previous studies of this system. For the protonated 2-phenethylamines, in the absence of solvent, there is a rather large (ca. 20 kJ/mol) preference for the gauche rotamers. The direction of the ring substituent effects suggests that the interaction is predominantly electrostatic in nature and varies depending on the orientation of the NH_2 rotors in the neutral cases.

The molecular mechanics force fields that were tested here performed poorly for the 2-phenethylamine system when the default parameters were used. In general the force fields significantly underestimated the effect of protonation on the conformational equilibria. However, the use of AM1-CM1A partial atomic charges in the AMBER* force field results in much closer agreement with the ab initio calculations. The rapid calculation of these charges makes this a very useful computational protocol for the study of larger systems with the possibility of aryl−amine interactions which are not accessible by ab initio methods, or when large sampling of conformational space is desired.

The use of AM1-CM1A charges also significantly improved the aqueous phase results obtained with the GB/SA solvation model. The GB/SA (with AM1-CM1A charges) and the SM2 solvation models result in very similar predictions of the relative solvation of the anti and gauche conformations of the 2-phenethylamines. The nearly equal distribution of anti and gauche rotamers observed experimentally in the aqueous phase results from the combination of the intramolecular aryl−amine interactions favoring the gauche conformation, offset by the preferential solvation of the anti conformation. Understanding the balance between the intramolecular interactions and the intermolecular interactions with water is especially important for bioactive compounds because of the varying environments in which these compounds are found (for example, an aqueous environment versus a hydrophobic pocket in a binding site). This perturbation of the conformational equilibrium of 2-phenethylamines by the surrounding environment may be important in gaining a better understanding of the biological activity of 2-phenethylamine and related compounds.

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Supporting Information Available: Total energies (in hartrees) for **1**−**7** and AM1-CM1A partial atomic charges for **1**−**6** (3 pages). See any current masthead page for ordering and Internet access instructions.

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