78. The Electronic Structure of Dopamine. An *ab initio* Electrostatic Potential Study of the Catechol Moiety

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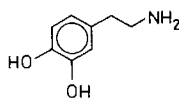
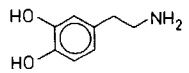
Electronic properties of dopamine were studied by the *ab initio* STO-3G MO method. The molecular electrostatic potential (MEP) around the aromatic ring and the catechol group remains practically the same in 3,4-dihydroxytoluene (a model compound) and in neutral dopamine examined in its two extended conformations, namely that found in the crystal (side-chain and aromatic ring almost perpendicular) and the one corresponding to 2-amino-6,7-dihydroxytetralin (6,7-ADTN) (side-chain and aromatic ring almost coplanar). In protonated dopamine and in dopamine hydrochloride, the electrostatic potential of the catechol moiety is overshadowed by the positive charge, but the main features remain discernible. The catechol moiety was examined in its two coplanar conformations containing a 'flip-flop H-bond'. The electrostatic potential around the catechol moiety is quite complex, with alternating positive and negative maxima. At increasing distances above and away from the catechol moiety, only two peripheral maxima, one negative and one positive, remain perceptible. The 'flip-flop' mechanism results in an approximate interchange of these two potential maxima, a fact which tends to level out the structural differences between the α- and β-rotamer of dopamine. Based on these results and on the structure of rigid agonists, some pharmacophoric features of dopamine agonists are proposed.

1. Introduction. – The active conformation of dopamine (DA, **I**) at its receptor sites is not fully established. Many rigid and semi-rigid analogs, holding the DA skeleton in a given conformation, have been synthesized to evaluate the topography of DA receptor(s) [1] [2]. It is currently accepted that DA binds in an extended (*trans*) form with the N-atom in, or very close to, the plane of the aromatic ring, as found in apomorphine (**IIa**). An uncertainty remains as to the orientation of the catechol ring, *i.e.* the α- or β-rotamer (**I**). The agonists (–)-(*R*)-apomorphine (**IIa**) and *N*-propylnorapomorphine (**IIb**) are rigid analogs of the α-rotamer, while 2-amino-6,7-dihydroxytetralins such as 6,7-ADTN (**IIIa**) and TL-99 (**IIIb**) [3] are potent β-rotamer analogs. There is some evidence, mainly from *in vitro* data [2], that the β-rotamer might be the more active form, but as aptly summarized

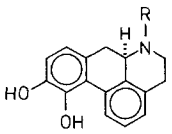


α-rotamer

I

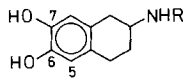


β-rotamer



IIa R = Me

IIb R = Pr



IIIa R = H

IIIb R = Me

by *Costall et al.* [4], the quest for a preferred rotameric conformation of DA agonists may be an illusory one. A possible partial explanation can be found in absolute configurations, since in the 2-aminotetralin series the 6,7-dihydroxy derivatives such as **IIIa** require the (2*R*)-configuration, while α-rotamer analogs such as 5,6-dihydroxy derivatives require the (2*S*)-configuration [5] which is geometrically identical with the (*R*)-configuration in apomorphine (**IIa**). N-Substitution also appears to play a role, since in 2-(*N*,*N*-dipropylamino)tetralins the α-rotameric 5,6-dihydroxy derivatives are more active than the β-rotameric 6,7-dihydroxy analogs [6].

It is also clear at present that the catechol function is not essential for dopaminergic activity, especially at DA autoreceptors [2] and at the postsynaptic D-1 receptor [7] where monohydroxy compounds show high potencies. The OH group is found mainly in positions *meta* to the attachment of the aminoethyl side-chain, with absolute configuration again playing a major role [5] [7]. Of considerable interest is the activity of ergot alkaloid and ergoline derivatives (*e.g.* [8]). Here, no OH-group is present, to be replaced by an endocyclic NH functionality.

The above suggests that structural factors other that chemical and spatial analogies with dopamine must be of significance. Lipophilicity may be one of these factors (*e.g.* [9]), but it will not be considered here. A second factor is the electronic structure of the molecules and their electrostatic potential, since it is clear that a certain charge distribution is required around a ligand to permit proper orientation and interaction with recognition sites. Protonation is an important factor in the charge distribution of a basic molecule. While dopamine has a pK_a of 8.9 in H_2O, it is not known whether its binding to the receptor(s) involves the neutral or protonated form. Sulfonium analogs, which are permanent cations, were found to display DA agonistic activity [10]. However, a sulfonium is a softer acid than an ammonium, and we know of no quaternary ammonium derivative having any DA receptor affinity. Furthermore, *Hamada et al.* [10] made the interesting observation that there are significant differences in the structure-activity relationships between sulfonium and amine analogs of DA, and that the permanent charge minimizes the otherwise important role played by other structural features.

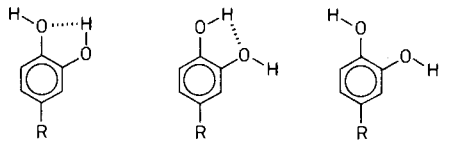
In recent years, molecular electrostatic potentials (MEP's) of a number of drugs have been used to obtain indirect information on receptor structure. Chlorpromazine and promazine were investigated by *ab initio* calculations, showing the remarkable long-range effect of the ring substituent [11] [12], while a number of other biomedical applications can be found in [13]. Adrenergic compounds have received constant attention (*e.g.* [12] [14–18]). Dopaminergic compounds were also studied [19] [20]; thus the aromatic regions of 5,6-ADTN, 6,7-ADTN, and of the ergoline skeleton were compared, showing interesting similarities and differences. In the present study, we examine the electronic structure of the aromatic region of dopamine in various conformations. The distance factor is also taken into account since this is of significance when searching for pharmacophoric patterns. The protonated form of dopamine is also included in the calculations.

2. Methods. – Wave functions and electronic densities were calculated using the semi-empirical CNDO/2 method (QCPE 382) and the *ab initio* MONSTERGAUSS program [21] operating in the STO-3G minimal basis set. MEP's were obtained with the VSS program (QCPE 245) and a modified version [22] of the program DENPOT (QCPE 360). As a general rule, the electrostatic potential were taken in a parallel plane 1.75 Å above the plane of the aromatic ring, *i.e.* just above the region of the π-electrons, as is

frequently the case (*e.g.* [11]). All calculations were performed on the CDC CYBER 170/720 and 170/855 computers of the Federal Institute of Technology in Lausanne.

As much as possible, bond lengths and valency angles were taken from crystallographic data [23]. In some cases, standard geometry was used, as described in [24]. No geometry optimizations were performed. Dopamine was investigated in two conformations, namely that found in the crystal, and the one corresponding to 6,7-ADTN; these conformers were based on the torsion angles, obtained by X-ray analysis, published by *Horn* and *Rodgers* [23].

In a catechol system, two planar, intramolecularly H-bonded conformers (**A** and **B**) can be discriminated when a ring substituent is present. The conformer **A** has the 3-OH group *syn* to the 4-OH, while the latter is *anti* to the 3-OH, hence its designation in the present paper as *syn-anti*. The conformer **B** is thus *anti-syn*, and the two conformers are characteristic of what has been coined a 'flip-flop H-bond' [25]. The energy of the two conformers differs by only 0.09 kcal/mol (STO-3G calculations), the *syn-anti* form being preferred. However, this minute difference is hardly meaningful since energies were calculated without geometry optimization. Both conformers were considered, but not the *anti-anti* form (**C**), which must be considerably less stable due to lone-pair repulsion and mainly to the absence of an intramolecular H-bond.



A (*syn-anti*) **B** (*anti-syn*) **C** (*anti-anti*)

3. Results. – 3.1. *MEP of 3,4-Dihydroxytoluene.* The model compound 3,4-dihydroxytoluene (= 4-methylpyrocatechol) was chosen in order to evaluate electronic features of the aromatic moiety of dopamine. The MEP plots as calculated by the CNDO/2 method (not shown) indicate that the potential above the ring is in part positive and in part negative, while the region above (and below) the OH groups is positive. The OH protons are calculated to exert a strong positive influence. The corresponding MEP as calculated by the STO-3G method is shown in *Fig. 1*. Large, even essential differences exist between the results from the two methods. At the STO-3G level, the sector above (and below) the aromatic ring is calculated to be entirely negative. Similarly, the region around the O-atoms is negative. These differences cast serious doubts on the validity of MEP's calculated be semi-empirical methods, as already well documented in the literature (*e.g.* [11] [12] [26]).

The MEP plots of 3,4-dihydroxytoluene in its *syn-anti* conformation *(Fig. 1)* must be compared to those for the compound in its *anti-syn* conformation *(Fig. 2)*. The region of greatest interest in the present context is that surrounding the two OH groups. Here, two negative and two positive maxima are seen, the strongest ones being the positive potential generated by the non-H-bonded H-atom, and the negative potential generated by the opposed O-atom. These two maxima are separated by a distance of 5.1 Å in the plane 1.75 Å above the ring. In planes further removed (2.0, 2.5 and 3.0 Å), this distance increases to 6.4 Å, while the two weaker, centrally located maxima progressively disappear. Thus, at a distance of 2.5–3 Å from the plane of the aromatic ring, the catechol moiety produces two

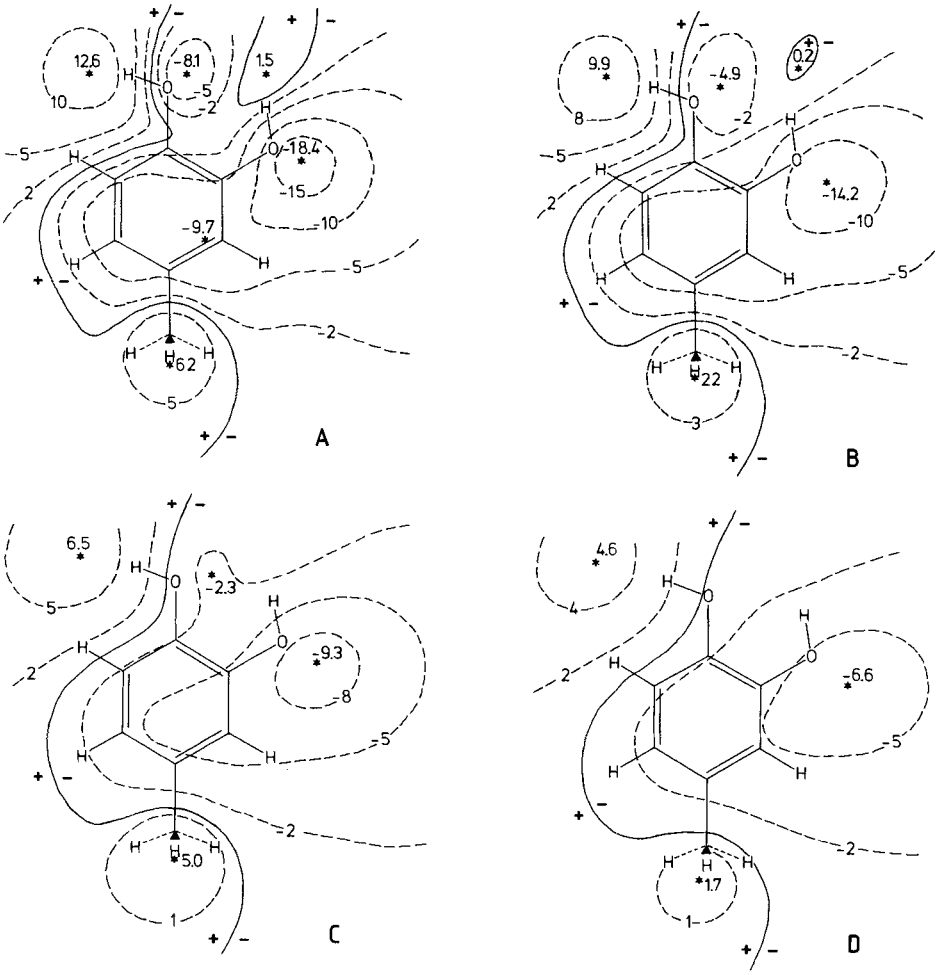


Fig. 1. *MEP* (calculated by the STO-3G *ab initio* method) *of 3,4-dihydroxytoluene* (*syn-anti* conformer) *in planes:* **A**, *1.75 Å;* **B**, *2.0 Å;* **C**, *2.5 Å; and* **D**, *3.0 Å above the plane of the aromatic ring.* The isoenergy contours are in kcal/mol.

potential maxima of opposite signs, one located in the 2,3-sector, the other in the 4,5-sector. The signs of these maxima alternate as the H-bond 'flip-flop' between the two conformations.

3.2. *MEP of Protonated Dopamine.* The MEP plot of protonated dopamine (in an almost planar conformation corresponding to 6,7-ADTN) is shown in *Fig. 3* for a plane 1.75 Å above the plane of the aromatic ring. The potential is entirely positive and rather monotonous, the cationic charge overshadowing all other electronic features. The OH proton not involved in the H-bond somewhat increases the positive potential in its vicinity, while this potential is decreased close to the O-atoms. Thus, the two maxima (positive and negative) noted for dihydroxytoluene have become a local maximum and a local minimum, both positive. In both cases, however, the energy difference at 1.75 Å is approximately 30 kcal/mol.

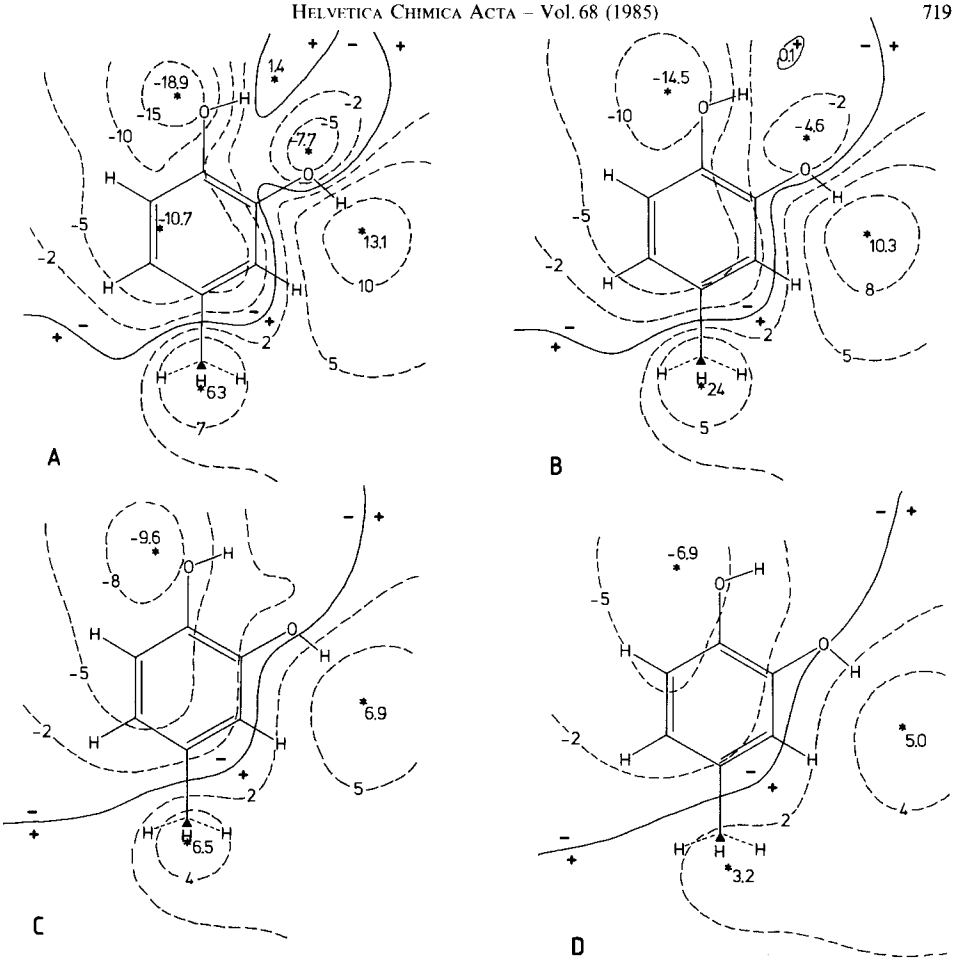


Fig. 2. *MEP* (calculated by the STO-3G *ab initio* method) *of 3,4-dihydroxycatechol* (*anti-syn* conformer) *in planes as in* Fig. 1

By adding a chloride counterion in the calculations, the MEP plot changes considerably *(Fig. 4)* due to a partial charge compensation by the counterion [27]. The overshadowing influence of the cation is markedly decreased, and more pronounced features become apparent around the catechol moiety. A small negative potential exists close to one O-atom, and qualitatively the two potential maxima of opposite signs found in the catechol region of dihydroxytoluene are also found in *Fig. 4*. The energy difference at 1.75 Å is again close to 30 kcal/mol, the net result being simply as if the zero line had been shifted. Thus, the electronic features of the catechol moiety are overshadowed by a cationic side-chain and modified only in sign, but energy differences are preserved. For these reasons, and due to a lack of definitive knowledge about the active form (neutral or protonated) of dopamine, subsequent calculations were performed with the neutral molecule.

3.3. *MEP of Neutral Dopamine in Two Extended Conformations.* MEP plots were calculated for neutral dopamine in two remarkable conformations, namely that corre-

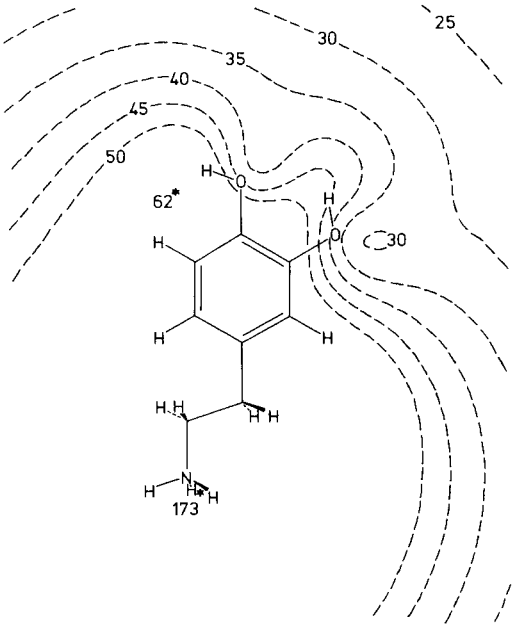


Fig. 3. *MEP* (calculated by the STO-3G *ab initio* method) *of the dopaminium cation in a plane 1.75 Å above the plane of the aromatic ring*

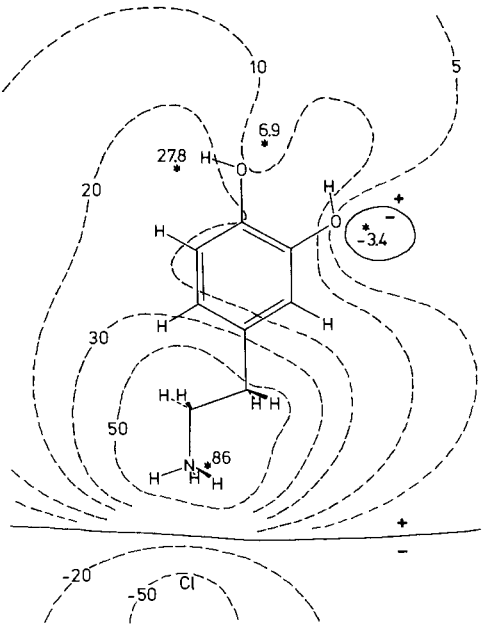


Fig. 4. *MEP* (calculated by the STO-3G *ab initio* method) *of dopamine hydrochloride*. The chloride ion is placed in the prolongation of the C–N bond, 3.1 Å away from the N-atom.

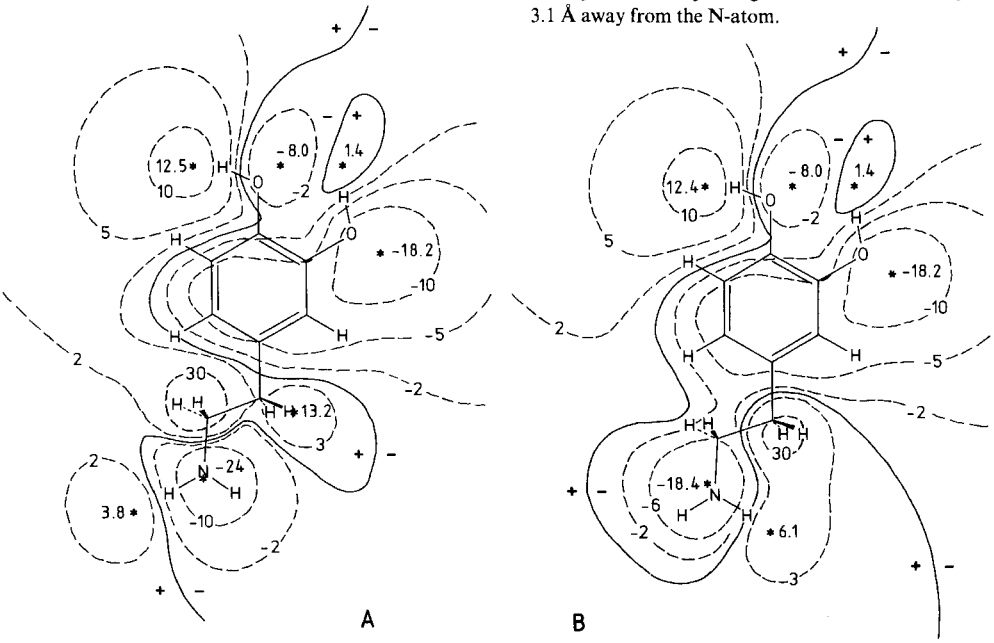


Fig. 5. *MEP* (calculated by the STO-3G *ab initio* method) *of dopamine in its almost planar conformation corresponding to 6,7-ADTN*. The isoenergy contours (in kcal/mol) are in planes: **A**, 1.75 Å; and **B**, – 1.75 Å away from the plane of the aromatic ring.

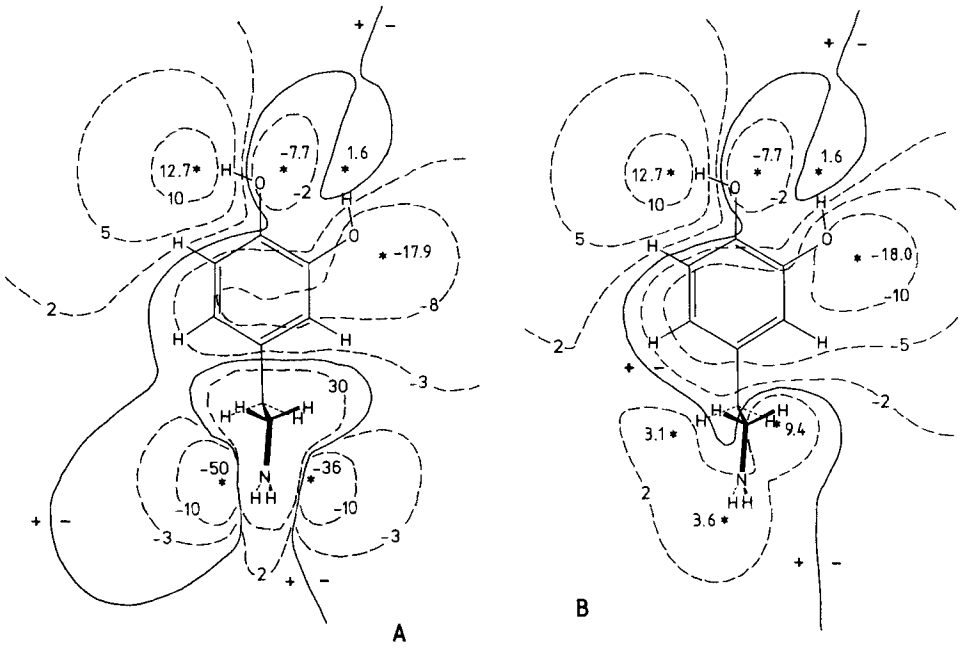


Fig. 6. *MEP* (calculated by the STO-3G *ab initio* method) *for the dopamine conformation found in the crystal.* Planes as in *Fig. 5*

sponding to 6,7-ADTN, and that found in the crystal [23]. The results are displayed in *Fig. 5* and *Fig. 6*, respectively, for planes 1.75 Å and – 1.75 Å away from the plane of the aromatic ring. Clearly, the electrostatic potential around the catechol moiety is only negligible influenced by the side-chain conformation. In fact, the extended side-chain itself has almost no influence, as apparent when comparing *Fig. 5* and *6* with *Fig. 1*. All conclusions drawn from *Fig. 1* and *2* thus remain valid for extended dopamine itself.

The electrostatic potential generated by the NH_2 group appears complex and would require a detailed study comparable to that published by *Barrett et al.* for the tetramethylammonium ion [28]. Rather than taking two-dimensional slices of the MEP, three-dimensional surface representations are likely to reveal more regular features. Briefly, however, a discrete positive region is seen to be generated by the H-atoms in the prolongation of the N–H bonds, while the N-atom itself produces broad negative potentials perpendicularly to the plane containing H–N–H. These features imply that the electrostatic potential around the NH_2 group is critically dependent upon dihedral and valency angles as influencing the direction of the electron lone pair.

4. Discussion. – No conclusions can be drawn from this study regarding the role played by the NH_2 group in the interaction between dopamine and its receptor(s). As already discussed, its state of protonation when binding to the receptor is not known, and the complex electrostatic potential surrounding the NH_2 group should change dramatically as the NH_2 group rotates around the C–N bond. The substitution around the N-atom also comes into play. Thus, *N*-propyl or di(*N*-propyl) substitution specifically maintains or increases the agonist activity of a number of dopaminergic agents, an effect termed the '*N*-propyl phenomenon' [29]. These facts indicate that an in-depth assessment

remains to be made regarding those features of the NH_2 group which influence the receptor binding and intrinsic activity of dopaminergic agents.

Another major part of the dopamine molecule is its catechol moiety. A number of conclusions emerge from this study, which may contribute to a better understanding of the recognition and binding of dopamine. We have shown that the electrostatic potential generated by the catechol moiety is almost independent from the presence of the aminoethyl side-chain when the latter is in an extended conformation. In the neutral molecule, the aromatic ring itself is entirely surrounded by a negative potential, while the two OH groups generate a more complex pattern. The catechol group was considered in two planar conformations which display a 'flip-flop H-bond'. The electrostatic potential thus generated contains two peripheral maxima, one positive and one negative, and two

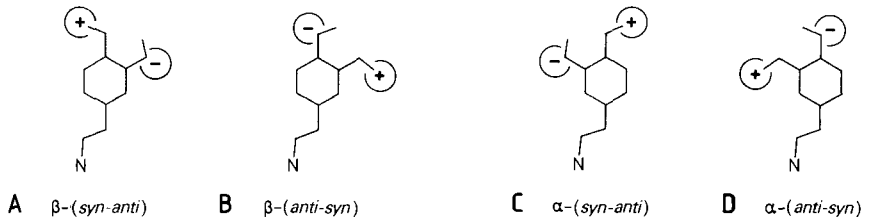


Fig. 7. *Potential maxima* (schematic representation) *in 4 dopamine conformers:* **A** *and* **B**, *β-rotamers;* **C** *and* **D**, *α-rotamers;* **A** *and* **C**, syn-anti *catechol conformation;* **B** *and* **D**, anti-syn *catechol conformation*

weaker, internal maxima. At increasing distances above and way from the aromatic ring, only the two former maxima remain influential, and these are postulated to play a predominant role in the recognition process between the neurotransmitter and its receptor(s).

As the catechol moiety 'flip-flop' between its two conformations, the positive and the negative maxima interchange, as illustrated in *Fig. 7A* and *7B*, and in *Fig. 7C* and *7D*. The former two figures represent dopamine as the *β*-rotamer, and the latter two as the *α*-rotamer. Of potential significance is the rather close analogy evident between the *β*-rotamer having a *syn-anti* conformation *(Fig. 7A)* and the *α*-rotamer with *anti-syn*

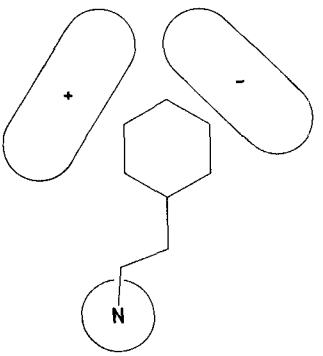


Fig. 8. *Postulated main features in the dopaminergic pharmacophore, as deduced from MEP's*

conformation (*Fig. 7D*). Both position a negative potential in the upper-right sector of the molecule when viewing it as in *Fig. 8*, and a positive potential in the upper-left sector. The same analogy as between *Fig. 7A* and *7D* also exists between *Fig. 7B* and *7C*. These analogies remove part of the difference between the α- and β-rotamers of dopamine, not in geometrical but in electronic terms. Such a congruence of electronic properties may help explain the activity of rigid analogs belonging to the α-rotameric series considered to be less favorable, and renders also meaningful from a physicochemical point of view the question raised by *Costall et al.*, namely: 'On the preferred rotameric conformation for dopamine agonist action: an illusory quest?' [4].

There is some evidence, deduced from rigid dopaminergic compounds such as monohydroxylated tetralins, ergolines [1], and recently troponylpiperazines [30], that an electronegative center corresponding to the negative potential shown in *Fig. 8* is necessary for dopaminergic activity. This would indicate the structure shown in *Fig. 8* as containing some key features of the dopaminergic pharmacophore, with the negative zone being essential.

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