Investigation of the Effect of the Solvent Medium on the Conformational Behavior of Phenylethylamines by Empirical Method

Mahadevappa Kumbar

Division of Research Laboratories, Queens Children's Psychiatric Center, Bellerose, New York 11426. *Received October 1, 1975*

The effect of the dielectric constant (solvent medium) on the conformational behavior of six phenylethylamines has been investigated using the empirical method. Various physical properties, such as rotamer population, dipole moment, optical anisotropy, and depolarization ratios, are examined. The effective intramolecular dielectric constant has been varied from 1.0 (vacuum) to 80.0 (highly polar medium). It is shown that all these properties truly depend on the magnitude of the dielectric constant (nature of the solvent medium), but the effect is more pronounced when the dielectric constant is less than about 30.0. In addition, the effect of various groups has been assessed by using the above-mentioned properties. In general, all the six compounds studied here possess three energy minima corresponding to one trans and two gauche forms. These energy minima have shifted only once when the dielectric constant is increased from 1.0 to 5.0. Thus, it is concluded that the nature of the solvent medium is critical in assessing percent population, ionic character, and polarizability of the molecule but not in describing the energy minima.

In the past decade, a number of theoretical investigations have been conducted to understand the conformational behavior of various drug molecules. Particularly, the phenylethylamines have been given the most consideration because of their medicinal and biochemical value. Among the theoretical methods, the molecular orbital (MO) methods, such as EHT (extended Hückel theory) and INDO (intermediate neglect of differential overlap), and PCILO (perturbative configuration interaction using localized orbitals) have been used to study the phenylethylamines.[1] When these theoretical methods are used without considering the option of variation in pH or the temperature or the nature of the solvent medium, the results may not be satisfactory for the study of drug interaction problems. Various approaches[2-9] have been employed to account for solvation effects. In general, the MO methods require much computer time; due to that often only a limited number of rotations around each bond are carried out. On the other hand, within the framework of the empirical method, the various above-mentioned effects might be studied by scaling the electrostatic term (see eq 4) in a simple manner. Since solute–solvent effects, such as reaction field effects, cavity effects, etc., are not independent of the effective dielectric constant for solute–solute interaction, we propose the use of an apparent dielectric constant as a variable parameter (not a constant) to account for both macroscopic and microscopic effects. The value of this apparent dielectric constant *must* be evaluated by comparing the computed and the experimental properties. Thus the adjusted value of this constant might represent the status of that particular system under the given experimental conditions.

The conformational behavior of a drug molecule in drug–receptor interactions, in general, may depend on various factors, such as the nature of the receptor site, neighboring molecules, temperature, pH, and the nature of the solvent medium in which the process of interaction takes place. Since various biological systems involve different environments, it is logical to assume that the nature of the solvent medium in each system is not identical. As a result, the conformational behavior of a particular drug molecule in various biological systems may not be the same. Therefore, it is quite essential to understand the conformational behavior in relation to the nature of the solvent medium.

Within the framework of the empirical method, the conformational energies are determined as the sum of contributions from various interactions, e.g., nonbonded, torsional, electrostatic, hydrogen bonding, etc. Among these interactions, the electrostatic interaction depends most critically on the nature of the solvent medium through the effective dielectric constant (ϵ, see eq 4). As a matter of fact, the magnitude of this constant measures the nature of the fluid that exists between the interacting species. Thus theoretically, the nature of the fluid can be altered by varying the value of the dielectric constant. The value of $\epsilon = 1$ refers to the vacuum (no medium) and $\epsilon = 80$ refers to highly polar nature. Hence, a gradual change of ϵ from 1 to 80 continuously increases the polarity of the medium starting from the nonpolar nature.

In a previous study,[10] the effect of solvent medium on the conformational behavior of tryptamine and 5-hydroxytryptamine (serotonin, 5-HT) has been examined. It has been shown that the conformational preference, dipole moment, anisotropy, and depolarization ratio, which are important determinants in drug–receptor interactions, truly depend on the solvent medium. Therefore, it seems worthwhile to extend the same idea and the concept to the important molecules like phenylethylamines to examine their conformational behavior.

Method of Calculation. a. Conformational Energies. The conformational energies of phenylethylamines are computed by using the following relation

$$E(\varphi,\psi) = E_{\text{nonbonded}} + E_{\text{torsional}} + E_{\text{electrostatic}} + E_{\text{H bond}} \quad (1)$$

where φ and ψ are the dihedral (torsional) angles (Figure 1). The nonbonded interaction energy between the pair of interacting atoms is calculated by using the Lennard-Jones 6–12 potential function, which is given by

$$E_{\text{nonbonded}} = \sum_{i,j} (d_{ij} r_{ij}^{-12}) - (e_{ij} r_{ij}^{-6}) \quad (2)$$

The first term in this equation represents the repulsive forces, whereas the second term describes the attractive forces. The r_{ij} is the distance between the ith and the jth interacting atoms, and e_{ij} and d_{ij} are the coefficients. The detailed procedure for obtaining these coefficients has been described previously.[11]

The torsional potential energy about C–C single bonds and the C–N single bond is calculated making use of the following equation[7]

$$E_{\text{torsional}} = (E_\varphi^\circ/2)(1 + \cos 3\varphi) + (E_\psi^\circ/2)(1 + \cos 3\psi) + (E_\tau^\circ/2)(1 + \cos 3\tau) \quad (3)$$

where E_φ°, E_ψ°, and E_τ° are the torsional energy barriers for φ, ψ, and τ. $E_\varphi^\circ = 0.5$ kcal mol^{-1} and $E_\psi^\circ = 2.8$ kcal mol^{-1} have been used.[12-14] A similar threefold potential function is also used for the rotation of the C–O bond with $E^\circ = 1.1$ kcal mol^{-1}. Since the τ was fixed at 60 or 180° in a staggered position with the preceding group, the last term in eq 3 vanishes.

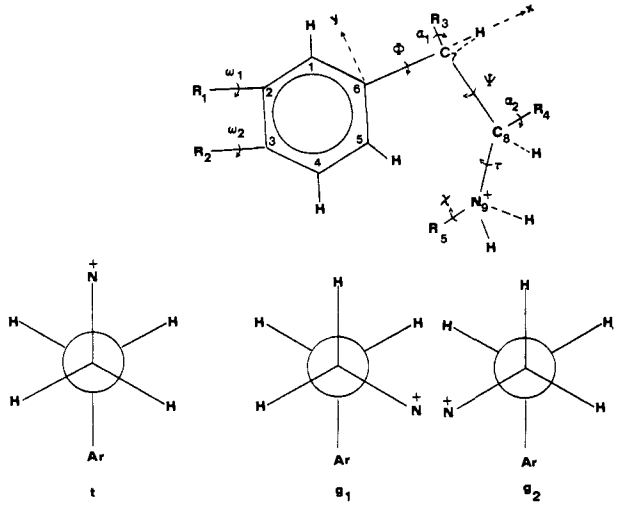

Figure 1. Definition of various dihedral angles: $\varphi = 0$, when C_7-C_8 bond is in planar cis position with C_5-C_6 bond; $\psi = 0$, when C_8-N_9^+ bond is in planar cis position with C_7-C_6 bond; $\tau = 0$, when N_9^+-R_5 bond is in planar cis position with C_7-C_8 bond; $\chi = 0$, when C-H bond is in planar cis position with C_8-C_9^+ bond; $\alpha_1 = 0$, when C-H bond is in planar cis position with C_6-C_7 bond; $\alpha_2 = 0$, when C-H bond is in planar cis position with C_7-C_8 bond; $\omega_1 = 0$, when O-H bond is in planar cis position with C_2-C_3 bond; and $\omega_2 = 0$, when O-H bond is in planar cis position with C_3-C_4 bond (upper diagram). The lower part of the figure indicates the Newman projections of three rotamers about the C_7-C_8 bond in phenylethylamines.

The electrostatic energy for the nonbonded pairs has been evaluated using the formula

$$E_{\text{electrostatic}} = 332 e_i e_j / \epsilon r_{ij} \tag{4}$$

where ϵ is the effective dielectric constant, and e_i is the charge on the ith atom. The charge e_i on each atom has been determined as the sum of π and σ charges. The π charges are computed by the Hückel method[15] and the σ charges by the method suggested by Del Re.[16] The φ and ψ are rotated in 10° intervals, and the necessary geometric input data are taken from Bergin.[17]

The hydrogen bond energy is added by using the potential of McGuire et al.[18] which is

$$E_{\text{H bond}} = A/r_{\text{O}\cdots\text{H}}{}^{12} - B/r_{\text{O}\cdots\text{H}}{}^{10} \tag{5}$$

where $A = 8488.8A^{0\,12}$ kcal mol^{-1}, $B = 3972.9A^{0\,10}$ kcal mol^{-1} for an O-H···O< type hydrogen bond, and $A = 4835.0A^{0\,12}$ kcal mol^{-1}, $B = 2262.2A^{0\,10}$ kcal mol^{-1} for the N-H···O< type hydrogen bond.

b. Percent Population. Let n_t, n_{g_1}, and n_{g_2} represent the mole fractions (or the percent population) of three stable conformations, one trans (t) and two gauches (g_1 and g_2), respectively (Figure 1). Then the mole fractions are estimated according to the following equation

$$n_t = \frac{1.0}{1 + f_1 + f_2} \qquad n_{g_1} = \frac{f_1}{1 + f_1 + f_2}$$
$$n_{g_2} = \frac{f_2}{1 + f_1 + f_2} \tag{6}$$

where f_1 and f_2 are

$$f_1 = 1.0/\exp[-\Delta G_1^\circ/RT]$$
$$f_2 = 1.0/\exp[-\Delta G_2^\circ/RT] \tag{7}$$

subject to the condition that $n_t + n_{g_1} + n_{g_2} = 1$. In the above expressions, the ΔG_1° and ΔG_2° are the free-energy differences between the trans and two gauche conformations, which are evaluated through the following set of equations.

$$\Delta G_1^\circ = \Delta H_1^\circ - T\Delta S_1^\circ = \Delta E_1 - RT \ln (\Omega_t/\Omega_{g_1}) \tag{8}$$
$$\Delta G_2^\circ = \Delta H_2^\circ - T\Delta S_2^\circ = \Delta E_2 - RT \ln (\Omega_t/\Omega_{g_2}) \tag{9}$$

In eq 8 and 9, we have set $\Delta H_i = \Delta E_i = E_t - E_{g_i}$ and $T\Delta S_i = RT \ln (\Omega_t/\Omega_{g_i})$. The Ω_t and Ω_{g_i} are the degeneracy factors or the number of trans and gauche rotamers having the same energy E_t and E_{g_i}, respectively.

c. Dipole Moment. The dipole moment of an ith rotamer is calculated using the relation

$$\mu_i = \sum_j e_j r_j \tag{10}$$

where e_j is the charge on the jth atom. Then the average dipole moment of a mixture is estimated according to the method suggested previously.[14,19] Thus

$$\langle\mu\rangle = \Sigma n_i \mu_i \tag{11}$$

where n_i is the mole fraction of the ith rotamer.

d. Molecular Polarizability. Optical Anisotropy and Depolarization Rate. The molecular polarizability tensor α is evaluated according to the valence optical scheme.[12,14,20] Within the framework of this scheme, the molecular polarizability becomes the tensor sum of the contributions of its individual bonds. Then the expression for α referred to bond 1 may be written as[20]

$$\alpha = \sum_{\substack{\text{all}\\ \text{bonds}}} \left(\prod_{k=2}^{j} T_k \right) \cdot \alpha_j \cdot \left(\prod_{k=j}^{2} T_k^{-1} \right) \tag{12}$$

The T_k is the product of transformation matrices, which is

$$T_k = \begin{bmatrix} \cos\theta & & \sin\theta & & 0 \\ -\sin\theta & \cos p_i & \cos\theta & \cos p_i & -\sin p_i \\ -\sin\theta & \sin p_i & \cos\theta & \sin p_i & \cos p_i \end{bmatrix}$$
$$p_i = \text{dihedral angles} \tag{13}$$

In eq 12, the α_j is the bond polarizability tensor, which is defined as

$$\alpha_j = \bar{\alpha}_j E + {}^1/_3 \eta_j S + \delta_j R \tag{14}$$

where

$$\eta_j = {}^1/_2 (2b_j^{(1)} - b_j^{(2)} - b_j^{(3)}) \tag{15}$$

$$\delta_j = {}^1/_2 (b_j^{(2)} - b_j^{(3)}) \tag{16}$$

$$S = \begin{bmatrix} 2 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} \qquad R = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{bmatrix} \tag{17}$$

Here E is the unit tensor and $\bar{\alpha}_j = {}^1/_3$ trace α. The $b_j^{(1)}$, $b_j^{(2)}$, and $b_j^{(3)}$ are the components of the principal polarizabilities of the jth bond. It is advantageous to define the traceless tensor β as follows.[20]

$$\beta = (\alpha - \bar{\alpha}_{\text{molecule}} E) \tag{18}$$

Then the anisotropy, γ_i^2, and the depolarization ratio, ρ_i, of the ith rotamer are respectively obtained from eq 19 and 20

$$\gamma_i^2 = {}^3/_2 \sum_{i,j} \beta_{ij} \tag{19}$$

$$\rho_i = 6\gamma_i^2/(45\bar{\alpha}^2 + 7\gamma_i^2) \tag{20}$$

Table I. Summary of Energy Minima, Dipole Moments, Anisotropies, and Depolarization Ratios of Phenylethylamines

Compound	Dielectric constant, ϵ	Number of minima[a] φ, deg	ψ, deg	τ, deg	χ, deg	ω_1, deg	ω_2, deg	α_1, deg	α_2, deg	μ, D	$\gamma^2 \times 10^{48}$ cc^2	$\rho \times 100$
Phenylethylamine	1.0	80	180 (t)	60						9.455	32.353	1.563
		80	50 (g_1)*							10.865	33.092	1.598
		100	310 (g_2)							9.415	33.106	1.599
	≥5.0	80	180 (t)	60						9.455	32.353	1.563
		70	60 (g_1)*							10.455	35.253	1.700
		100	290 (g_2)							9.058	33.059	1.597
Dopamine	1.0	80	180 (t)	60		70	290			4.509	33.213	1.323
		70	50 (g_1)*							13.946	36.249	1.442
		100	310 (g_2)*							15.900	33.778	1.345
	≥5.0	80	180 (t)	60		70	290			4.509	33.213	1.323
		70	60 (g_1)*							13.173	36.263	1.443
		100	290 (g_2)							15.040	33.736	1.344
Norepinephrine	1.0	240	170 (t)	60		70	300			12.844	42.050	1.651
		240	60 (g_1)*							21.128	42.175	1.696
		300	310 (g_2)							13.892	35.251	1.422
	5.0	60	170 (t)	60		70	290			9.812	40.530	1.631
		240	70 (g_1)*							21.071	42.174	1.696
		300	310 (g_2)							13.892	35.251	1.422
	≥10.0	60	170 (t)	60		70	70			9.812	40.530	1.631
		60	70 (g_1)*							18.139	41.649	1.675
		300	310 (g_2)							13.892	35.251	1.422
Epinephrine	1.0	230	160 (t)	60	60	70	300	60				
		60	70 (g_1)*									
		320	290 (g_2)									
	≥5.0	60	160 (t)	60	60	70	290	60				
		60	60 (g_1)*									
		140	290 (g_2)									
	1.0	240	170 (t)	60	180	70	300	60		18.115	43.595	1.440
		240	70 (g_1)*							22.856	44.568	1.478
		300	310 (g_2)							15.175	35.522	1.182
	≥5.0	60	170 (t)	60	180	70	290			14.466	43.219	1.434
		60	70 (g_1)*							19.347	44.051	1.182
		300	310 (g_2)							15.175	35.522	1.182
β-Phenylethanol-amine	1.0	60	180 (t)	60				60		11.164	38.815	1.757
		60	60 (g_1)							18.033	39.936	1.807
		300	310 (g_2)*							12.564	34.209	1.553
	≥5.0	60	170 (t)	60				60		13.979	38.823	1.758
		60	70 (g_1)*							18.128	39.942	1.807
		300	310 (g_2)							12.564	34.209	1.553
Amphetamine	1.0	70	190 (t)	60					60	7.205	41.689	1.611
		90	50 (g_1)							8.425	48.080	1.853
		290	300 (g_2)*							8.390	45.481	1.754
	≥5.0	80	180 (t)*	60					60	7.305	37.552	1.454
		80	60 (g_1)							8.461	49.532	1.907
		290	290 (g_2)*							8.318	45.216	1.744

[a] An asterisk indicates the global minimum; secondary minima lie within 0.5 kcal mol^{-1} above the global minimum.

where β_{ij} are the components of the traceless tensor β. The average anisotropy and the depolarization ratio for a mixture are given below

$$\langle\gamma^2\rangle = \sum_j n_i\gamma_i^2 \quad (21)$$

$$\langle\rho\rangle = 6\Sigma n_i\gamma_i^2/(45\bar{\alpha}^2 + 7\Sigma n_i\gamma_i^2) \quad (22)$$

where n_i is the mole fraction of the ith rotamer. The bond polarizabilities are taken from Stuart[21] and Londolt-Börnstein.[22]

Results and Discussion

The effect of the dielectric constant (solvent medium) on various aspects of conformational behavior has been examined and is presented in the following sections. The dielectric constant has been altered from $\epsilon = 1.0$ (vacuum) to $\epsilon = 80.0$ (highly polar nature).

(a) Effect on Energy Maps (Contour Diagrams). The conformational energies are computed using eq 1 as a function of the dielectric constant. The contour maps are reproduced in Figures 2–9 (see paragraph at the end of paper regarding supplementary material). The contours are drawn in the 1 kcal mol^{-1} interval from the global minimum (lowest energy state) and the contours above 5 kcal mol^{-1} have been omitted. The results are summarized in the Table I. In the case of dopamine, norepinephrine, and epinephrine, the process of energy calculation was carried out in two stages. (i) Since the ring hydroxyl groups have no influence on the side-chain conformation, the most stable positions of the ring OH groups are obtained by rotating ω_i from 0 to 360° for each chosen value of ϵ. The values of ω_i corresponding to the most stable positions are listed in Table I. (ii) Fixing the hydroxyl groups in their most stable positions, the energy maps for the side chains are determined by rotating φ and ψ from 0 to 360° in 10° intervals. From Figures 2–9 (supplementary material), it is clear that the shapes of the contours depend on the magnitude of ϵ and also on the selected torsional angles for the asymmetric group [cf. Figures 5 and 6, and 7 and 8 (supplementary material)]. However, the shapes have changed considerably only in the region $1.0 \leq \epsilon \leq 30.0$ indicating the greater influence of ϵ in this region. Each map consists of three energy minima corresponding to one global and two secondary. The positions of these minima have shifted only once, that is, when ϵ is increased from 1.0 to 5.0. After that, the

Table II. Most Probable Conformations Reported by Various Methods

Compound	PCILO[a]		EHT[b]		Empirical[c]		X-Ray[d]	
	φ, deg	ψ, deg[e]	φ, deg	ψ, deg	φ, deg	ψ, deg	φ, deg	ψ, deg
Phenylethylamine	90	180 (t)*					247	189
	90	60 (g_1)						
	90	300 (g_2)*						
Dopamine	70	180 (t)*	90	60			261	174
	70	70 (g_1)*	90	300				
	80	290 (g_2)*	150	300				
			30	60				
Norepinephrine	120	180 (t)*					263	176
	90	300 (g_2)*						
	240	180 (t)						
	270	300 (g_2)						
Epinephrine	120	180 (t)*						
	310	300 (g_2)						
	100	300 (g_2)						
Amphetamine	120	180 (t)*			275	45 (CV)	251	185
	90	60 (g_1)*			275	175 (CAS)	253	187
	90	300 (g_2)*					246	188
							260	194

[a] B. Pullman, J. L. Coubeils, Ph. Courriere, and J. P. Gervois, *J. Med. Chem.*, 15, 17 (1972). [b] L. B. Kier, *J. Pharmacol. Exp. Ther.*, 174, 94 (1970). [c] H. J. R. Weintraub and A. J. Hopfinger, *J. Theor. Biol.*, 41, 53 (1973). CV = charged species in vacuo; CAS = charged species in aqueous solution. [d] Reference 18. [e] An asterisk indicates the global minimum.

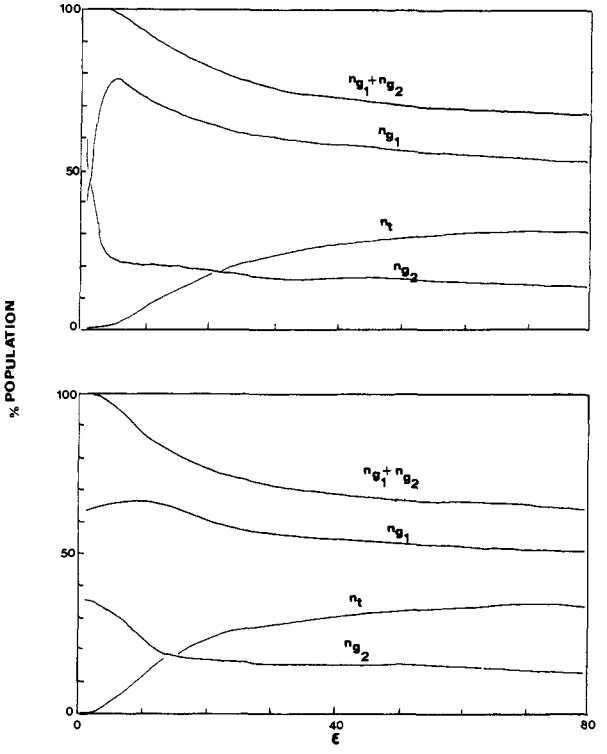

Figure 10. Effect of variation in dielectric constants (ϵ) on percent population of trans (t), gauche$_1$ (g_1), and gauche$_2$ (g_2): dopamine (upper diagram) and phenylethylamine (lower diagram).

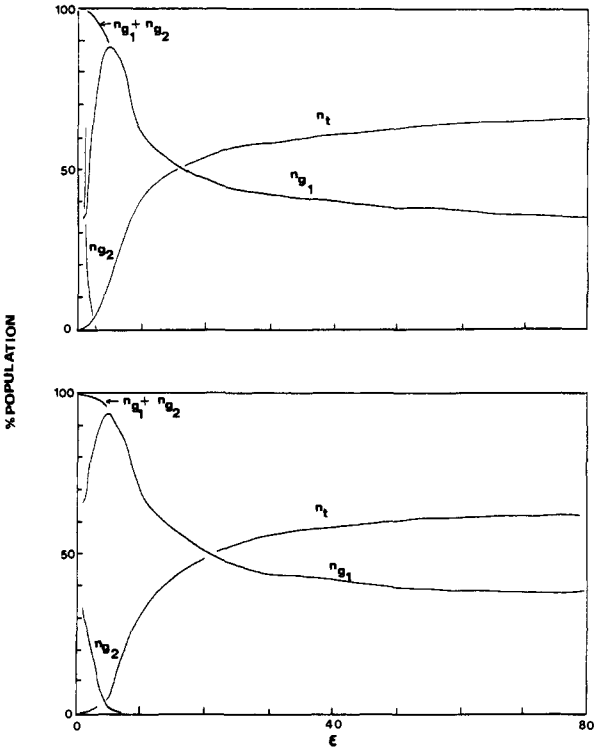

Figure 11. Effect of variation in dielectric constant (ϵ) on the percent population of t, g_1, and g_2: norepinephrine (lower diagram) and β-phenylethanolamine (upper diagram).

positions have remained unaltered, even though the shapes of the contours have changed quite a bit. In Table II the most stable conformations predicted by other methods have been listed. A qualitative agreement between our results (Table I) and other methods (Table II) is observed.

(b) Effect on Conformational Preference. It is quite interesting to see the effect of ϵ on the conformational preference of amines studied here (Figures 10–12, Table III). When $\epsilon = 1.0$ (vacuum), only the gauche forms occur due to the high degree of interaction between the side chain and the ring portion. The exaggerated preference for gauche conformation when $\epsilon \approx 1.0$ may also be interpreted as due to the use of both electrostatic and a specific hydrogen bond potential functions. As ϵ increases (as if one is increasing the polarity of the medium), the proportionality of the trans conformations is predicted to increase and, at the same time, the dominance of the gauche forms decreases. Thus a gradual increase in trans conformations may be considered as due to increased electrostatic interactions between the side chain and the solvent medium (modeled by decreasing solute intramolecular interactions).

Thus from the above discussion it is evident that the conformational preference, which plays an important role in biological activities, truly depends on the nature of the solvent medium. Both extended and folded forms might

Table III. Conformational Preference of Phenylethylamines

Compound	Present method		PCILO[a]		NMR[a]	
	% trans	% gauche	% trans	% gauche	% trans	% gauche
Phenylethylamine	0 (ϵ = 1.0)	100 (ϵ = 1.0)	42	58	56	44
	34 (ϵ = 80)	64 (ϵ = 80)				
Dopamine	0 (ϵ = 1.0)	100 (ϵ = 1.0)	35.2	64.8	43	57
	32 (ϵ = 80)	68 (ϵ = 80)				
Norepinephrine	0 (ϵ = 1)	100 (ϵ = 1)	75.5	24.5	76	24
	62 (ϵ = 80)	38 (ϵ = 80)				
Epinephrine[b]	0 (ϵ = 1)	100 (ϵ = 1)	95.5	4.5	77	23
	57 (ϵ = 80)	43 (ϵ = 80)				
	17 (ϵ = 1)	83 (ϵ = 1)				
	33 (ϵ = 80)	67 (ϵ = 80)				
β-Phenylethanolamine	0 (ϵ = 1)	100 (ϵ = 1)			84	16
	64 (ϵ = 80)	36 (ϵ = 80)				
Amphetamine	0 (ϵ = 1)	100 (ϵ = 1)			50	50
	66 (ϵ = 80)	34 (ϵ = 80)				

[a] As reported by R. R. Ison, P. Partington, and G. C. K. Roberts, *Mol. Pharmacol.*, 9, 756 (1973). [b] Two sets of values are reported; the first set refers to τ = 60° and the second set to τ = 180°.

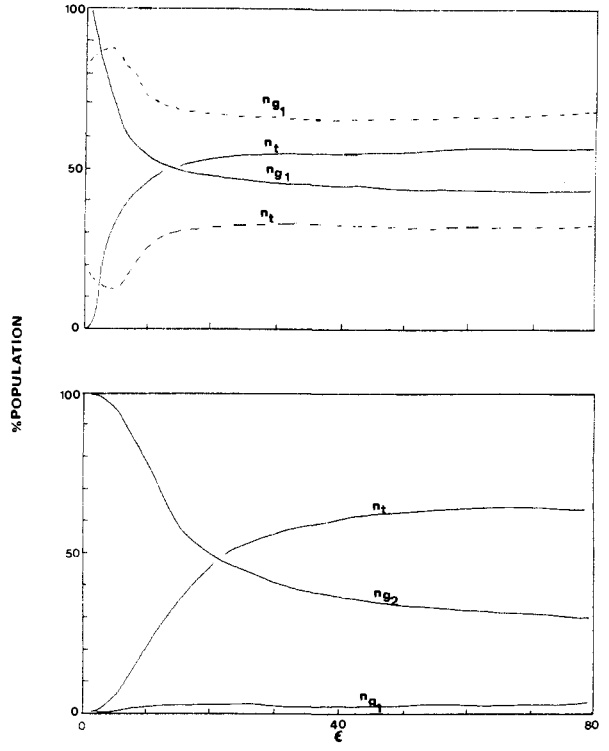

Figure 12. Effect of variation in dielectric constant (ϵ) on percent population of t, g_1, and g_2: amphetamine (lower diagram) and epinephrine (upper diagram). (——) τ = 180°, χ = 60°; (- - -) τ = 60°, χ = 60°.

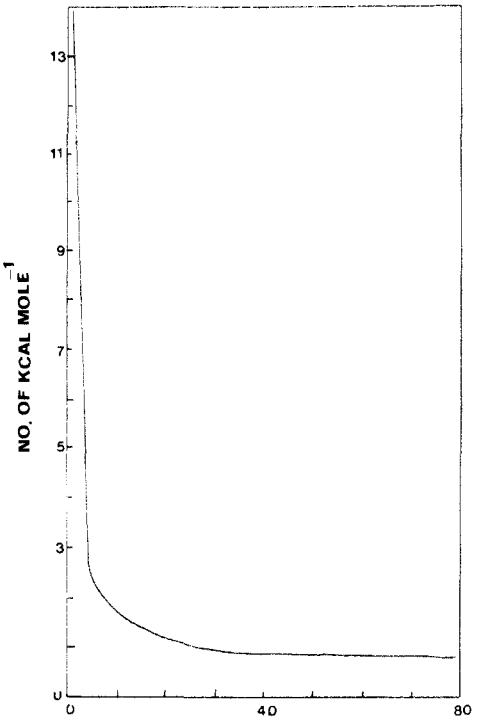

Figure 13. Effect of dielectric constant (ϵ) on the x-ray conformation. The number of kcal mol^{-1} above the global minimum is plotted vs. ϵ for dopamine hydrochloride. Similar behavior is also observed for phenylethylamine hydrochloride, norepinephrine hydrochloride, and amphetamine sulfate.

coexist in an equilibrium mixture only when the dielectric constant is high (polar medium), say about 20. Thus it appears that if the molecule contains a polar side chain and if the medium is polar then, most probably, the molecule might assume, to a greater extent, an extended form. On the other hand, if the medium is nonpolar, then the proportionality of the folded form might increase.

In Table III the conformational preferences are also compared with the NMR and PCILO results.[23] Only a qualitative agreement is obtained except for the amphetamine, where the NMR results correspond to $\epsilon \approx$ 25. This discrepancy might be attributed to the method of calculation of the percent trans and gauche population. More precisely, these have to be evaluated by integrating over the energy surfaces.

(c) X-Ray Conformations. Out of six amines studied here, the x-ray structures of only four amines, namely, phenylethylamine, dopamine, norepinephrine, and amphetamine, are available.[24] All these structures, however, exist only in extended forms [see Figures 2–4 and 9 (supplementary material) and Table II]. The number of kcal mol^{-1} of the x-ray conformations above the global minimum is indicated in Figure 13 as a function of ϵ. As ϵ increases, the number of kcal mol^{-1} above the global minimum decreases in an exponential manner indicating that x-ray structures are best generated by using the high value of ϵ.

(d) Effect on the Dipole Moment, Anisotropy, and Depolarization Ratio. In Table I, we have listed the computed values of the dipole moments (μ), anisotropies (γ^2), and depolarization ratio (ρ) for trans and gauche conformers (using the coordinate system described in Figure 1). The magnitude of these quantities depends on the dihedral angles. In most cases, μ, γ^2, and ρ are smaller for the trans conformer compared to gauche conformer,

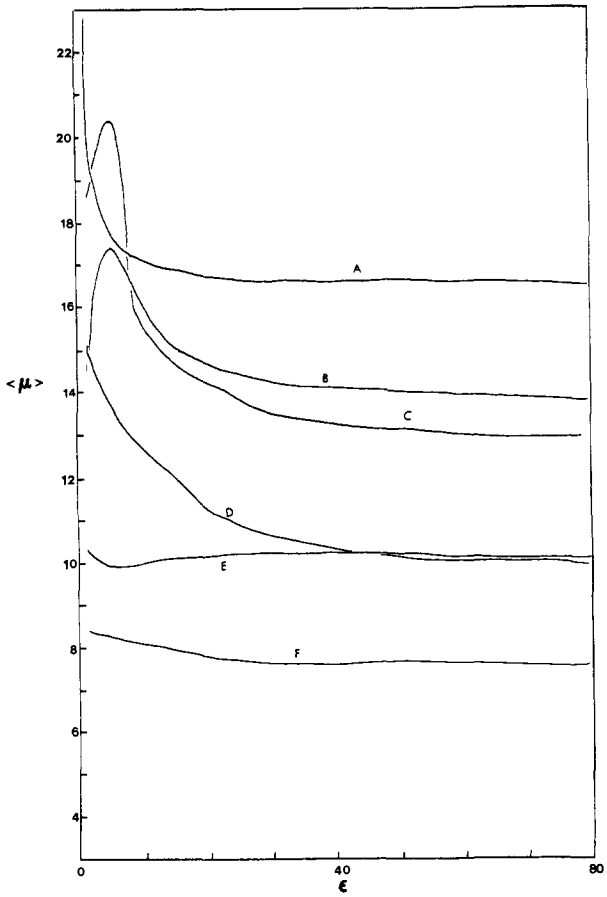

Figure 14. Effect of dielectric constant (ϵ) on the average dipole moment calculated according to the eq 11: (A) epinephrine, (B) β-phenylethanolamine, (C) norepinephrine, (D) dopamine, (E) phenylethylamine, and (F) amphetamine.

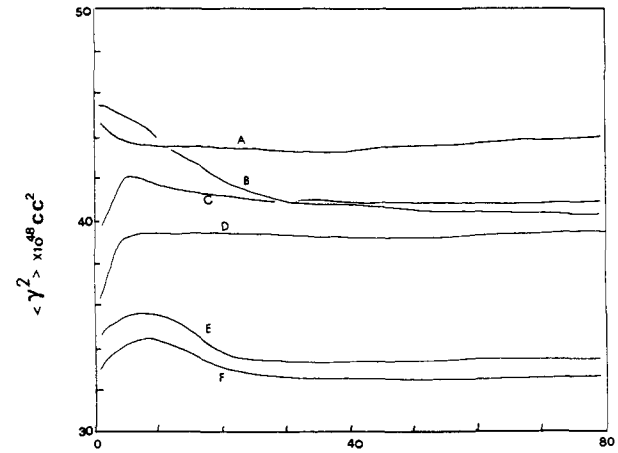

Figure 15. Effect of dielectric constant (ϵ) on the average optical anisotropy of mixture of t, g_1, and g_2 calculated according to eq 22: (A) epinephrine, (B) amphetamine, (C) norepinephrine, (D) β-phenylethanolamine, (E) dopamine, and (F) phenylethylamine.

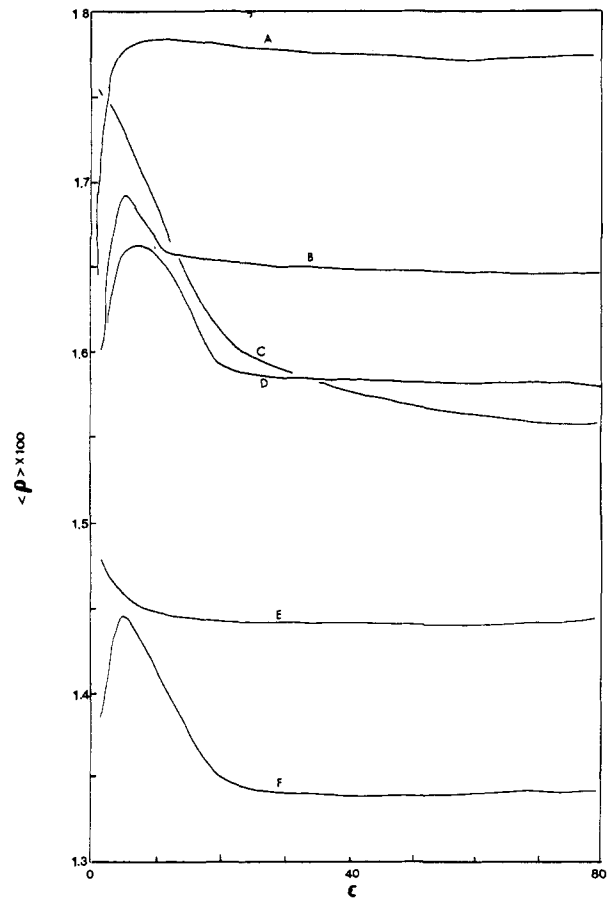

Figure 16. Effect of dielectric constant on the depolarization ratio of a mixture of t, g_1, and g_2 calculated according to the eq 23: (A) β-phenylethanolamine, (B) norepinephrine, (C) amphetamine, (D) phenylethylamine, (E) epinephrine, and (F) dopamine.

which is an indication that the guache conformer is better polarizable than the trans conformer. Morever, the gauche conformer is of high electrostatic nature. Figures 14–16 indicate the effect of ϵ on the average properties, which are calculated by using the mixture of three rotamers (t, g_1, and g_2) from eq 11, 21, and 22. It is evident that the behavior of these quantities is dependent of the nature of the solvent medium. However, the effect is more pronounced in the range $1.0 \leq \epsilon \leq 30.0$. Outside this range, the influence is small. In any case, with the aid of Figures 14–16, one can assess the degree of ionic character and extent of polarization at various ϵ values and can describe the behavior of these amines in various solvents. For example, when the solvent medium is of highly polar nature ($\epsilon = 80$), the order of increasing ionic character is epinephrine > β-phenylethanolamine > norepinephrine > phenylethylamine > dopamine > amphetamine, while the increasing order of polarizability is epinephrine > norepinephrine > amphetamine > β-phenylethanolamine > dopamine > phenylethylamine.

(e) Effect of Various Substitutions. The effect of substitution of ring OH groups can be easily assessed by comparing the conformational behavior of dopamine with that of phenylethylamine or of β-phenylethanolamine with that of norepinephrine. When OH groups are substituted in the ring portion, the shapes of the energy contours alter to some extent [cf. Figures 2 and 5, and 4 and 7 (see supplementary material)]. A slight shift in positions of the energy minima is observed in the case of only norepinephrine and for low ϵ values, which might be the result of an interaction between the side chain and ring OH groups. The nonalteration in energy minima of dopamine and also of norepinephrine (only for high ϵ values) might be explained in terms of noninteraction between the side chain and ring OH groups. The effect of ring OH groups on $\langle\mu\rangle$, $\langle\gamma^2\rangle$, and $\langle\rho\rangle$ is of considerable interest. These properties are quite sensitive to the substitution. Not only that, they depend considerably on the orientation of OH groups with respect to one another and also with respect to the plane of the benzene ring. The behavior of $\langle\mu\rangle$

depends on the nature of the solvent medium. Dopamine and norepinephrine have higher $\langle\mu\rangle$ in the region of low ϵ and lower $\langle\mu\rangle$ in the region of high ϵ compared to phenylethylamine and β-phenylethanolamine, respectively. On the other hand, the substitution decreases the anisotropy tending toward a decrease in polarizability.

The influence of the OH group at the β position (C_7) can be evaluated by comparing dopamine and norepinephrine or phenylethylamine and β-phenylethanolamine. Since this group is closer to the ring portion, it not only alters the shapes of the contours but also shifts the positions of the energy minima. The presence of the OH group on C_7 increases the trans population (Table III, Figures 10 and 11), $\langle\mu\rangle$, and decreases the $\langle\gamma^2\rangle$. Thus the effect of this group is to increase the electrostatic nature and to decrease the polarizability.

The conformational behavior of these amines not only depends on the presence of the OH group at the C_7 atom but also on its orientation. For example, the contour diagrams in Figures 7 (A) and 8 (supplementary material) are obtained by fixing the OH group at 60, 180, and 300°, respectively. The percent trans population at these three positions are respectively 64, 18, and 53% for $\epsilon \geq 30.0$. Since the NMR study has indicated somewhat greater proportion for trans population, the calculations were carried out by fixing the OH group at 60°.

The influence of the methyl group (CH_3) at the C_α (C_8) position can be described by comparing the conformational behavior of phenylethylamine with that of amphetamine. Since the CH_3 group is symmetric, the ω_2 is fixed at 60°. The positions of the minima and contour shapes alter (Table I, cf. Figures 2 and 9, supplementary material). The trans population increases considerably (Table III). The $\langle\mu\rangle$ decreases and $\langle\gamma^2\rangle$ increases exhibiting a decrease in ionic character and increase in polarizability (Figures 14 and 15).

The effect of the *N*-methyl group is seen by comparing the dopamine and epinephrine. The conformational behavior also depends on the orientation of the CH_3 group, that is, the τ value (cf. Figures 5 and 6, supplementary material). Since $\tau = 180°$ produced a higher percent trans population, this value is used in the remaining computations. The effect of this substitution is to alter the positions of minima and contour shapes. The $\langle\mu\rangle$ and $\langle\gamma^2\rangle$ both increase indicating higher electrostatic and polarizable nature.

Thus from the above discussion and also from Figures 2–16, it is evident that the conformational behavior depends on (i) the nature of the solvent medium, (ii) various substitutions, and (iii) orientation of substitutions. Furthermore, a significant influence of the effective dielectric constant is observed only when the value of this constant is approximately less than about 30. Finally, one should note that like the electrostatic term, other energy terms given in eq 1, namely, nonbonding and hydrogen bonding potentials, will also depend on ϵ. Since their dependence on ϵ is likely to be of less significance for conformational analysis such as we see here, the solvent effect is accounted only through the electrostatic term. Therefore, the conclusions drawn in the present work should be used very cautiously due to the simplicity of the model. We are, in essence, minimizing solvent–solute interactions by scaling the strength of intramolecular interactions through the intramolecular electrostatic term. In addition to the above-mentioned deficiencies, the current model also neglects cavity effects, reaction field effects, and other pertinent macroscopic effects. Nevertheless, as mentioned in the introduction, it is intended to use the apparent dielectric constant as a variable rather than a constant. If the calculated properties are adjusted to the experimental properties using this variable then, most probably, the macroscopic effects might have already accounted.

Acknowledgment. I am greatly indebted to Dr. D. V. Siva Sankar for valuable discussion and to Dr. Gloria Faretra for her interest and support of this work.

Supplementary Material Available: Figures 2–9 which describe the energy maps as a function of dielectric constant (8 pages). Ordering information is given on any current masthead page.

References and Notes

(1) J. P. Green, C. L. Johnson, and S. Kang, *Annu. Rev. Pharmacol.*, 14, 319 (1974).
(2) A. Pullman and B. Pullman, *Q. Rev. Biophys.*, 7, 505 (1974).
(3) D. L. Beveridge, M. M. Kelly, and R. J. Radna, *J. Am. Chem. Soc.*, **96**, 3769 (1974).
(4) M. D. Newton, *J. Chem. Phys.*, **58**, 5833 (1973).
(5) G. Klopman, *Chem. Phys. Lett.*, 1, 200 (1967).
(6) J. Hylton, R. E. Christoffersen, and G. G. Hall, *Chem. Phys. Lett.*, **26**, 501 (1974).
(7) O. Tapia and O. Goscinski, *Mol. Phys.*, **29**, 1653 (1975).
(8) B. Linder, *Adv. Chem. Phys.*, **12**, 225 (1967).
(9) J. Jortner, *Mol. Phys.*, **5**, 527 (1962).
(10) M. Kumbar and D. V. Siva Sankar, *J. Am. Chem. Soc.*, **97**, 7411 (1975).
(11) M. Kumbar, *J. Theor. Biol.*, **53**, 333 (1975).
(12) P. J. Flory, "Statistical Mechanics of Chain Molecules", Interscience, New York, N.Y., 1969.
(13) A. M. Liquori, A. Damiani, and J. L. DeCoen, *J. Mol. Biol.*, **33**, 443 (1968).
(14) M. V. Volkenstein, "Configurational Statistics of Polymeric Chains", Interscience, New York, N.Y., 1963.
(15) B. Pullman and A. Pullman, "Quantum Biochemistry", Interscience, New York, N.Y., 1963.
(16) G. Del Re, *J. Chem. Soc.*, 4031 (1958).
(17) R. Bergin, Ph.D. Dissertation, Karolinska Institute, Stockholm, 1971.
(18) R. F. McGuire, F. A. Momany, and H. A. Scheraga, *J. Phys. Chem.*, **76**, 375 (1972).
(19) C. P. Smyth, "Dielectric Behavior and Structure", McGraw-Hill, New York, N.Y., 1955.
(20) R. P. Smith and E. M. Mortensen, *J. Chem. Phys.*, **32**, 502 (1960).
(21) H. A. Stuart, "Die Struktur des Frein Molekules", Springer-Verlag, Berlin-Gottingen-Heidelberg, 1952.
(22) Landolt-Börnstein, "Zahlenwarte und Function", Part 3, Springer-Verlag, Heidelberg and New York, 1952.
(23) R. R. Ison, P. Partington, and G. C. K. Roberts, *Mol. Pharmacol.*, **9**, 756 (1973).
(24) R. W. Baker, C. Chothia, P. Pauling, and H. P. Weber, *Mol. Pharmacol.*, **9**, 23 (1972).