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Conformationally restricted dopamine congeners—a molecular mechanics-based study

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Potential energies of several systems containing the phenylethylamine fragment were computed by the QCFF/PI method and some of them also by the PCILO method. The systems considered are: octahydrobenzo [f]- and [g]-quinolines, aporphine, 1-phenylbenzazepine, 4-phenyltetrahydroisoquinoline, 3-phenylpiperidine and 9-aminodihydrophenanthrene. No common set of torsion angles defining the stereostructure around the amine head is apparent if only the lowest energy conformations are considered. Leaving out the orientation of the N-CH_3 group, and considering also some higher energy conformations, two groups of systems may be formed, A and B, the members of which are congruent amongst themselves in parameters defining the spatial relations of the amine site and the catechol ring, and in the orientation of the N^+-H bond. The stereostructure of the rigid representatives of group A is postulated to be the one required by the brain and cardioaccelerator nerve receptor. A corresponding postulate for the vascular bed DA receptors cannot be made since systems forming group B, the derivatives of which are active both on brain and vascular bed receptors, have more conformation space and, moreover, they carry additional potential anchoring groups.

Molecules in which the dopamine (DA) moiety is spanned in a more or less rigid molecular framework are important tools for the definition of stereostructural requirements of the DA receptor. The acceptable spatial relations between the key functional groups, i.e. the nitrogen atom and the phenolic oxygens have been recently summarized (Seeman 1980). The negative role of obstructing parts of molecules was also noted (Seeman 1980; Erhardt 1980). Besides the spatial relations of the key groups, the *N*-alkyl substituents are highly important for activity on DA receptor subtypes as shown particularly in the series of dihydroxy-2-amino tetrahydronaphthilenes (tetralins) (Cannon et al 1978; Goldberg et al 1981). The current stereostructural considerations are based mainly on a molecular model derived minimal energy conformations of the DA agonists and corroborated by available crystal structure data (Giesecke 1973, 1980; Horn & Rodgers 1980). For more detailed correlations of the stereostructure with pharmacological properties it is necessary to have consistent sets of data which should include not only the key distances in the minimal energy conformation, but also in other conformations which are energetically not too high above the lowest one. A possibly precise definition of the torsional angles τ_1; τ_2; τ_3 and $\tau_{3'}$ (see Fig. 1) which determine the position of the nitrogen substituents (N^+-H and N-alkyl) is desirable particularly in view of the possible role of these parameters in determining the potency on the DA receptor subtypes. The only practicable approaches are molecular mechanics methods of which the QCFF/PI scheme is particularly suited for the type of molecules considered (Marsh et al 1980; Warshel & Lappicirella 1981). We have previously used both this and the semi-empirical PCILO method on 2-aminotetralin (I), the basic system for the most explored semi-rigid DA analogues, and found QCFF/PI to be satisfactory (Kocjan et al 1983).

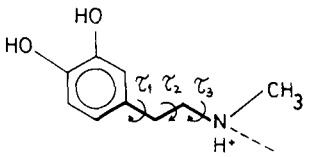

FIG. 1. Definition of the torsion angles for dopamine $\tau_1(C_6C_1C_\beta C_\alpha)$, $\tau_2(C_1C_\beta C_\alpha N)$, $\tau_3(C_\beta C_\alpha NH)$, $\tau_{3'}(C_\beta C_\alpha NC)$. The torsion angle τ(A-B-C-D) is positive for clockwise rotation of C-D when looking from B to C ($\tau = 0$ for the *cis*-planar arrangement of A-B and C-D).

In this paper we have applied the QCFF/PI method throughout for calculating the relative potential energies of some conformations of aporphine (II), *trans*- and *cis*-octahydrobenzo[f]-quinolines (III), *trans*-octahydrobenzo[g] quinoline (IV), 9-aminodihydrophenathrene (V), 4-phenyltet-

* Correspondence.

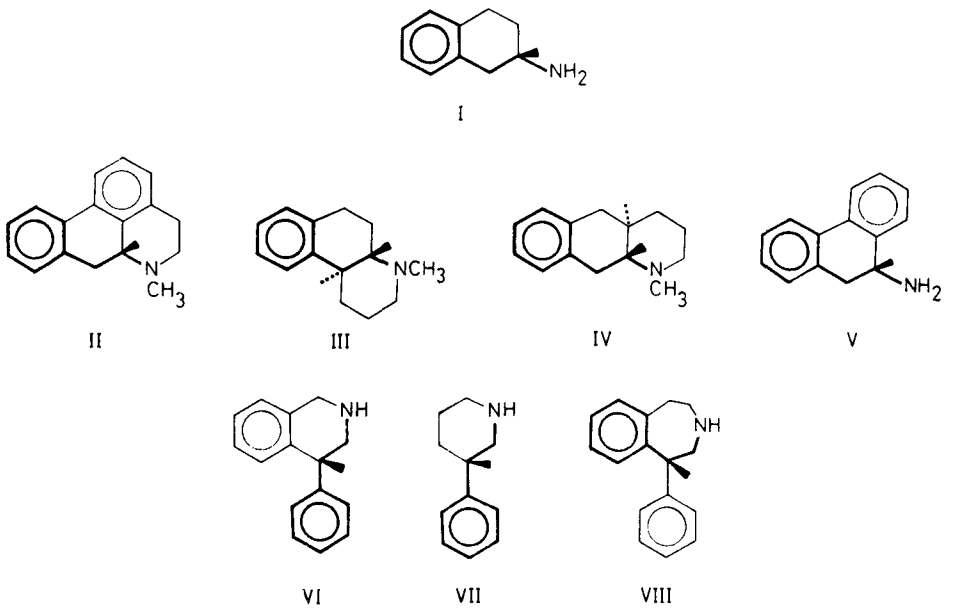

FIG. 2. Structural formulae of some dehydroxy (semi) rigid dopamine congeners: I 2-amino-tetralin, II aporphine, III *trans*-octahydrobenzo[f]quinoline, IV octahydrobenzo[g]quinoline, V 9-amino-dihydrophenanthrene, VI 4-phenyl-tetrahydroisoquinoline, VII 3-phenyl-piperidine, and VIII 1-phenyl-1H-tetrahydro-3-benzazepine.

rahydroisoquinoline (VI), 3-phenylpiperidine (VII) and 1-phenyl-1H-tetrahydro-3-benzazepine (VIII) (Fig 2). Some conformations were also calculated by the PCILO method for comparison. We have considered the systems without hydroxyl groups since these do not influence the conformational energies concerning the vicinity of the nitrogen (Pullman et al 1972). There is only one pair of structures that conforms in all torsion angles: II and IV. II and *trans*-III agree fairly in all, but in $\tau_{3'}$, i.e. they differ in the orientation of the N-CH_3 bond. Considering the higher energy conformations, a reasonable agreement in the angles τ_1; τ_2; and τ_3 is found with II, VI and VII. Possible inferences of these results supplemented by the previously obtained ones on I, to the potency of their hydroxylic derivatives on DA receptor subtypes will be briefly discussed. Some preliminary results have been communicated (Kocjan et al 1981).

METHODS

In the QCFF/PI method the intramolecular potential energy is expressed in terms of empirical functions (bond length and angle distortions, torsional and non-bond contributions) and of π SCF MO energy within the PPP scheme (Warshel & Karplus 1972; Warshel & Lappicirella 1981). The search for stationary points of the resulting potential function was performed by the combination of the steepest descent and the Newton-Raphson iterations. The calculated Cartesian coordinates were used as input for the PCILO computations (Diner et al 1969). Lacking the activity data on resolved enantiomers of III, IV and V derivatives, McDermed's hypothesis (McDermed et al 1979) on the relation of the rotameric form of the catechol ring to the configuration of the asymmetric centers of the more potent enantiomer was used to model the configurations of these structures (Fig. 3). Their configurations as drawn in Fig. 2 should correspond to the α-rotameric form of the catechol ring.

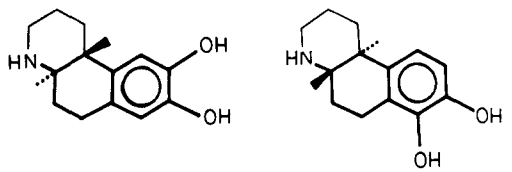

FIG. 3. Relation between the rotameric form of the catechol ring and the configuration of the asymmetric centre of the aminotetralin fragment in the benzo[f]quinoline system.

RESULTS AND DISCUSSION

In Table 1 are collected the relative energies of the important stationary points in the QCFF/PI potential surfaces characterized by the torsional angles τ_1–τ_3'. The corresponding data (Kocjan et al) for AT are included for comparison. The τ_3 and τ_3' values of I

Table 1. Torsion angles[a] τ_1, τ_2, τ_3 and $\tau_{3'}$ of the dopaminic fragment in systems I–VIII with the corresponding relative potential energies E_p[b] and the height h_N of the *N*-atom relative to the aromatic plane.

		System conformation	τ_1	τ_2	τ_3	$\tau_{3'}$	h_N (Å)	E_p (kJ mol^{-1}) QCFF/PI	PCILO
I	1	halfchair-eq	195°	189°			0·23	0·0	0·0
	2	halfchair-ax	162	281			−1·91	4·2	2·6
	3	halfboat-eq	222	181			1·14	12·7	14·4
	4	halfboat-ax	138	275			−2·40	16·4	21·7
II	5	N-Me_{eq}	216	179	54	295	0·88	0·0	
	6	N-Me_{eq}	212	184	262	17	0·51	41·0	
III	7	*trans*-halfchair/chair	195	184	62	181	0·73	7·4	10·3
	8	-halfchair/chair	226	184	64	182	0·87	20·7	21·6
	9	-halfchair/chair A	193	187	67	184		41·6	16·3
	10	-halfchair/chair B	197	183	109	226		40·2	14·5
	11	*cis*-halfchair/chair A	198	186	176	293	0·29	0·0	0·0
	12	-halfchair/chair B	164	286	66	184	−1·99	11·2	13·7
IV	13	*trans*-halfchair/chair	198	186	58	300			
V	14	eq	216	179			11·7		
	15	ax	146	286			0·0		
VI[c]	16	min[d]	103	170	60	178	−1·52	0·0	0·0
	17	max	191	160	60	179	0·83	45·3	32·5
VII[c]	18	min[d]	117	178	66	184	−1·30	0·0	0·0
	19	max	207	178	66	184	0·72	18·1	2·9
VIII[c]	20	chair	115	81	173	57	−1·40	0·0	
	21	twist-boat	149	83	194	77	0·0	20·9	

[a] Torsion angles refer to the configurations of the asymmetric centres as drawn in Fig. 2.
[b] Calculations refer to protonated molecules.
[c] Only the equatorial position of the phenyl ring was considered with the halfchair and chair conformations of the piperidine ring.
[d] Conformations corresponding to the minimum (maximum) of the potential energy curve for τ_1 torsion.

and V are not given because of their small influence on the potential energy. The conformations 7, 8, 9 (Table 1) of *trans*-III contain the phenylethylamine fragment in nearly identical forms. For the two lower energy conformations the QCFF/PI and PCILO energies are in good agreement whereas the PCILO energies for the other two are considerably lower than the QCFF/PI energies. This reflects the well known property of the semi-empirical zero-differential overlap methods to favour the closed structures over the open ones (Zerner 1981). The QCFF/PI energies are thus more realistic and the two boat conformations 9, 10 have too high an energy to be involved in binding. The same applies for the halfchair-boat conformations of cis-III which we did not consider in detail. The energy of II with the inverted piperidine ring is also substantially higher than the one found in crystals of apomorphine HCl (Giesecke 1973). The calculated energy of V with the amino group axial is lower than equatorial which is in agreement with the interpretation of the n.m.r. spectra of related structures (Nichols 1978). The chair conformation of VIII has the lower energy and this conformation corresponds to that found in the crystals of VIII HCl (Kaiser et al 1982). The recent finding that 2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1H-3-benzazepine methiodide assumes the twist-boat form (Kaiser et al 1982) may be explained by the effect of the quaternary *NN*-dimethyl group which causes crowding in the chair conformation and/or by crystal packing effects. In order to clarify this point we have also calculated the relative potential energy of *NN*-di-Me-PBA and found that the *NN*-di-Me substitution diminished the potential energy difference between the chair and the twist-boat conformation for 6 KJ mol^{-1}. The main steric problem with VII is the restricted rotation around the phenyl-tetrahydroisoquinoline bond, described by the angle τ_1. The energy as a function of this angle is shown in Fig. 4. In the pertinent calculation we have locally minimized all other degrees of freedom. Such relaxation increases the distance between the hindering protons from 108 pm to 185 pm. The rigid rotor approximation yields an unrealistically high barrier. With VII the hindrance to rotation is about halved (relaxed systems).

Looking for congruence of the torsional angles in the equilibrium conformation we note that the values of τ_1; τ_2; and τ_3 in I, II, *trans*-III and IV (conforma-

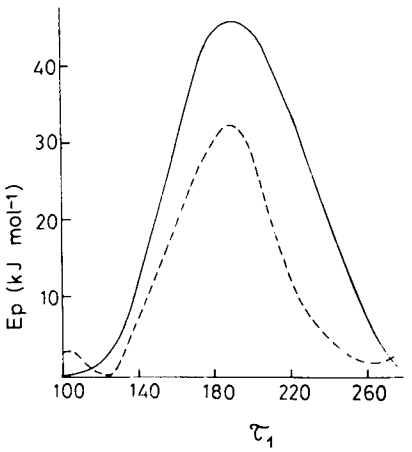

FIG. 4. QCFF/PI (——) and PCILO (– – – –) relative potential energy of 4-phenyl-isoquinoline versus τ_1 torsion angle.

tions 1, 5, 7, 13 in Table 1) do cluster around 200°, 180° and 60°, respectively. Neither of the *cis*-III low energy conformations fits into this series nor do so VI, VII and VIII. For convenience we shall designate the first group A and the second B (16–21 in Table 1) leaving out of further consideration *cis*-III and V the hydroxylic derivatives of which are reported to be inactive in DA activity models (Nichols et al 1978; Cannon et al 1975, 1978, 1979, 1980). This seems understandable in view of the fact that the conformation around the nitrogen radically departs from that of the active compounds. However, even series A is not homogenous: *trans*-III differs from II and IV in the orientation of the N-CH_3 bond. Whether this parameter is important for biological activity or not is difficult to say since both apomorphine and the dihydroxyderivatives of III are potent DA agonists in the brain and on the cardioaccelerator-nerve (Cannon et al 1980).

However, a different influence of *N*-alkyl substituents in the inhibition of binding of [^{3}H]apomorphine might be significant in this respect. Whereas the potency of 7,8-dihydroxy-*trans*-III in the striatum is 5 times that of the *N*-alkyl analogues (there is practically no difference between methyl, ethyl and propyl), norapomorphine has about the same potency as apomorphine, *N*-propylnorapomorphine being 2·5 times weaker (Seeman 1980; Neumeyer et al 1981). Lacking affinity data on various *N*-alkyl derivatives of other DA agonists in this series we must refrain from further conjecture. On the whole, it seems that congruence in all torsion angles is not critical and we shall continue the discussion with somewhat less restrictive parameters in order to remove the constraint of that topological fit of the atoms of the dopamine fragment. These are: the distance r between the centre of the aromatic ring and the projection of the nitrogen atom onto the ring plane, the vertical distance h of this atom from the plane, and the angles θ and ζ defining the orientation of the N^+-H bond (Fig. 5). In Table 2 only the values of representative systems are shown. Groups A and B are not congruent in the low energy conformations. Note that in group B are systems which retain some flexibility and that a certain level of congruence appears between its members if conformations are considered that are of reasonably higher energy with respect to the ligand receptor interaction energies. Considering the possible piperidine *N*-atom inversion, II may be classified also under group B, and clearly so, I.

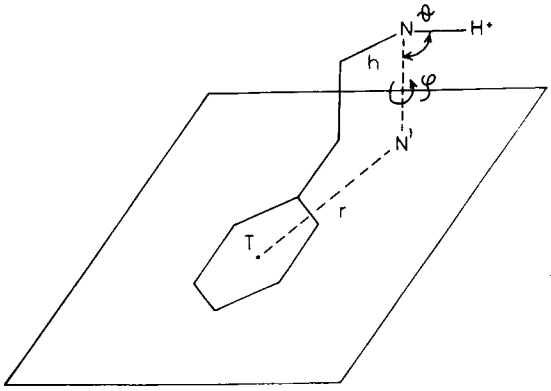

FIG. 5. Definition of the geometrical parameters for the position of the amine head relative to the benzene ring (see text).

Seeking a correlation of the stereostructure with activity on various types of DA receptor it would in principle be necessary to include the substitution pattern of the catecholic hydroxyl groups, i.e. consider the analogues of the α- and β-rotameric forms of DA. However, in order to consistently carry out the comparisons with the stereoselectivity of the DA receptors as revealed by the finding that opposite enantiomers of 5,6- and 6,7-dihydroxy-I have higher activity (McDermed et al 1979) biological data on configurationally defined congeners would be needed. Lacking such data, we must limit the discussion to the possible role of the conformation around the nitrogen assuming that the configuration-activity relation found with the enantiomer pair of I (McDermed et al 1979) may be

Table 2. Geometrical parameters, defined in Fig. 5 of some representative (semi)rigid dopamine congeners.

			r	h	θ	ζ
	Benzo[f]quinoline (III)	$N\text{-}Me_{eq}$	5·2 Å	0·3 Å	17°	131°
A	Aporphine (II)	$N\text{-}Me_{eq}$	5·0	0·9	21	154
	Aporphine (II)	$N\text{-}Me_{ax}$	5·0	0·9	122	103
	4-Phenyl-isoquinoline[a,b] (VI)	N-H′	5·1	0·7	101	−104
B		N-H″	5·1	0·7	131	131
	1-Phenyl-benzazepine[c] (VIII)	N-H′	4·5	0·0	130	139
		N-H″	4·5	0·0	51	219

[a] Geometrical parameters of VI correspond to the conformation with $\tau_1 = 138°$.
[b] Both enantiomers of VI have compatible geometrical parameters with those of II. The isoquinoline rings have different stereopositions (N-alkyl inversion is necessary for N-alkyl derivatives).
[c] The active enantiomer of VIII (1 *R* configuration Kaiser et al 1982) has a better fit of the directionality of the N–H bond than its antipode.

extended to other DA congeners. This approach is supported by the fact that the systems III and IV are not active on the vascular DA receptors which, taken together with the high potency of III and II derivatives, suggests that the conformation of group A is the one required by the brain DA receptors. The dichotomy concerning the brain and cardioaccelerator receptors as introduced by the variation in the hydroxyl substitution pattern (8,9-dihydroxyoctahydrobenz[f]quinoline is active only on the cardioaccelerator nerve) may be considered as a more subtle differentiation (Cannon et al 1980). Group B derivatives except for 3-(3-hydroxyphenyl)-*N*-n-propylpiperidine (3-PPP) are active both on the brain and the vascular receptors (Woodruff et al 1979; Jacob et al 1981; Hacksell et al 1981; Kaiser et al 1982). It is not possible at this stage to define the optimal conformation for the vascular DA receptors, because the members of this group in the low energy conformation are not congruent amongst themselves, but may attain other parameters after some energy expenditure. It seems, however, that the conformational requirements of the vascular receptors are different from those of the brain receptors. The question may immediately be raised as to how is it that DA congeners, for instance VIII, that are neither congruent with group A nor have the optimal conformation for the vascular bed receptor, are nevertheless active on both?

An explanation to this may be sought in additional anchoring of the ligands, which would compensate for the potential energy used for adjusting to the proper conformation. In the case of VIII the 1-phenyl ring appears to be such an anchoring group (Kaiser et al 1982) its active role in the interactions with the receptor being shown by the difference in activity of the enantiomers. A corresponding role may be played by the quinolinic benzene ring of VII. Additional bonding groups are assumed to be important for potency also with DA antagonists in which the congruence of parameters concerning the stereostructure of the amine site is not very strict (Olson et al 1981). To the best of our knowledge, there are no published data on vascular DA activity of derivatives of VII, but only on their pre- and postsynaptic brain DA activity (Hacksell et al 1981). If our hypothesis was correct, then an analogue of VII with the proper hydroxy and *N*-substituents should have at least some activity on the vascular bed DA receptors since this system is more flexible than VI and hence there is less need for additional anchoring. For further evolution of such hypotheses more experimental data are needed, particularly from binding assays using configurational defined ligands.

CONCLUSIONS

The computed torsion angles which determine the stereostructure of the amine site of several more or less rigid dopamine analogues show a rather poor overall congruence if all parameters and only the lowest energy conformations are considered. When the orientation of the $N\text{-}CH_3$ groups was left out of consideration, but higher energy conformations were included, a clustering into two groups, A and B, became apparent which differ mainly in the orientation of the $N^+\text{-}H$ bond. Representative of group A is octahydrobenzo[f]quinoline the phenylethylamine fragment of which can assume virtually one conformation only. The congeners of DA based on this system may attain high dopaminergic potency in the brain and on the cardioaccelerator nerve, but not in the vascular bed. Thus its conformation may be the one preferred by the former type of DA receptor and unsuitable to the latter. Such unique steric preference of the vascular bed DA receptors cannot be

defined on hand of parameters of group B which is formed by less rigid systems containing groups capable of additional bonding. The latter may compensate for the expenditure of energy needed for adjustment of the conformation both to the brain and vascular bed DA receptors.

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