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A Molecular Orbital Study of 2,4,5-Trihydroxyphenethylamine and Related Polyhydroxyphenethylamines

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SUMMARY

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Complete neglect of differential overlap (CNDO) calculations indicate that 6-hydroxydopamine (2,4,5-trihydroxyphenethylamine), 2,3,5-trihydroxyphenethylamine, and 2,3,4,5-tetrahydroxyphenethylamine have the same minimum energy conformations. 6-Hydroxydopamine is known to cause neurodegeneration; all three compounds have recently been shown to have long-term effects on the accumulation of [^{3}H]norepinephrine in mouse heart *in vivo*. The minimum energy conformations are *gauche* forms in which the proton on the nitrogen atom, at the end of the rotated side chain, and the 2-hydroxyl oxygen atom are 1.29 A apart, a likely intramolecular hydrogen bonding distance. All three of these compounds contain *para*-oriented hydroxyl groups. These 2,5-dihydroxy substituents display about the same interatomic distance as that between the oxygen atom in the 5-hydroxyl group and the nitrogen atom in the minimum energy conformers, and it is proposed that this distance might be important for interaction of these compounds with macromolecules. The criteria of a specific interatomic distance, combined with their ease of oxidation to 1,4-quinones via anion-radical mechanisms when a third hydroxyl group is present in the molecule, and adequate uptake at the active site are sufficient to define the biological activity of long-term reduction in the cardiac uptake of norepinephrine. The minimum energy conformations, interatomic distances, and net electronic charge distributions in isomeric 2,3,4-, 3,4,5-, 2,3,6-, and 2,4,6-trihydroxyphenethylamines and 2,5-dihydroxyphenethylamine have also been obtained. These compounds do not meet one or more of the listed criteria for inducing long-term reduction in cardiac uptake of [^{3}H]norepinephrine.

INTRODUCTION

2,4,5-Trihydroxyphenethylamine (6-hydroxydopamine) (I, Fig. 1) is known to be effective in releasing norepinephrine from cardiac storage sites (1). It causes long-term reduction of cardiac uptake of norepinephrine and selective destruction of the noradrenergic nerve terminals (1). Recent work on isomeric trihydroxyphenethylamines by Lundstrom, Ong, Daly, and Creveling[2] has shown that 2,3,5-trihydroxyphenethylamine (II) and 2,3,4,5-tetrahydroxyphenethylamine (III) also cause long-term reduction of cardiac uptake of norepinephrine. 2,5-Dihy-

[1] Visiting Fellow, 1971–1973.

[2] J. Lundstrom, H. Ong, J. Daly, and C. R. Creveling. personal communication.

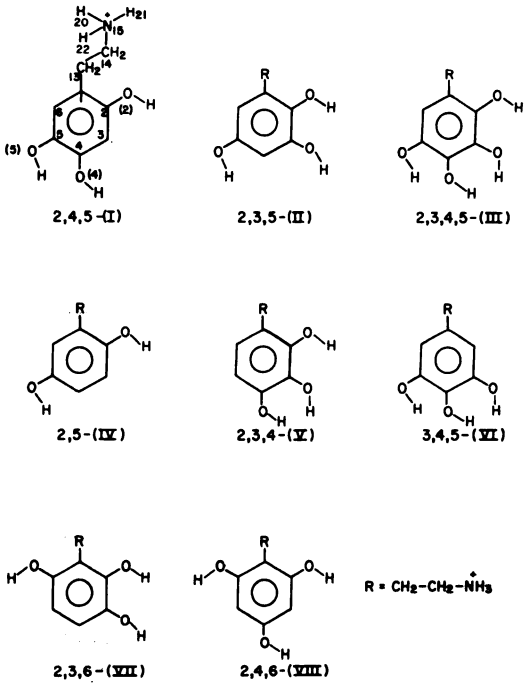


FIG. 1. *Structures and numbering system of polyhydroxyphenethylamines*

droxyphenethylamine (IV)[3] and two isomeric trihydroxyphenethylamines [the 2,3,4- (V) and the 3,4,5-substituted (VI) compounds] are potent in releasing [^{3}H]norepinephrine but do not cause long-term reduction of uptake. Lastly, 2,3,6- (VII) and 2,4,6-trihydroxyphenethylamine (VIII) were comparatively ineffective [^{3}H]norepinephrine-releasing agents, showing little inhibition of [^{3}H]norepinephrine uptake in the mouse heart.

We were intrigued by the differences in biological activity of 6-hydroxydopamine, dopamine, and norepinephrine, their fairly similar chemical structures notwithstanding. We have used CNDO[4] calculations in order to rationalize some of the differences in biological activity of the protonated polyhydroxyphenethylamines (I–VIII) and to see whether these compounds would have characteristics derived from molecular orbital theory similar to those which we found for dopamine and norepinephrine.[5]

METHODS

We used a compilation of computer programs[6] for our molecular orbital calculations. These programs include an *xyz* Cartesian coordinate generator (2) and a DCRT X-ray modeling system (3) leading to the CNDO/INDO calculations (4, 5) and to a subroutine for plotting, called PLUTO.[7] We used the parameterization of the original CNDO/INDO program (4, 5). Modification of the array variable pickup, conversion to single precision, modification of output of the program to list bond distances and net electronic charge distribution, and a more complete description of the computer system used are described elsewhere.[5]

X-ray diffraction data for catechol (6) were used as input to the *xyz* coordinate generator for the compounds shown in Fig. 1. The additional necessary atoms were added using standard bond angles and bond lengths, for similar reasons and in a manner consistent with those described by Katz, Heller, and Jacobson.[5] As a comparison, we used X-ray diffraction data for 6-hydroxydopamine HCl (7). There was little essential difference in the variation of relative energy vs. bond rotation, and in energy barriers, when these data were used as compared with our original data. 6-Hydroxydopamine, from the X-ray diffraction study, had considerably shorter N—H, O—H, and C—H bond distances than those we obtained from standard tables. It is well known that considerable uncertainty exists as to the exact positions of hydrogen atoms from X-ray diffraction data. The difference between the results of these two calculations (from X-ray vs. stan-

[3] J. Lundstrom, E. McNeal, and C. R. Creveling, personal communication.

[4] The abbreviations used are: CNDO and INDO, complete and intermediate neglect of differential overlap.

[5] R. Katz, S. R. Heller, and A. E. Jacobson, unpublished results.

[6] The computer programs were compiled and interwoven by Dr. S. R. Heller, Division of Computer Research and Technology (DCRT), National Institutes of Health.

[7] The PLUTO program was obtained from Dr. S. Motherwell, Chemistry Department, Cambridge University, and was adapted to the X-ray modeling system by R. J. Feldmann, Division of Computer Research and Technology, National Institutes of Health.

ard tables) was almost entirely in the calculated total energies. The total energy of the protonated 6-hydroxydopamine molecule from X-ray diffraction data was about 678 kcal higher (less stable) than the structure we used as input in this paper.

The conformation used as a starting point in all our calculations was the extended ethylamine side chain ("*trans*" or "anti" form), in which the benzene ring and side chain atoms 13, 14, 15, and 21 are planar (see I, Fig. 1, for numbering system). For simplification, the variation of the dihedral angle enclosed by atoms 6, 1, 13, and 14 will be referred to as the rotation angle around the 1,13 bond; the dihedral angle enclosed by atoms 1, 13, 14, and 15, as the rotation angle around the 13,14 bond; and the dihedral angle enclosed by atoms 13, 14, 15, and 21, as a rotation angle around the 14,15 bond. Final minimum energy conformations are designated by the magnitude of the rotation angle around the 13,14 bond. For example, the 120-degree minimum energy conformation of I·HCl refers to the final rotation of the 13,14 bond after rotation of the 1,13 and 14,15 bonds. Energy minimization was done for each bond rotation of the ethylamine side chain, usually starting with the 1—13 bond, followed by the 13—14, 14—15 bonds, etc., all counterclockwise. Usually diagrams such as Fig. 2 represent minimum energy conformations obtained by the aforementioned sequential rotation of bonds. However, we again minimized all the rotation angles after obtaining an initial minimum energy conformation for a molecule. Thus our bond angles (1,13 and 14,15) show greater variation than those commonly found in diagrams of relative energy vs. bond rotation, and may be closer to true minimum energy conformations than those usually obtained. Figure 1 depicts the calculated orientation of the phenolic protons in their minimum energy conformations. All these phenolic hydroxyl groups are in the plane of the benzene ring.

RESULTS

Minimum energy conformations. Molecular orbital calculations performed on protonated compounds I–VIII are exemplified here by a detailed analysis of 2,4,5-trihydroxyphenethylamine hydrochloride (protonated I) and its free base (IX).

The results of the CNDO calculations for protonated I are shown in Fig. 2. Zero relative energy, in Fig. 2, corresponds to a calculated total energy of −132.8140 a.u. The minimum energy conformations for this molecule are in a fairly wide well (90–150-degree rotation angle around the 13,14 bond). Because the (22)H atom[8] is oriented in a straight line between the (15)N and the (2)O atoms, in order to maintain the hydrogen bond, this (22)H atom describes an arc (in the deep well area) with a radius of approximately 1.29 A, centered at the (2)O atom. The retention of this distance as the 13,14 bond rotation angle varies necessitates modification of the 1,13 and 14,15 bond angles, in order to obtain the minimum energy conformations, as observed in Fig. 2. If the (22)H is brought closer than 1.29 A to the (2)O atom (N—O distance = 2.32 A) there is a rapid increase in the energy content of the molecule. Increasing distances between the (22)H and (2)O atoms bring about a slower increase in energy content. When the proton on the (2)O atom was used for hydrogen bonding to the (15)N atom, higher energy conformations resulted. The energy well around the 120-degree position is deep enough (compared with dopamine hydrochloride) to allow the presumption that most of the protonated I molecules will exist most of the time within its limits. The calculated 15-kcal/mole barrier to rotation away from these conformations probably precludes passage under normal circumstances. 6-Hydroxydopamine HCl was found, by X-ray crystallography, to exist in the *trans* form, with the 14,15 bond almost perpendicular to the plane of the benzene ring. No doubt this occurs because of the intermolecular hydrogen bonding observed in the crystal structure. The stability gained from this intermolecular hydrogen bonding would, of course, be lost in dilute solution (e.g., biological media). However, intermolecular

[8] The (22)H is the proton on nitrogen closest to either the (2)O or (6)O atom, when present, in the minimum energy conformations of compounds I–IX.

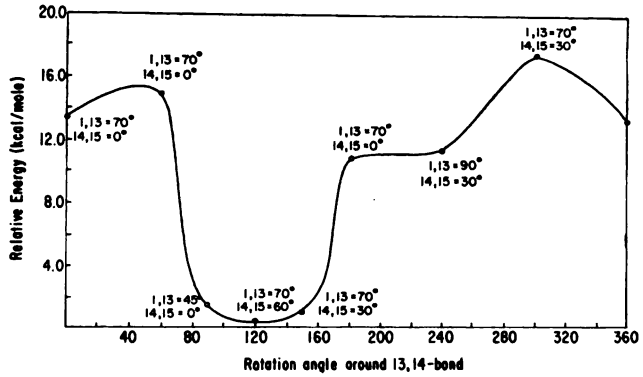


FIG. 2. *Calculated relative energies of protonated 6-hydroxydopamine (I.HCl) as a function of side chain rotation*

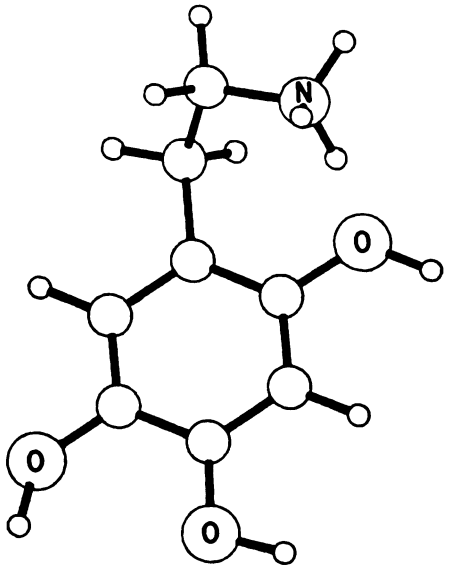


FIG. 3. *120-degree minimum energy conformation of protonated 6-hydroxydopamine (I.HCl)*

hydrogen bonding with water in dilute solution, *in vitro* or *in vivo*, may cause preferential stabilization of some of the molecular conformations. We are not able to calculate this stabilization by molecular orbital theory. It should be noted that CNDO may overestimate stabilization due to hydrogen bonding (8). Comparisons between our CNDO calculations on protonated dopamine[5] and protonated 6-hydroxydopamine show that this overestimation (if it occurs) is at most about 30%. Our calculated barrier of 15 kcal/mole between the *gauche* and the *trans* conformers in Fig. 2 thus may be closer to 10 kcal/mole in reality. This approximately 30% overestimation would not, however, effect our conclusions. The 120-degree minimum energy conformation is shown in the PLUTO diagram in Fig. 3.

In order to confirm the idea that the stabilization of the molecule is due to hydrogen bond formation between the (22)H on the (15)N atom and the (2)O atom, we calculated the minimum energy conformations of 6-hydroxydopamine free base (IX). CNDO calculations resulted in the fairly symmetrical curve shown in Fig. 4. Zero relative energy, in Fig. 4, corresponds to a calculated total energy of −132.2870 a.u. This figure, in contrast to Fig. 2, shows relatively small energy barriers to rotation, and is quite similar to the results of CNDO calculations on nonprotonated dopamine.[5] The location of one of the minimum energy conformations is still at a 13,14 bond angle rotation of 120 degrees, but there is no correlation between the minimum energy of the molecule and the (22)H—(2)O atom distance. That is, the presence of the (2)O atom does not appear to influence the minimum energy conformation of IX. The three calculated minimum energy conformations are the "*trans*" at 0 degrees and the 120- and 240-degree *gauche* conformations, all with about the same energy or stability. The PLUTO plot of the 120-degree conformation is shown in Fig. 5, as a comparison with Fig. 3.

The protonated compounds II, III, IV, and V (Fig. 1) gave calculated (CNDO) re-

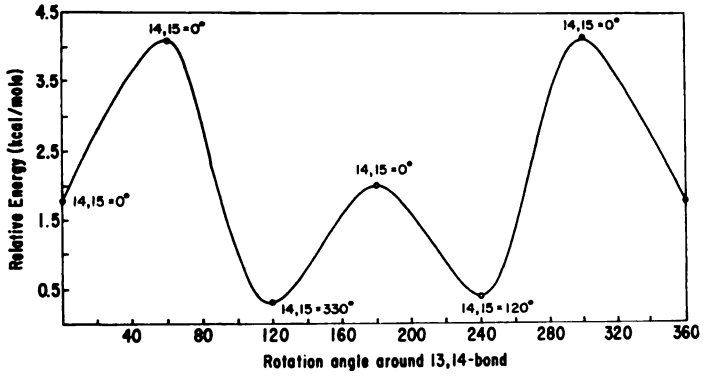


FIG. 4. *Calculated relative energies of 6-hydroxydopamine (base, IX) as a function of side chain rotation* Rotation around the 1,13 bond = 90 degrees.

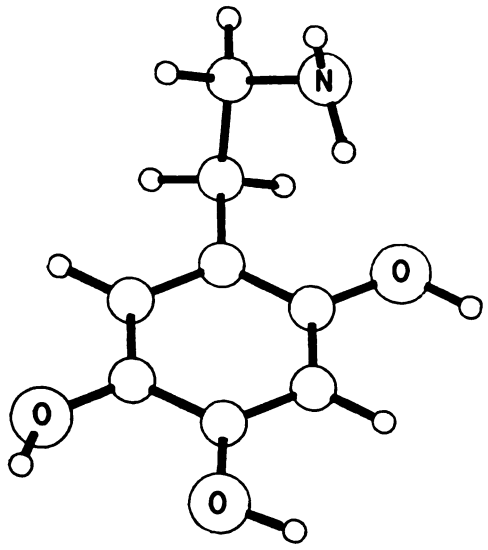


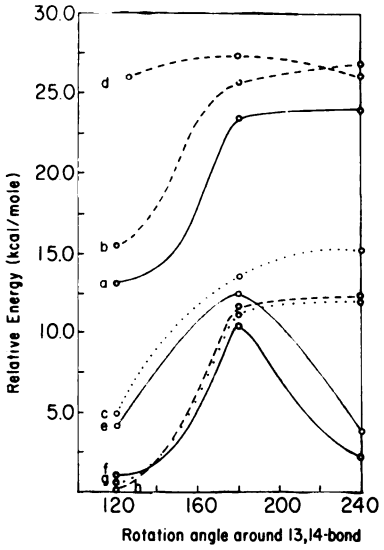
FIG. 5. *120-degree minimum energy conformation of 6-hydroxydopamine (base, IX)*

sults similar to those obtained with protonated I, and these are shown in Fig. 6. The minimum energy conformations of all these compounds exist at about the 120-degree position.

Compound VI, the 3,4,5-trihydroxy isomer, was calculated to give minimum energy conformations similar to those which we have shown for protonated dopamine,[5] at 0, 120, and 240 degrees. The 120- and 240-degree conformations are indicated on the graph in Fig. 6. Obviously passage between these positions is not precluded; there is not much of an energy barrier at 180 degrees (perhaps 2 kcal/mole).

Only compounds VII and VIII, the 2,3,6- and 2,4,6-trihydroxy isomers, exhibit two almost equally stable minimum energy conformations at 120 and 240 degrees. The energy barrier at the 180-degree position (about 10 kcal/mole) is high enough to preclude the possibility of easy interconversion by direct rotation. This barrier is displayed graphically in Fig. 6. For clarity, Fig. 6, unlike Fig. 2, does not show the calculated intermediate (150 degrees, etc.) rotations, and thus does not display the wide minimum energy well obtained for all these compounds except VI. The relative energies of compounds I–VIII are given in Fig. 6. Zero relative energy for Fig. 6, curves *a–f*, corresponds to a calculated total energy of −132.8350 a.u., to −151.2287 a.u. for the 120-degree conformation of III (Fig. 6, *g*), and to −114.3566 a.u. for the 120-degree conformation of IV (Fig. 6, *h*). We did not find impassable barriers to rotation from the presumed (*trans*) crystallographic structures into our CNDO calculated minimum energy *gauche* conformations even though, in certain cases, the passage between the two *gauche* conformations might be precluded (Fig. 6, *b* and *f*). A PLUTO plot of the 240-degree minimum energy conformation of compound VII is shown in Fig. 7; the 120-degree minimum energy conformation is shown in Fig. 8.

Electronic charge distribution. The net electronic charge distribution about the various atoms of compounds I–VIII, in their mini-



Compound \ Bond	Rotation angle 1,13	13,14	14,15
(I) 2,4,5-a	70	120	60
	70	180	0
	90	240	30
(II) 2,3,5-b	70	120	60
	70	180	0
	90	240	30
(V) 2,3,4-c	70	120	60
	70	180	0
	90	240	30
(VI) 3,4,5-d	90	120	90
	70	180	0
	90	240	30
(VII) 2,3,6-e	70	120	60
	70	180	0
	110	240	60
(VIII) 2,4,6-f	70	120	60
	70	180	0
	110	240	60
(III) 2,3,4,5-g	70	120	60
	70	180	0
	90	240	30
(IV) 2,5-h	70	120	60
	70	180	0
	90	240	30

FIG. 6. *Comparison of calculated relative energies of polyhydroxyphenethylamines as a function of side chain rotation*

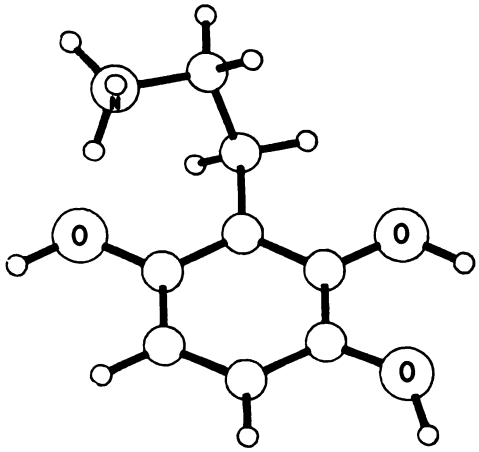


FIG. 7. *240-degree minimum energy conformation of protonated 2,3,6-trihydroxyphenethylamine (VII)*

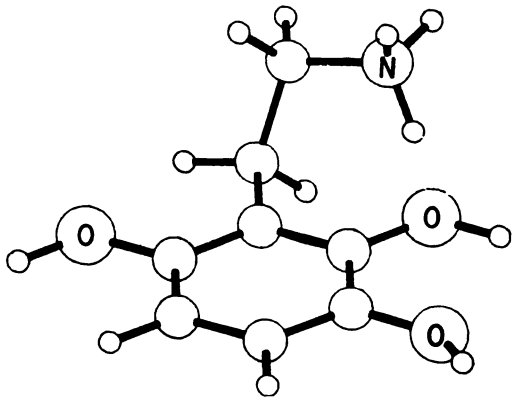


FIG. 8. *120-degree minimum energy conformation of protonated 2,3,6-trihydroxyphenethylamine (VII)*

mum energy conformations, is shown in Table 1. The side chain carbon atoms (13)C and (14)C have not been included in the table, since their electronic distributions were essentially constant in compounds I–VIII. The net charge distribution about the (13)C atom varied from 0 to −0.02, and the (14C) varied from 0.09 to 0.10. It can be noted that the net charge distribution about (1)C varies only slightly in most of these compounds. All the other carbon atoms vary significantly. The nonsubstituted aromatic carbon atoms are negatively charged in all these compounds except for the 2,3,4-trihydroxy isomer (V) and the (5)C atom of the 2,3,6-trihydroxy isomer (VII), which are positively charged, and the (3)C atom of IV, which has zero charge. As the protonated amino group approaches the (2)O or (6)O atom, the net negative charge on these oxygen atoms increases. This can be clearly seen in compounds VII and VIII in Table 1, in which the net charge distributions on the

TABLE 1

Net charge distribution in minimum energy conformation

Atom No.	I (120°)	II (120°)	III (120°)	IV (120°)	V (120°)	VI		VII		VIII		IX	
						120°	240°	120°	240°	120°	240°	120°	240°
(1)C	−0.01	0.03	0.01	0.01	−0.02	0.03	0.03	−0.05	−0.05	−0.10	−0.10	−0.01	0.00
(2)C	0.14	0.05	0.17	0.12	0.02	−0.10	−0.08	0.18	0.14	0.19	0.23	0.16	0.16
(3)C	−0.07	0.20	0.17	0.00	−0.04	0.18	0.18	−0.03	−0.04	−0.13	−0.12	−0.09	−0.08
(4)C	0.15	−0.10	0.08	−0.03	0.16	0.08	0.08	−0.01	−0.01	0.24	0.23	0.13	0.13
(5)C	0.17	0.24	0.19	0.21	0.12	0.19	0.19	0.14	0.14	−0.12	−0.12	0.14	0.14
(6)C	−0.03	−0.07	−0.05	−0.04	0.11	−0.07	−0.09	0.12	0.16	0.23	0.20	−0.03	−0.03
(2)O	−0.29	−0.28	−0.28	−0.28	−0.28			−0.27	−0.24	−0.28	−0.25	−0.25	−0.25
(3)O		−0.21	−0.32		−0.27	−0.22	−0.23	−0.28	−0.26				
(4)O	−0.22		−0.22		−0.22	−0.21	−0.21			−0.22	−0.22	−0.23	−0.23
(5)O	−0.26	−0.26	−0.26	−0.26		−0.25	−0.26					−0.27	−0.27
(6)O								−0.25	−0.29	−0.24	−0.28		
(15)N	−0.12	−0.12	−0.12	−0.12	−0.12	−0.03	−0.03	−0.11	−0.12	−0.12	−0.12	−0.21	−0.21
(22)H	0.31	0.31	0.31	0.31	0.31	0.23	0.23	0.31	0.31	0.31	0.31		

TABLE 2

Interatomic distances in minimum energy conformers

Atoms	I (120°)	II (120°)	III (120°)	IV (120°)	V (120°)	VI		VII		VIII	
						120°	240°	120°	240°	120°	240°
	A	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
(2)O—(15)N	2.30	2.30	2.30	2.30	2.30			2.30	4.80	2.30	4.81
(3)O—(15)N		4.62	4.64		4.63	5.00	6.02	4.63	6.27		
(4)O—(15)N	6.24		6.24		6.20	6.24	6.21			6.24	6.20
(5)O—(15)N	6.27	6.27	6.27	6.27		6.02	4.97				
(6)O—(15)N								4.81	2.30	4.80	2.30
(2)O—(3)O		2.75	2.77		2.72			2.70	2.70		
(2)O—(4)O	4.81		4.81		4.75					4.81	4.81
(2)O—(5)O	5.50	5.50	5.50	5.50				5.50	5.50		
(2)O—(6)O								4.78	4.78	4.76	4.76
(2)O—(22)H	1.29	1.29	1.29	1.29	1.28			1.29		1.29	
(6)O—(22)H									1.29		1.29

(2)O and (6)O atoms vary according to the angular position of the protonated amino group. The highest net negative charge is observed on the (3)O atom of compound III. In every case the (15)N atom of the protonated amino group is negatively charged. The net charge distribution on the (15)N atom increased in minimum energy conformations when the (15)N atom was close to the (2)O or (6)O atom, as compared with the net charge on (15)N observed in VI, the 3,4,5- trihydroxy isomer. Although no variation in net electronic charge was observed on the (15)N atom in the various minimum energy conformations of IX, the net excess electronic charge on this atom was, of course, greater than in the protonated amines I–VIII. In fact, it was comparable to the net excess electronic charge on the phenolic oxygen atoms. The net positive charge on the (22)H atom increased from 0.23 to 0.31 in those minimum energy conformers, in which it could participate in hydrogen bonding to the (2)O or (6)O atom.

Interatomic distances. In the minimum energy conformations of compounds I–IV (Table 2) there are identical interatomic distances between atoms (2)O and (15)N (2.3 A), (5)O and (15)N (6.27 A), and (2)O and (22)H (1.29 A) because of hydrogen bond formation between the hydrogen of the protonated amine and the (2)O atom. The (2)O—(5)O interatomic distance of 5.5 A is obviously the same in compounds I–IV, for structural reasons. When compounds I–IV are in their 120-degree minimum energy conformations, the differences in interatomic distance between the (2)O and (5)O atoms and the (5)O and (15)N atoms [and the (2)O and (15)N atoms in V and VI] are no greater than 0.8 A. The (5)O—(15)N distance can vary, depending on the 13,14 bond rotation angle. The variation from 90 to 150 degrees for this angle might result in less difference between these interconnecting atoms than that noted above. That is, in the 90-degree conformation (see Fig. 2) the (5)O—(15)N interatomic distance is 6.86 A, and in the 150-degree conformation the distance is 5.77 A. The identical distances pertain, of course, to the symmetrical (by 180 degrees) positions on the reverse side of the plane determined by the benzene ring.

It is of interest that dopamine hydrochloride, in its 120-degree energy conformation, also displays a similar (approximately 6 A) distance between the (5)O and (15)N atoms, as does norepinephrine hydrochloride.[5]

DISCUSSION

Polyhydroxyphenethylamines I–VI (Fig. 1) have been found to be taken up and to cause the release *in vivo* of [^{3}H]norepinephrine from cardiac storage sites. Our molecular orbital calculations show that they all have the same minimum energy conformation at 120 degrees. It is suggested that these conformers are responsible for the uptake of

the polyhydroxyphenethylamines I–VI and the release of norepinephrine. Compounds VII and VIII are poor releasing agents of [^{3}H]norepinephrine and are rather ineffective at inhibiting its uptake. They both possess two definite minimum energy conformations (at 120 and 240 degrees) and display a high energy barrier between them. It seems that if both the 120 and 240-degree conformations exist with a high energy barrier between them, little norepinephrine release is elicited.

We have also noted a striking similarity in interatomic distance between three pairs of atoms, the (2)O—(5)O, (5)O—(15)N, and (2)O—(15)N atoms, and the very similar charge densities around the (2)O and (15)N atoms, in minimum energy conformations. Compounds I, II, and III cause long-term reduction in the cardiac uptake of norepinephrine.[2] Saner and Thoenen (9) have postulated that the oxidative products from I can interact nonspecifically with macromolecules to give covalently bound or cross-linked products. However, it is also possible that these polyhydroxyphenethylamines can specifically interact with essential proteins within the vesicle or cytoplasm or at uptake sites in the plasma membrane or vesicular membrane. The approximately 6A-separated O—N or O—O atoms, in the minimum energy conformations of compounds I–III, might be responsible for attachment of these compounds by hydrogen bonds to macromolecules.

Heikkila and Cohen (10, 11) postulated that the toxicity of I could be due either to the quinone or to hydrogen peroxide, which was found to be formed in experiments *in vitro*. These authors preferred the latter as the toxic agent. Studies by Lundstrom *et al.*[2] indicate that the long-term inhibition of norepinephrine uptake displayed by compounds I–III appears to be correlative with their ease of oxidation *in vitro* and that the oxidation of these polyhydroxy compounds is concentration-dependent. The oxidation of I to a quinone has been observed *in vitro* (12). The two hydroxyl groups of compounds I–III, namely, the *para*-oriented ones [(2)O—(5)O], which may be hydrogen-bonded to essential proteins, would be in excellent position to cause maximal destruction on oxidation to the intermediate semiquinone or the final quinone compound, or on the formation of some by-product like hydrogen peroxide.

A theory for *p*-quinone formation, invoking initiation by a third hydroxyl group, has been offered by Stone and Waters (13) from their work on chemical oxidation of catechol derivatives using electron spin resonance spectroscopy. A possible catalytic effect of the third hydroxyl group can be observed by comparison with 2,5-dihydroxyphenethylamine (IV), which displays the conformational requirements for long-term reduction of norepinephrine uptake found for compounds I–III in our calculations. However, because it oxidizes at a very slow rate,[2] the radical-anion reaction *in situ* either cannot be initiated or cannot be propagated with the concentration of this compound found at the active site, and thus it does not cause long-term reduction of norepinephrine uptake. The tetrahydroxy compound III should be, and is,[2] the most easily oxidized of the polyhydroxy compounds. The lesser effect of this tetrahydroxy compound on long-term reduction of norepinephrine uptake, as compared with the two trihydroxy compounds I and II,[2] may be due to partial oxidation before uptake. The resultant oxidation product could have different uptake properties.

We are presently engaged in examining the electron paramagnetic resonance spectra of some of these compounds under conditions *in vitro*, with the hope of detecting intermediate radical species.

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