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Conformational analysis of dopamine by the INDO molecular orbital method

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The results of INDO calculations on dopamine are reported. A conformational energy map and an isodistance map for the key distances N–OH_1, N–OH_2 in dopamine as functions of the two main torsion angles τ_1 and τ_2 were constructed. In addition to the three known minima of dopamine corresponding to the *trans* and *gauche* forms, two new minima were found. The key distances of the rigid analogues of dopamine, apomorphine, isoapomorphine, 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene and isoquinoline were plotted on the isodistance map of dopamine. By taking the corresponding τ values as coordinates on the energy map, conformations of dopamine, resembling the rigid analogues, could be found. When a conformation is close to a local minimum it is assumed that this conformation is energetically favourable. The possible relation between the energy minima and the biological action of dopamine is discussed. An explanation is suggested for the lack of dopaminergic activity of isoapomorphine.

It is well established that dopamine (I) acts as a neurotransmitter in the central nervous system. Much emphasis has been placed upon its conformation (Carlström, Bergin & Falkenberg, 1973; Horn, Post & Kennard, 1975), which is undoubtly an important parameter besides its electrochemical properties. Previous molecular orbital (MO) calculations indicated that it was energetically possible for dopamine to assume conformations other than that found by X-ray analysis (Bergin & Carlström, 1968). These calculations used the EHT (Kier, 1973), PCILO (Pullman, Berthod & Courriere, 1974) and CNDO (Katz, Hellen & Jacobsen, 1973) methods. Energy minima were found for the two *gauche* and the *trans* forms of the side chain, with the phenyl ring perpendicular to the plane through this side chain (Fig. 1).

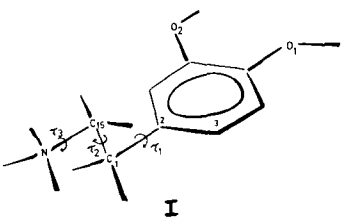

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Fig. 1. The three torsion angles are τ_1 (C_{15}–C_1–C_2–C_3), τ_2 (N–C_{15}–C_1–C_2) and τ_3 (H–N–C_{15}–C_1). The NH^+_3 group is considered to be in a staggered conformation with $\tau_3 = 180°$. The torsion angle (A–B–C–D) between the atoms A–B–C–D represents the angle between the planes ABC and BCD viewed from the direction of A, ABC rotating clockwise.

* Correspondence.

Because the barriers between the different conformations were small all conformers can probably exist in solution and consequently the distances N–OH_1 and N–OH_2, probably important for the interaction with the receptor, can take a variety of values. We have examined the relation between these key distances and the energies as a function of the conformations of dopamine. The key distances were calculated for the various values of τ_1 and τ_2 and an isodistance map was constructed for the N–OH_1 and the N–OH_2 distance (Fig. 2).

As well as the distances the total energy of dopamine was calculated by the semi-empirical LCAO–MO–SCF method at the INDO level of approximation at various angles of τ_1 and τ_2 and a conformational energy map was constructed. The energy map shows 10 minima, corresponding with 5 conformations and their mirror images, which had the same key distances (Fig. 3).

Our finding of two energy minima for dopamine with $\tau_1 = 40°$, $\tau_2 = 30°$ and $\tau_1 = 140°$, $\tau_2 = 330°$ in addition to the two *gauche* and *trans* forms shows that by constructing energy maps with movements of 30° in the torsion angles an energy minimum may be overlooked as we also found these new minima, when calculations were performed with the CNDO/2 method, already previously used.

As the minima of dopamine do not show any exceptional energy barrier between them it is difficult to point out a certain minimum which might be the conformation in which dopamine is biologically active. The calculations do not allow

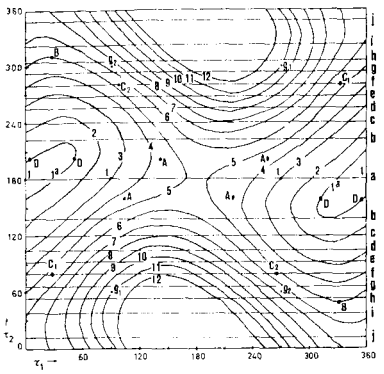

Fig. 2. Isodistances map for dopamine where each line gives a fixed value for the N–OH_1 distance (a-j) or the N–OH_2 distance (1–12) in dopamine. The N–OH_1 distances are 0·25 Å beyond the maximal distance of 7·85 Å (a) and the N–OH_2 distances are 0·25 Å beyond the maximal distance of 7·35 Å (1–12) with 1^a being 7·25 Å. A,B,C,D indicate the conformations of dopamine in which the key distances N–OH_1 and N–OH_2 are the same as the comparable distances in resp. apomorphine, isoquinoline III, ADTN with the NH_2 group axial and ADTN with the NH_2 group equatorial.

for the effects of water, however, but although it is theoretically possible to take these into consideration by the method of Pullmann & Pullman (1975) it is difficult to know what parameters are correct for dopamine. Another approach in which theoretical calculations might be valuable constitutes the comparison of the dopamine conformations with the structure of conformationally rigid analogues. Rigid analogues which have the same biological effects as dopamine probably will interact with a dopaminergic receptor and it is possible that the conformation in which dopamine acts at this receptor will resemble the conformation of the rigid analogue. By plotting the calculated or measured key distances of the rigid analogues on the isodistance map the conformation of dopamine with the same key distances can easily be found. The τ_1 and τ_2 values so obtained can indicate on the energy map whether this conformation of dopamine will be energetically favourable. This will be the case when it approximately coincides with a local minimum of dopamine. Apomorphine, II, an example of a rigid analogue, mimicks the effect of dopamine on the central nervous system, probably by a direct effect on the dopaminergic receptor (Ernst, 1969). Calculations based upon published X-ray data for apomorphine (Giesecke, 1973) give interatomic distances between the two catechol oxygens (OH_1 and OH_2) and the nitrogen atom of 7·78 and 6·48 Å respectively. These distances are the same as in dopamine when dopamine has the conformation indicated by A in Fig. 2. Plotting these conformations on the energy map shows that they lie within 1–2 kcal (4–8 kJ) above the local minimum of dopamine at $\tau_1 = 90°$, $\tau_2 = 180°$ (t).

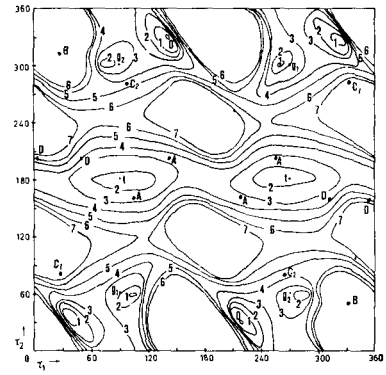

Fig. 3. Conformational energy map of dopamine constructed with iso-energy curves 1 kcal mol^{-1} above the global minimum at $\tau_1 = 220°$, $\tau_2 = 30°$. g_1, g_2 and t are the two *gauche* forms and the *trans* form of dopamine. A, B, C and D are the conformations of dopamine transposed from the isodistance map in Fig. 2 into the energy map.

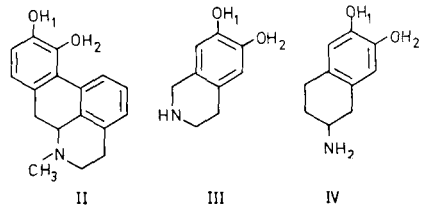

Fig. 4. Apomorphine II, 6,7-dihydroxytetrahydroisoquinoline III, and 2-amino-6,7-dihydroxy-1,2,3 tetrahydronaphthalene IV (ADTN).

Other rigid compounds in which the dopamine structure can be recognized are the 6,7-dihydroxytetrahydroisoquinoline III and the 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene IV (ADTN).

Dopamine in the conformation indicated on the energy map as B has similar key distances as the isoquinoline III. This conformation however is probably too far away from a local minimum to be significantly populated. This finding is in agreement with the fact that III is much less active as a dopamine agonist (Horn, 1974; Sheppard & Burghardt, 1974).

In contrast to the isoquinoline III the aminonaphthalene derivative IV is as potent as dopamine in

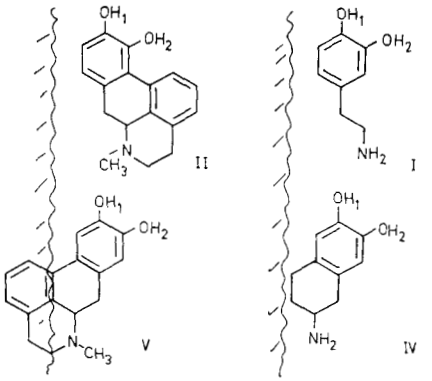

Fig. 5. Apomorphine II, dopamine I, isoapomorphine V and ADTN IV all constructed in the same stereochemical shape with regard to a "receptor boundary".

effecting a stimulation of cyclic AMP production in rat striatal homogenates (Miller, Horn & others, 1974). Further evidence that this compound is a dopamine agonist has been obtained by the effect on locomotor activity in mice after intraventricular injection (Woodruff, Elkhawad & Pinder, 1974) and by electrophysiological and behavioural studies (Woodruff, Elkhawad & others, 1974). The ADTN molecule can exist in two conformations, one with the NH_2 group in an axial and one with this group in an equatorial position. It is clear from the positions on the energy map that one of the dopamine conformations (C1) with the same distances as the axial ADTN molecule, is energetically unfavourable. The other conformation (C2) however is close to a minimum and therefore in principle possible. Of the dopamine conformations (D in Fig. 2) in which the key distances are the same as in the *equatorial* ADTN conformation, at least one is energetically possible and falls like the apomorphine conformation in the region of the *trans* form of dopamine. Support for the assumption that the equatorial conformation of ADTN is the pharmacologically active one was obtained by comparison of the calculated total energies of "axial" and 'equatorial" ADTN, equatorial ADTN being 8·7 kcal mol^{-1} (35 kJ) more stable. We might conclude from these considerations that for compounds to achieve dopamine like activity the key distance N–OH_2 can at least vary between 0·5 Å below (apomorphine) and 0·5 Å above (ADTN) the N–OH_2 distance in the *trans* conformation of dopamine (6·87 Å). When the N–OH_2 distances of ADTN and isoapomorphine are considered it can be seen that although isoapomorphine V and ADTN (a molecular fragment of iso-apomorphine) have the same key distances (Table 1), isoapomorphine is not active as a dopaminergic agent (Pinder, Buxton & Woodruff, 1972; Neumeyer, McCarthy & others, 1973; Saari, King & others, 1974).

Because apomorphine and isoapomorphine are isomers their physicochemical properties will be essentially the same and also their distribution. A possible reason for the lack of dopaminergic activity

Table 1. *Calculated key-distances in Angstroms.*

	N-OH_1	N-OH_2
Dopamine ($\tau_1 = 90°$, $\tau_2 = 180°$) t.	7·85	6·87
Apomorphine II		
x-ray	7·78	6·48
calc.	7·86	6·44
ADTN IV equatorial	7·77	7·32
Isoapomorphine V	7·77	7·31
Isoquinoline III	6·04	6·35
Benzomorphan VI	6·53	
Morphine VII X-ray	7·07	5·49
Dopamine ($\tau_1 = 90°$, $\tau_2 = 300°$) g_2.	6·21	5·99
ADTN IV axial	6·63	6·33
Dopamine ($\tau_1 = 90°$, $\tau_2 = 60°$) g_1.	6·19	4·89

of isoapomorphine may be rationalized by the stereochemical shape of the molecule. The three-dimensional structure of the dopaminergic receptor may hamper the interaction with molecules, bearing bulky groups on the side of the molecule opposite the OH_2 group.

Indications for such a stereochemical requirement for dopaminergic activity are also found in the observations of Cannon, Khonje & Long

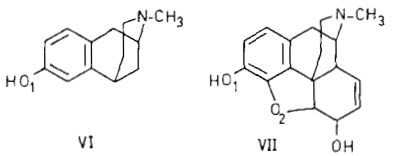

Fig. 6. 2′-Hydroxy-2-methyl-6,7-benzomorphan VI and morphine VII.

(1975), who investigated some analogues of dopamine, bearing bulky groups on that side of the molecule.

Compounds in which the ADTN molecule, with one hydroxyl group, is further recognized are the morphine and the benzomorphan series.

In these molecules the N atom of the ADTN fragment is fixed in the axial position by an ethylene bridge. As can be seen from the isodistance map

one of the conformations in which dopamine mimicked the ADTN molecule in the axial form (C2) lies close to the gauche form of dopamine (g_2). So it might be possible that dopamine in this conformation is involved in the analgesic receptor system. Support for this idea is found in the observation that narcotic analgesics interact with dopamine receptors in a way different from that of the neuroleptics (McKenzie & Sadof, 1974; Goroni, Kumakura & others, 1975; Wende, Spoerlein & Luc, 1975).

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