A Computational Study of Solvent Effects on the Conformation of Dopamine

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Abstract: The solution conformation of the neurotransmitter dopamine is investigated with the AM1-SM1 solvation model as implemented in the program AMSOL. AMSOL invokes the AM1 Hamiltonian and evaluates solvent effects based on a continuum model of solvation free energy. In the current work, calculations are performed on the neutral, N-protonated, and OH-deprotonated forms of dopamine with both AM1 (gas phase) and AM1-SM1 (aqueous solution). For both N-protonated and OH-deprotonated dopamine, the gas-phase AM1 calculations predict the anti conformation to be much higher in energy than gauche conformations. AMSOL, however, predicts the anti conformation to be an important contributor to the solution conformer population at neutral pH, in agreement with experimental observations.

1. Introduction

Dopamine is the major neurotransmitter for the extrapyramidal motor tracts of the central nervous system. Its receptors are the major sites of action of antipsychotic as well as anti-Parkinsonism drugs.[1-3] Dopamine is also centrally involved in the mechanism of psychostimulant addiction. The mechanism of action of cocaine, for instance, is believed to involve a blocking of dopamine reuptake.[4] There is great interest in the conformational properties of dopamine and other catecholamines because of their important role in the function of the central nervous system. A thorough understanding of the conformational preferences of dopamine in solution has the potential to aid in the design of improved drugs for the treatment of diseases associated with a malfunction of the dopaminergic system, and can also lead to a better understanding of the activity of this neurotransmitter at the molecular level.

The conformation of dopamine can mainly be described by the two dihedral angles ϕ_1 and ϕ_2 depicted in Figure 1. The three staggered conformers obtained by rotation about ϕ_1 are shown in Figure 2. The important conformers resulting from rotation about ϕ_2 include the perpendicular arrangement of the catechol ring relative to the N-C-C triad (as in structure **b** of Figure 2) and two structures with the catechol ring coplanar with the C-C-N triad which will be identified as α and β conformations. In the α conformation, $\phi_2 = 0°$, while in the β conformation $\phi_2 = 180°$ (as shown in Figure 1).

There have been both experimental and computational investigations of the conformational properties of dopamine in the past. The aqueous solution NMR study of Solmajer et al.[5] showed that the mole fraction of the trans conformer (**b** in Figure 2) increases as the pH is increased. At low pH the combination of the two gauche conformers (**a** and **c** in Figure 2) outweighs the population of the anti conformer while at high pH the opposite ordering is observed. No information regarding the orientation of the catechol ring in solution was obtained from this study due to rapid rotation about ϕ_2. In the solid state the aminoethyl side chain is in an anti conformation, and the catechol ring is in a perpendicular arrangement.[6] However, based on the activity of rigid dopamine analogues, it has been postulated that the receptor-site conformation of dopamine is anti-α-coplanar,[7,8] in contrast to what is observed in the solid state. Many of the past computational studies have been concerned with conformational properties of dopamine and its analogues in the gas phase and/or have been performed with techniques that are now somewhat outdated.[9-12] However, in recent years there has been a tremendous effect in molecular modeling to incorporate the effects of solvation into the calculations. For this reason, we have reexamined the solution- and gas-phase conformational properties of dopamine with respect to ϕ_1 and ϕ_2.

The dopamine molecule is an appropriate choice for this study not only because of its important standing in biochemistry, but also because it offers an opportunity to study the conformational properties of a flexible molecule which has exhibited a number of important conformations, but whose potential energy surface can be reasonably approximated by consideration of only two conformational degrees of freedom. Also, the neutral dopamine molecule (DA) can be N-protonated or OH-deprotonated to yield both cationic (DA^+) and anionic (DA^-) species with essentially the same steric characteristics as the parent DA.

In general, hydration effects can play a major role in determining a molecule's conformational properties, and one would certainly expect these effects to be even more dramatic for charged species. We are therefore interested in comparing the results of gas-phase AM1 calculations with those of the AM1-SM1 solvation model (as incorporated in the program AMSOL[13]) for DA, DA^+, and DA^- in order to determine how the consideration of solvent effects changes the predictions one would make concerning the relative importance of various conformations. This is a rather direct comparison because the AM1-SM1 model employs the AM1 Hamiltonian augmented to include solvent effects.

The aqueous solution conformational properties of dopamine may, of course, differ significantly from those at its receptor sites where the environment may be considerably hydrophobic.[14] The goal of this work, however, is to evaluate the abilities of the AM1-SM1 solvation model in predicting aqueous solution conformational properties for biomolecules. For the reasons stated above, dopamine serves as a useful model compound for this purpose.

There is some question as to what is the appropriate course of action in studying the conformational properties of a charged,

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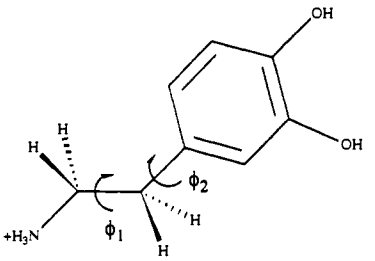

Figure 1. Dihedral angles ϕ_1 and ϕ_2 of dopamine. In the conformation shown here $\phi_1 = 180°$ and $\phi_2 = 180°$.

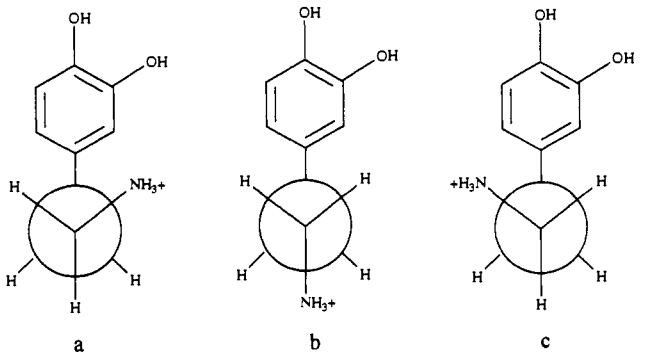

Figure 2. Staggered conformations of dopamine resulting from rotation about ϕ_1 with $\phi_2 = 90°$.

biologically active molecule. In cases where the solvent effects are not included at all in the calculation, one approach is to perform calculations on the neutral species, the rationale being that the importance of intramolecular electrostatic interactions is likely to be greatly exaggerated if the calculation is performed on a charged molecule in vacuo. Also, it is common to assume that the regions of a molecule that are formally charged will be involved in intermolecular interactions with oppositely charged regions of the receptor. Such an approach was recently applied to a theoretical study[15] of the alkaloid pilocarpine (a muscarinic cholinergic agonist) where the potential energy surface was calculated for the neutral base. There are numerous cases, however, where a neutral form of the molecule of interest cannot be arrived at by simple addition or subtraction of a proton. Like many biologically important substrates, the neurotransmitter acetylcholine possesses a quaternary nitrogen. Many calculations have been performed on this ion with no consideration of hydration effects, explicit or implicit.[16-18]

2. Methods

All calculations reported here were performed with the AMSOL program of Cramer and Truhlar[13] running on a Cray-2 and/or Cray-X-MP/48. AMSOL is a modification of the AMPAC[19] program that incorporates hydration free energy effects in a continuum fashion and employs the AM1[20] Hamiltonian for the solute. The approach represents an extension of the previous work of Still et al.[21] in that solvation is considered to be a combination of cavity effects and dispersive interactions (both dependent on solvent accessible surface area), as well as polarization effects (described with a generalized Born model). In this work, the AM1-SM1 solvation model of AMSOL was employed for the aqueous phase calculations. The method has been presented in detail elsewhere,[22] and only a brief summary will be provided here.

In the AM1-SM1 approach, a portion of the standard-state free energy of the solution is partitioned into two terms:

$$G^0_S = G_{ENP} + G^0_{CD} \quad (1)$$

Here, G_{ENP} is the electronic SCF (E) and nuclear repulsion (N) terms for the solute as well as the polarization (P) free energy arising from solute–solvent interactions. The G^0_{CD} term represents the standard-state free energy for cavity formation in the solvent (C) as well as any dispersive (D) solute–solvent interactions. The latter term is given by

$$G^0_{CD} = \sum_{k=1}^{N} \sigma_k A_k \quad (2)$$

where N is the number of atoms, A_k is the solvent accessible surface area for atom k, and σ_k is a parameter for atom k that has been termed the accessible-surface tension. In the SM1 solvation model, σ_k depends only on atomic number. Alternative solvation models are contained in AMSOL. For example, SM1a[22] and SM2[23] allow for different types of the same atom (alcohol oxygen versus carbonyl oxygen, for example). Also, the PM3-SM3[24] solvation model incorporates solvent effects with the solute described by the PM3[25] Hamiltonian.

G_{ENP} can be further broken down to

$$G_{ENP} = E_{EN} + G_P \quad (3)$$

where E_{EN} is the solute ground-state SCF electronic energy and nuclear repulsion terms in the presence of the solvent, and the G_P term is arrived at using the generalized Born formula

$$G_P = -\frac{1}{2}\left(1 - \frac{1}{\epsilon}\right)\sum_{k=1}^{N}\sum_{k'=1}^{N} q_k q_{k'} \gamma_{kk'} \quad (4)$$

N is the number of atoms in the solute, ϵ is the solvent dielectric constant, q_k and $q_{k'}$ are partial atomic charges from Mulliken population analysis,[25] and $\gamma_{kk'}$ is a Coulomb integral.

The energy resulting from an AMSOL optimization is the self-consistently determined heat of formation of the solute in the presence of the solvent, plus the free energy of hydration for the optimized structure. The assumption is made that the contributions to the free energy in solution from vibrations and electronic excitations are identical with those in the gas phase. For simplicity, in this work this quantity will be referred to as the AMSOL energy. Changes in solute geometry and electron density due to solvent interaction are accounted for in this term. Energetic results for gas-phase calculations are heats of formation as calculated with the AM1 Hamiltonian of AMPAC. All geometry optimizations were complete optimizations of all internal coordinates except those defining a reaction coordinate (ϕ_1 and/or ϕ_2).

3. Results

3.1. Gas-Phase Calculations. Potential energy surfaces were calculated for the neutral, protonated, and hydroxyl deprotonated forms of dopamine in vacuo with AM1. The results and structural formulas are shown in Figures 3, 4, and 5. The potential energy surfaces were calculated using a 19 × 19 grid generated by rotating through ϕ_1 and ϕ_2 in 20° increments from −180 to 180°. At each point a complete geometry optimization was performed with ϕ_1 and ϕ_2 frozen at their respective grid values.

For neutral dopamine the lowest energy structures are the combinations of gauche ϕ_1 and perpendicular ϕ_2. These can be seen in the contour and surface plots of Figure 3 as the four minima centered at $\{\phi_1, \phi_2\} = \{-60, 90\}$, $\{-60, -90\}$ and their symmetry-related partners $\{60, -90\}$ and $\{60, 90\}$. These four have essentially the same calculated heats of formation. The set of symmetry-related anti-coplanar structures $\{\pm 180, \pm 180\}$ lie approximately 1.0 kcal/mol above the gauche-perpendicular set.

The gas-phase conformational map for protonated dopamine (Figure 4) is rather complicated compared with that of neutral dopamine. Most noticeable is the fact that the symmetry of the gauche-perpendicular regions has become somewhat distorted. This is not entirely unexpected given that in these structures there is a relatively close approach of the ammonium nitrogen and catechol ring giving rise to a situation where the calculated heat of formation will be rather sensitive to slight changes in geometry. Qualitatively, the features of the gas-phase potential energy surface of protonated dopamine are similar to those of neutral dopamine

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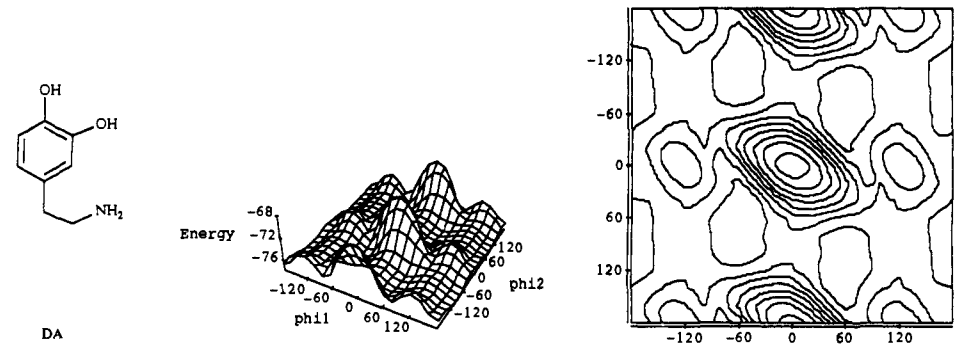

Figure 3. Gas-phase AM1-calculated heats of formation (kcal/mol) for neutral dopamine (DA) shown as function of ϕ_1 and ϕ_2 (degrees).

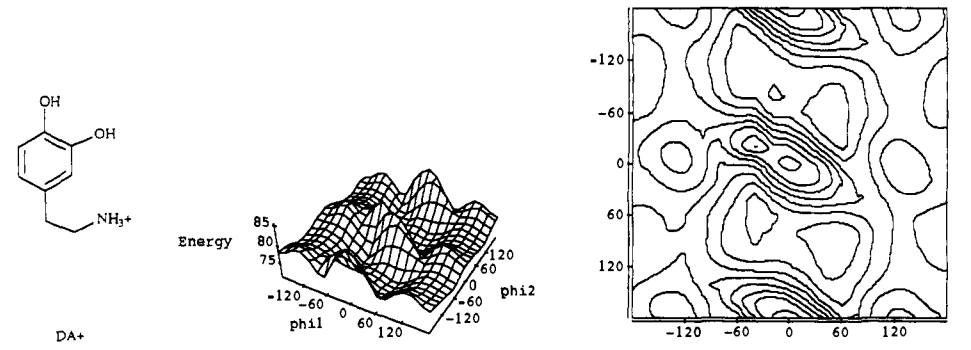

Figure 4. Gas-phase AM1-calculated heats of formation (kcal/mol) for protonated dopamine (DA^+) shown as function of ϕ_1 and ϕ_2 (degrees).

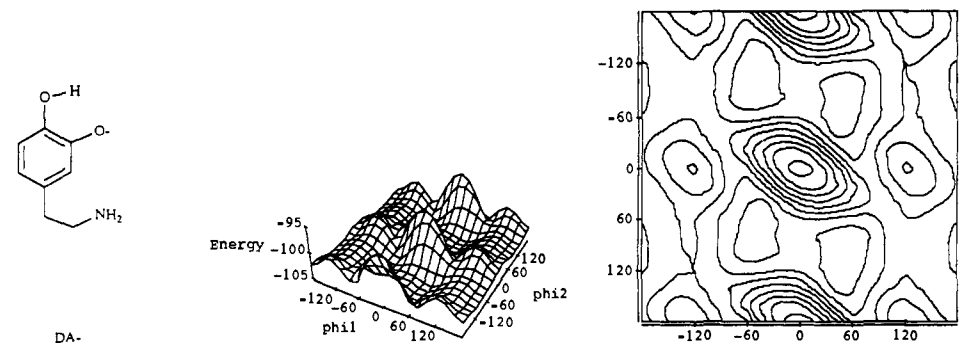

Figure 5. Gas-phase AM1-calculated heats of formation (kcal/mol) for hydroxy-deprotonated dopamine (DA^-) shown as function of ϕ_1 and ϕ_2 (degrees).

with stationary points at the possible combinations of gauche and anti for ϕ_1 and perpendicular and coplanar for ϕ_2. In the gas-phase surface of DA^+, however, the collection of gauche-perpendicular structures is stabilized relative to the anti-perpendicular conformer by an average of 2.2 kcal/mol. This difference is larger than that observed for neutral dopamine.

The gas-phase conformational map of DA^- is shown in Figure 5. Qualitatively, this surface resembles very closely the gas-phase conformational map of neutral dopamine (Figure 3). The location of local minima is very similar to that of neutral dopamine. In all three cases (DA, DA^+, DA^-), the calculated gas-phase heats of formation span a range of approximately 10 kcal/mol. The most notable difference in the gas-phase conformational surfaces of DA, DA^+, and DA^- is the flattening out of the corners of the DA^+ potential relative to that of the DA and DA^- surfaces. In the gas-phase DA^+ surface, the anti-β conformer lies approximately 2 kcal/mol higher in energy than the gauche-β arrangement, whereas these two conformers are of approximately the same energy on the DA and DA^- surfaces.

All three gas-phase surfaces (Figures 3, 4, and 5) indicate that rotation about ϕ_1 is least hindered when the aromatic ring is in a perpendicular arrangement. It is therefore instructive to examine more closely this cross section of the potential energy surfaces. The calculations used to create the surfaces in Figures 3–5 were performed at 20° increments, meaning that no calculations were performed with $\phi_2 = 90°$. Examination of the data reveals that the potential is rather flat in this region (i.e., there is very little difference between the $\phi_2 = 80°$ and $\phi_2 = 100°$ cross sections). For convenience we have arbitrarily chosen the $\phi_2 = 100°$ cross section to represent the gas-phase ϕ_1 rotational profile for a perpendicular arrangement of ϕ_2. The data are shown for DA, DA^+, and DA^- in Figure 6.

There are two possible gauche-perpendicular conformations for DA, DA^+, and DA^-. In one the nitrogen is proximal to the *meta*-catechol oxygens (**a** in Figure 2), and in the other the nitrogen is distal to the *meta*-catechol oxygens (**c** in Figure 2). With $\phi_2 = 100°$ (as in Figure 6), the proximal conformation occurs at $\phi_1 = -60°$ and the distal occurs at $\phi_1 = 60°$. In the gas phase, for neutral dopamine, the distal conformer is calculated to be slightly more stable (by 0.2 kcal/mol) than the proximal conformer. The anti arrangement is 0.1 kcal/mol less stable than the proximal and 0.3 kcal/mol less stable than the distal. The barrier in going from a distal gauche arrangement ($\phi_1 = 60°$ in Figure 6) to an anti arrangement is 1.9 kcal/mol. The barrier between the two distal gauche ($\phi_1 = 60°$) conformer and the proximal gauche conformer ($\phi_1 = -60°$) is 1.7 kcal/mol. Finally, the barrier for taking the proximal gauche conformer to the anti conformer is 1.8 kcal/mol.

In the case of the gas-phase DA^+ ϕ_1 rotational profile, there is a large well spanning the $\phi_1 = -60°$ to $\phi_1 = 60°$ region corresponding to all conformations involving an approach of the ammonium ion to the aromatic ring. Thus, at least in the absence

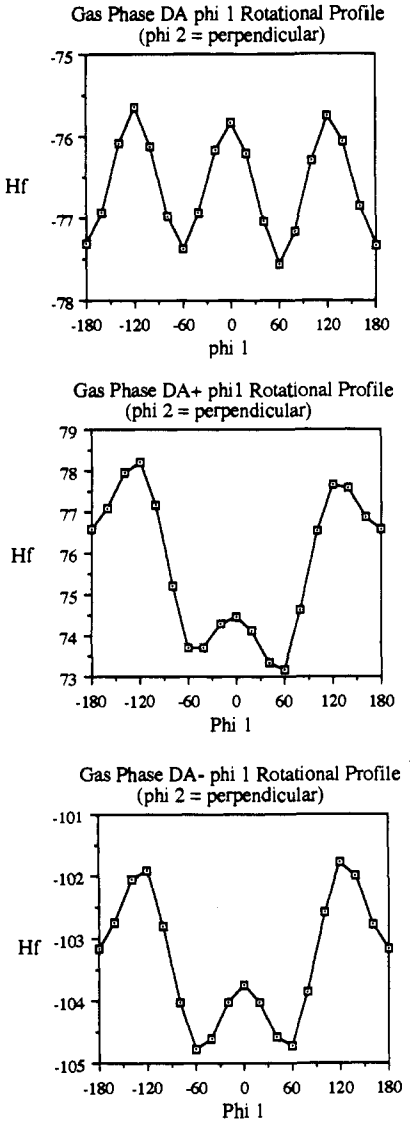

Figure 6. Gas-phase AM1-calculated heats of formation (H_f, in kcal/mol) shown as a function of ϕ_1 (degrees) for DA, DA^+, and DA^- with the catechol ring frozen in a perpendicular arrangement (see text).

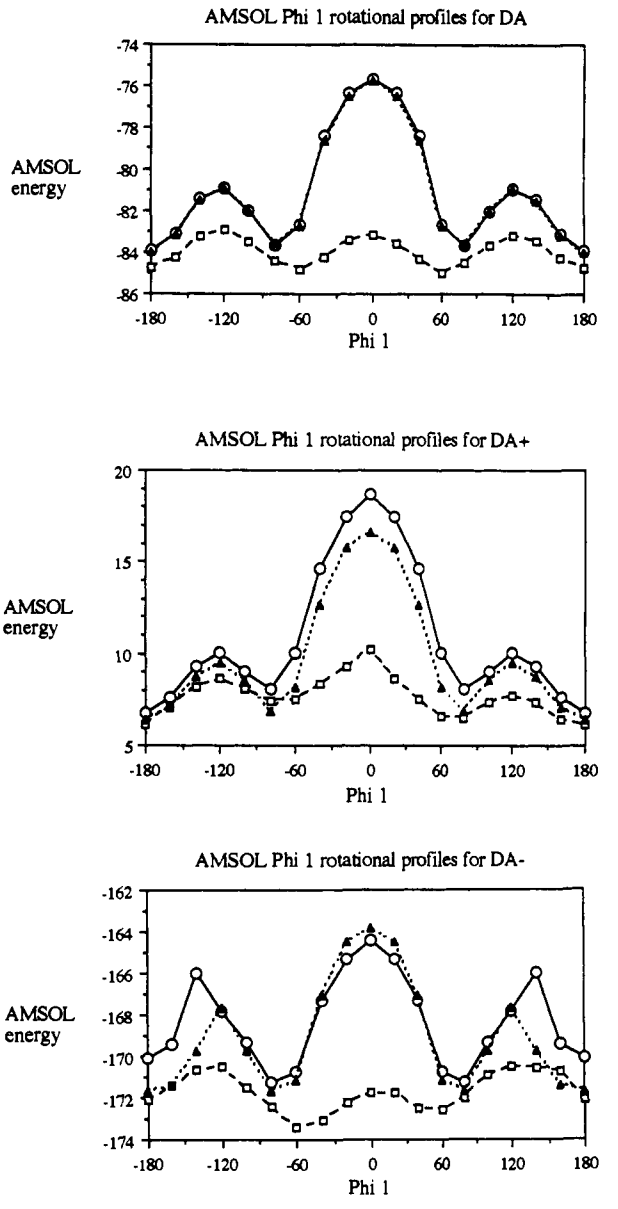

Figure 7. AMSOL energy (see text) profiles for rotation about ϕ_1, with ϕ_2 fixed at 0° (○), 90° (□) and 180° (▲), for DA, DA^+, and DA^-. The AMSOL energy is reported in kcal/mol and ϕ_1 is in degrees.

of solvent, there appears to be a stabilization reminiscent of the π-cation interactions noted in intermolecular complexation.[27]

For DA^-, a substantial stabilization of the gauche forms relative to the anti form is also observed. Again, this is in contrast to what is seen for neutral DA in the gas-phase calculations. The effects for DA^-, however, are far less dramatic than for DA^+. The barrier at $\phi_1 = 0°$ is 1.0 kcal/mol relative to the proximal gauche ($\phi_1 = -60°$) conformer. This value is 0.7 kcal/mol smaller than the corresponding barrier in DA, but is larger than that for DA^+. It is interesting to note that the relative energy ordering of the proximal and distal gauche forms changes when comparing DA, DA^+, and DA^-. For both DA and DA^+ the distal form is calculated to be slightly more stable than the proximal form, but for DA^- the reverse ordering is calculated. The energy differences are extremely small and it is rather difficult to consider them significant. It is clear, however, that, for gas-phase calculations employing the AM1 Hamiltonian, N-protonation or OH-deprotonation of neutral dopamine acts to increase the importance of the gauche-perpendicular structures.

The potential energy surfaces shown in Figure 3–5 also allow for an evaluation of the characteristics of rotation about ϕ_2 for DA, DA^+, and DA^-. In all three cases the gas-phase calculations predict the anti-perpendicular conformation to be lower in energy than either the α or β anti-planar conformations. For DA and DA^-, the α and β anti-planar structures are very similar in energy and lie approximately 0.8 kcal/mol above the perpendicular structures. For DA^+, the corresponding barrier is slightly larger.

3.2. Aqueous Solution Calculations. a. Rotation about ϕ_1. To explore the aqueous-phase conformational properties of dopamine, AMSOL was used to generate energy profiles describing rotation about dihedral angle ϕ_1 with ϕ_2 fixed at 0, 90, and 180° (α, perpendicular, and β conformations, respectively). The results of these calculations are provided in Figure 7. For $\phi_2 = 90°$, the rotational profile was obtained from AMSOL calculations at 20° increments of ϕ_1 ranging from −180 to 180°. The calculation was performed in two steps to provide stable geometries and SCF's. ϕ_1 was driven from 180 to 0° through positive dihedral angles and then, in a separate run, through negative dihedral angles. In all cases, differences in calculated energies for duplicate points were found to be extremely small (on the order of 0.1 kcal/mol), and the lower energy was used in the rotational profiles. At each point, all degrees of freedom except ϕ_1 and ϕ_2 were fully optimized. For $\phi_2 = 0$ or 180°, the rotational profile is symmetric and therefore calculations were performed on the range $\phi_1 = 180$ to 0°. The other half of these rotational profiles (Figure 7) was obtained by mirror reflection of the data.

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In general, the data represented in Figure 7 indicate that in solution, as was found in the gas-phase AM1 calculations, the lowest barriers to rotation about ϕ_1 are encountered when ϕ_2 is in a perpendicular arrangement. A comparison can be made between the gas-phase AM1 ϕ_1 rotational profiles shown in Figure 6 and the AMSOL ϕ_1 rotational profiles for $\phi_2 = 90°$ shown in Figure 7.

For neutral DA, the general shape of the ϕ_1 rotational profile (with ϕ_2 fixed in a perpendicular arrangement) changes very little upon going from the gas-phase AM1 calculations to the solution AMSOL calculations. All three minima (gauche-proximal, anti, and gauche-distal; **a**, **b**, and **c**, respectively, in Figure 2) are approximately isoenergetic as are the barriers between them. In the solution calculations, the barriers are slightly increased relative to the gas-phase calculations. As is seen in the gas-phase calculations, the distal form of the gauche-perpendicular arrangement is calculated to be slightly lower in energy than the proximal in the AMSOL calculations.

For the protonated DA^+ species, the solvent effects on this particular bond rotation are much more dramatic. The overwhelming stabilizing effect of the intramolecular ammonium nitrogen–catechol ring interaction is not a factor when solvation is considered. In fact, the syn ($\phi_1 = 0°$) conformer becomes the overall maximum energy structure along the rotational profile when solvent effects are included in the calculations. In the gas-phase results, the syn structure was significantly lower in energy (ca. 4 kcal/mol) than the highest energy conformer along the ϕ_1 rotational profile (Figure 6). Also, when solvation is considered, the anti-perpendicular conformer becomes lower in energy than either gauche-perpendicular conformation, although by a rather small amount. The reverse is found in the gas-phase calculations where the anti-perpendicular conformer is significantly higher in energy than either gauche-perpendicular. As far as the question of relative ordering of the proximal and distal gauche forms is concerned, it is once again difficult to draw any conclusion because the energy differences are so small. However, as in the gas-phase calculations for DA^+, the distal form is calculated with AMSOL to be slightly lower in energy than the proximal form.

Qualitatively, there is little observed change in the shape of the ϕ_1 (with ϕ_2 fixed at 90°) rotational profile for DA^- when solvent effects are included in the calculation with AMSOL. The barriers between the anti and gauche forms are larger than those between the two gauche forms. Quantitatively, the rotational potential is also relatively unchanged by solvent with the exception that the energy difference between the two gauche forms becomes larger in the AMSOL calculations. The proximal form is calculated to be 0.1 kcal/mol lower in energy in the gas-phase calculations. When solvent effects are included with AMSOL, this difference is increased to 0.8 kcal/mol. And, once again, the relative ordering is opposite to that calculated for either DA^+ or DA.

b. Rotation about ϕ_2. The gas-phase data energy surfaces in Figures 3–5 indicate that, with ϕ_1 in an anti conformation, rotation about ϕ_2 involves a minimum near 90° and maxima at 0° and 180°. The AMSOL technique is much more computationally intensive than its gas-phase counterpart, and, for that reason, a full conformational energy surface was not calculated with AMSOL. Rather, the ϕ_1 rotational profiles were calculated at these three important values (0°, 90°, and 180°) of ϕ_2. While this is not as informative as a full conformational map, some features of rotation about ϕ_2 can be gleaned from the data in Figure 7.

For the neutral species DA, it appears that a similar situation exists as in the gas phase. The lowest energy structure (with ϕ_1 in an anti conformation) occurs with a perpendicular arrangement of the ring ($\phi_2 = 90°$). The α and β forms of the anti-coplanar structures are found to be nearly isoenergetic in solution. Assuming the solution potential is shaped as is the gas-phase potential, the barrier to rotation about ϕ_2 (with ϕ_1 anti) in solution is 0.7 kcal/mol. For the protonated DA^+, the perpendicular arrangement is again the minimum of the three structures considered here. Interestingly, the β coplanar form ($\phi_2 = 180°$) is found to be lower in energy than the α coplanar conformer (by 0.3 kcal/mol) and only 0.2 kcal/mol higher in energy than the anti-perpendicular conformation. For DA^-, the lowest energy structure with ϕ_1 in an anti arrangement is also the perpendicular. In this case, however, the barrier to rotation is much higher at 2.1 kcal/mol with the maximum occurring at the α coplanar structure. In the case of DA^-, the β coplanar structure is only 0.5 kcal/mol above the perpendicular conformation.

Table I. Conformer Populations in Aqueous Solution as Determined by Solmajer et al.[a] with NMR

	conformer[b]	
pH	**b**	**a + c**
2.0	0.44	0.56
4.0	0.40	0.60
5.0	0.41	0.59
7.0	0.42	0.58
9.0	0.50	0.50
10.0	0.55	0.45
11.0	0.70	0.30
11.5	0.71	0.29

[a] Data are taken from ref 5. [b] The dopamine conformations are defined in Figure 2.

Table II. Comparison of Conformer[a] Populations from AM1 and AMSOL Calculations

	a	**b**	**c**
	AM1 (gas phase)		
DA+	0.33	0.01	0.66
DA	0.30	0.28	0.42
DA-	0.51	0.03	0.46
	AMSOL		
DA+	0.06	0.63	0.31
DA	0.31	0.27	0.42
DA-	0.73	0.08	0.19

[a] The dopamine conformations are defined in Figure 2.

At physiological pH, dopamine exists as the protonated form DA^+.[27] The AMSOL calculations suggest that the barrier to rotation about ϕ_2 is smaller for the protonated form of dopamine than for either the neutral or hydroxyl-deprotonated forms. In fact, for DA^+, AMSOL predicts that the perpendicular and β coplanar conformations are nearly isoenergetic with only a very small barrier between them at the α coplanar structure. This is consistent with the fact that rapid rotation of the catechol ring is seen in solution experimentally with NMR[5] at least for DA and DA^+.

3.3. Conformer Populations in Solution. As stated above, the solution NMR study of Solmajer et al.[5] indicated that as the pH of the solution is raised the relative population of the anti conformer increases. The data from this study are summarized in Table I. The arrangement of the aromatic ring could not be specified because of rapid rotation about ϕ_2. Also, the anti conformer (**b**) could be distinguished from the gauche conformers **a** and **c**, but **a** and **c** could not be distinguished from each other. In the current study, we are in the position to compare, at least in an approximate way, the predictions that would be made about such pH-dependent population effects with gas-phase AM1 calculations and those arising from AMSOL calculations.

A rough estimate of ϕ_1 conformer populations can be made by assuming a Boltzmann distribution of anti and gauche conformers as in eq 5:

$$X_n = C_i/C_j = \exp(-\Delta E_{ij}/RT) \quad (5)$$

Here, X_n represents the ratio between two conformations i and j. For simplicity, i and j will be taken to lie along the rotational profile for ϕ_1 with ϕ_2 in a perpendicular arrangement, and a temperature of 298 K will be assumed. For gas-phase calculations, ΔE_{ij} is the difference in AM1-calculated heats of formation for conformers i and j. In solution ΔE_{ij} represents the difference between the AMSOL energies (solute electronic and nuclear terms in the presence of the solvent plus the free energy of solvation) for i and j. The results of this approximate analysis are collected

in Table II. Conformer populations arrived at in this way are only meant to provide an alternate way of representing the large amount of data contained in conformational plots presented here in a very simplified manner. There are numerous factors lacking in this treatment: namely, the inherent discrepancies between actual free energy differences between conformations in solution observed experimentally and the calculated energy differences substituted for that quantity above. On the other hand, the major contributor to the differences between the true solution free energy of a solute and the AMSOL energy is the gas-phase $T\Delta S$ term. It is reasonable to expect this to be effectively a constant for the conformational processes under study here.

As would be expected, there is a great difference between the predictions one would make based on the gas-phase calculations and what is observed experimentally. In the gas-phase AM1 calculations, the relative importance of the anti conformation (**b**) diminishes dramatically for DA^+ or DA^- relative to that of neutral DA. In these structures (DA^+ and DA^-), there is an overwhelming preference for the gauche conformations due to the strong intramolecular interactions described above. Qualitatively, the differences between the gas-phase AM1 and AMSOL results reflect what one would expect to see in solution: a diminished importance of intramolecular electrostatics due to competing solvation effects. The populations in Table II based on the AMSOL calculations agree remarkably well with those observed experimentally. AMSOL predicts a trans population for the N-protonated DA^+ species of 63%, compared to an experimental population at low pH (where DA^+ is the sole component) of ca. 40%. The conformer populations estimated in eq 5 are extremely sensitive to the calculated energy differences. An energy difference of only ca. 0.4 kcal/mol will double the ratio X_n.

Experimental studies indicate that, at physiological pH, catecholamines exist to over 95% as the N-protonated species[28] and that this species is the dominant form up to pH values approaching 10.[29] When the pH is raised above the 9 to 10 region, however, the situation is much more complicated. There appears to be an equilibrium established between neutral DA, a zwitterionic form of dopamine (N-protonated, hydroxyl-deprotonated), and the anionic form DA^- studied here. Ionization of the second phenol group does not occur until the pH approaches 13.[29] Comparisons between the calculations reported here and the experimental data collected in Table I is much more direct for the pH range of 2 to 9 where in solution dopamine exists almost exclusively as the single species DA^+.

4. Conclusions. Often one of the goals of a molecular modeling study is to ascertain a molecule's conformational preferences under the conditions that it is most often found. For biologically active compounds, this condition is often in the presence of water. However, due to lacking techniques or computational power, computational studies in the past have often been limited to the realm of the molecule in isolation. The purpose of this work is to compare the description of the potential energy surface derived from gas-phase AM1 calculations and aqueous-phase AM1–SM1 calculations. This work illustrates the great importance of hydration effects on conformational equilibria for molecules, such as dopamine, which can exist in a variety of ionized species. The gas-phase AM1 calculations predict that introducing a charge, either positive due to N-protonation or negative due to OH deprotonation, essentially eliminates the importance of the anti conformation of dopamine. That, however, is in contradiction with what would be expected intuitively for an aqueous solution and with what is observed experimentally.[3] In this sense, the AMSOL program proves extremely useful in that it predicts the anti conformation to be an important component of the equilibrium mixture of dopamine conformations, at least at physiological pH.

There is little difference between the AM1–SM1 and the gas-phase AM1 results for neutral dopamine indicating that all conformations of the neutral species are roughly equally well solvated. If the option of including solvent effects were not available, it could be argued that the gas-phase potential surface of *neutral* dopamine is probably more representative of the conformational preferences of dopamine in solution (at pH = 7) than is the gas-phase surface for *protonated* dopamine. In fact, the estimated gas-phase anti population value for neutral dopamine is 0.28 (Table II) which agrees about as well with the experimental anti population (0.42) at pH = 7 as the AMSOL DA^+ value. However, the inclusion of hydration effects *is* available in the form of AMSOL and other continuum approaches,[21,30-34] as well as with explicit water approaches.[35-40] And, performing gas-phase calculations on the neutral species of molecules that are charged in solution may not always be a valid approximation. Also, as stated above, often the charge does not arise simply from solvent protonation or deprotonation but is inherently present in the solute, as in the case of acetylcholine.

The AM1–SM1 model has been shown in past studies to accurately represent solvation effects on acid–base reactions, as well as tautomeric and rotameric equilibria.[41] In this work, the application of the technique has been extended further in the area of conformational analysis to the neurotransmitter dopamine. The results obtained here indicate that AM1–SM1 can be a very useful technique in predicting solvent effects on conformational equilibria even for charged molecules where these effects may be dramatic.

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