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A molecular orbital study on the conformational properties of dopamine [1,2-benzenediol-4(2-aminoethyl)]and dopamine cation

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Abstract

The results of a series of ab initio (3-21G) and semiempirical (PM3) molecular orbital (MO) calculations on neutral, zwitterionic and cationic forms of dopamine [1,2-benzenediol-4(2-aminoethyl)] are reported. In particular, optimised geometries, relative stabilities, dipole moments and electron charge distributions for the relevant conformational states of the studied molecules are presented and the conformational dependence of some relevant structural parameters is used to characterise the most important intramolecular interactions present in the studied conformers. It is shown that all the studied molecules have a considerably high degree of conformational flexibility, and may exist as a mixture of several conformers of similar energies differing by the relative orientation of the aromatic ring with respect to the alkylamine chain or of the hydroxyl groups. For both neutral dopamine and dopamine cation, the conformational ground state corresponds to a form where the *meta*-hydroxy group has its hydrogen atom directed towards the *para*-hydroxy group, the aromatic ring and the alkylamine axis are nearly perpendicular and the C–C–C–N axis assumes a gauche geometry, with the amine group in the same side of the *meta*-hydroxy group. In turn, the zwitterionic form of dopamine is predicted not to correspond to a minimum in the potential energy surface (PES) for the isolated molecule situation. However, in the zwitterion dimmer, the conformation assumed by the individual molecules is predicted to be similar to that previously observed in crystalline dopamine hydrochloride.

Keywords: Dopamine [1,2-benzenediol-4(2-aminoethyl)] neutral and zwitterionic forms; Dopamine cation; Molecular structure; Conformational properties; Ab initio and semiempirical (PM3) molecular orbital calculations

1. Introduction

One of the most challenging questions in biomedical research is that of relating manifestations of neuropsychiatric diseases to chemical processes in different parts of the brain. The development of positron emission tomography (PET) and appropriate radioactive tracers labelled with positron-emitting radionuclides has enabled to relate regional biochemistry within the brain and specific human diseases such as, for example, in Alzheimer's or Parkinson's diseases [1–5], depression [6] or schizophrenia [7]. The neurotransmitter dopamine [1,2-benzenediol-4(2-aminoethyl)] appears to be associated with abnormalities related with some of the afore mentioned diseases (e.g., Parkinson's disease [4,5], schizophrenia [8,9]), as the highest density of dopaminergic neurons could be found in the relevant brain regions and the number of dopamine receptors was found to increase significantly in patients with these

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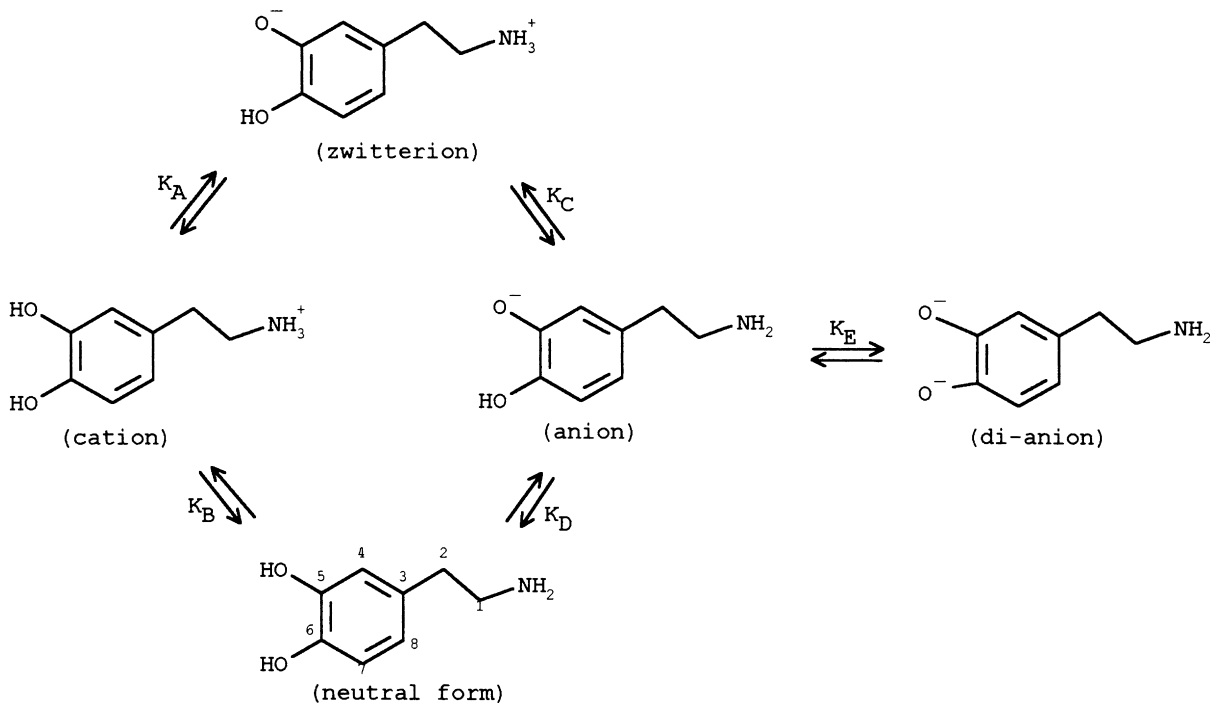


Fig. 1. Acid–base equilibria in dopamine. The macroscopic dissociation constants, $K_1 = K_A + K_B$, $K_2 = K_A K_C / K_1 = K_B K_D / K_1$, $K_3 = K_E$ [12,13], as determined experimentally by Granot [14] or Grgas-Kuznar et al. [15] are $10^{-9.5}$, $10^{-11.1}$ and $10^{-12.0}$, respectively. The numbering scheme presented is used thoroughly in this article.

diseases [4,10,11]. This fact justifies the interest to study the mechanisms of interaction between dopamine and its receptor and, as these mechanisms must involve a process of conformational selection which assumes that the initial contact between the drug molecule and the receptor is dependent upon an optimum spatial orientation of certain atoms in the drug molecule, it appears to be essential to have a detailed knowledge of the structures and relative energies of its preferred and less-preferred conformations. However, despite its fundamental importance, not many systematic studies were undertaken on this subject.

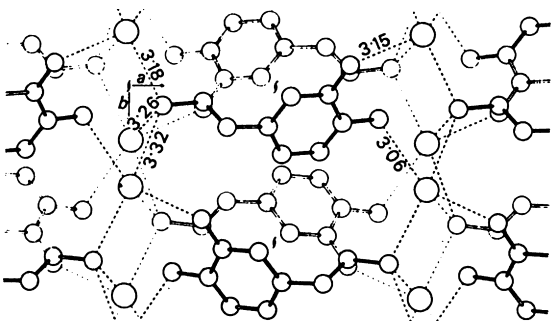


Fig. 2. Schematic representation of the crystalline unit cell of dopamine hydrochloride [20]. Projection of the structure along the c axis, showing intermolecular hydrogen bonds (Å).

Dopamine possesses one amine and two phenol groups, which may participate in acid–base equilibria and, in solution at pH 7.4, besides the neutral molecule, both the amine protonated cation and the zwitterionic form are, populated (Fig. 1). In fact, at this pH value, the dopamine cation was found to be by far the most populated form (ca. 95% [16]) while the relative populations of the zwitterionic and neutral species were found to be only 3% and 0.2%, respectively [16]. The anionic forms are only significantly populated at pH greater than 11 [14–16] and do not seem to play any relevant role within the biochemical processes. Thus, great emphasis must be given to the study of the properties of the dopamine cation, in

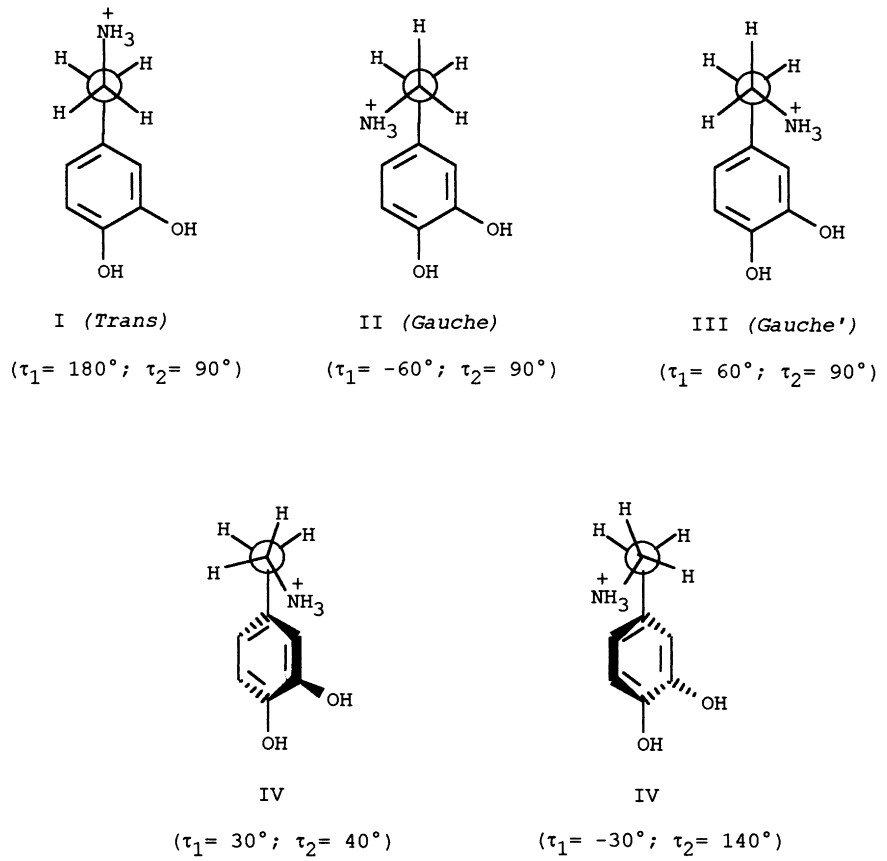


Fig. 3. Schematic representation of the previously reported main conformational states of dopamine cation[21–26] (ι_1 = N–C1–C2–C3; ι_2 = C1–C2–C3–C8).

particular when compared with those of the neutral molecule, which is the species that corresponds to the lowest energy structure both in the gaseous phase and for the isolated molecule situation, usually assumed by theoretical methods [17–19].

The crystal structure of dopamine hydrochloride [Cl^- + $NH_3CH_2CH_2C_6H_4(OH)_2$] was determined in the late sixties [20] by X-ray analysis and it was found to be an extended conformation (Fig. 2), whereby the structure is stabilised by extensive network of hydrogen bonds with the chlorine ion as acceptor [20]. However, the preferred conformations of dopamine cation in other experimental conditions are still under discussion. An early NMR study of dopamine hydrochloride in aqueous solution [21] indicated that under these conditions, this species adopts preferentially a conformation where the dopamine cation side chain assumes the *trans* conformation about the CH_2–CH_2 and the chain is perpendicular to the aromatic ring (form I in Fig. 3). This result is in consonance with theoretical predictions obtained using Extended Huckel Theory (EHT) calculations where the preferred conformations about the CH_2–CH_2 and CH_2-ring bonds were analysed [21–23]. In addition to the *trans* form, the EHT calculations predicted the existence of two different gauche conformers about the CH_2–CH_2 bond (forms II and III in Fig. 3) which should have a slightly higher energy than the *trans* conformer ($\Delta E_{\text{gauche–}trans} \approx 8$–12 kJ mol^{-1} [21–23]). Later on, semiempirical CNDO [24] and PCILO [25], and single point minimum basis STO-3G ab initio molecular orbital (MO) calculations undertaken at the semiempirically optimised geometries [25] enabled

to reach essentially the same conclusions as the previous studies [21–23], but this time the *trans* form was predicted to be higher in energy than the gauche forms about the CH_2–CH_2 bond by ca. 4–8 kJ mol^{-1} [24,25]. More recently, a different semiempirical study undertaken using the INDO approximation [26] predicted the existence of two additional low energy minima in the potential energy surface (PES) of dopamine cation (forms IV and V in Fig. 3), corresponding to conformers that, contrarily to the previously considered forms, should not exhibit the CH_2–CH_2 chain and the aromatic ring perpendicular to each other.

On the whole, the results obtained by the various studies previously undertaken clearly indicate that the dopamine cation has a considerably high degree of conformational flexibility, thus stressing the importance to submit such a system to a more systematic and detailed structural study carried out at a higher level of theory. In addition, to the best of our knowledge there are no previous studies reported on the conformations of either the neutral or zwitterionic forms of dopamine. Thus, in the present work a series of systematic MO calculations were undertaken in order to define the conformational states of dopamine (in both its neutral and zwitterionic forms) and dopamine cation. Firstly, the PESs of the studied systems were investigated in detail at the semiempirical (PM3 [27]) level of theory, in order to search for energy minima and find approximate geometries of the most relevant conformers. This preliminary energy surface scanning allowed the computational time required by the main body of calculations, carried out at the considerably more expensive ab initio Hartree–Fock level of theory within restricted regions of the molecular configurational spaces, to be kept within tractable bounds. In the ab initio calculations, the popular split-valence 3-21G basis set [28] (which uses a linear combination of three primitive Gaussian functions for inner-shell representation and has its valence shell functions split into two and one Gaussian functions, respectively) was used, as this basis set was extensively proved to yield very reliable structural and energetic results for nitrogen containing molecules [29,30] and thus it allows a good compromise between the quality of the results and computer time requirements.

2. Computational methods

The MO calculations were performed both at the ab initio 3-21G [28] and semiempirical (PM3 [27]) levels of theory, using GAUSSIAN 92 for Windows (Revision G-3) [31]. The semiempirical calculations were systematically used to search the conformational space of dopamine in order to find approximate geometries of the most relevant conformers. Molecular geometries were fully optimised by the force gradient method using Berny's algorithm [32]. The largest residual coordinate forces were always less than 3×10^{-4} hartree bohr^{-1} (1 hartree = 2625.5001 kJ mol^{-1}; 1 bohr = 5.29177×10^{-11} m) or hartree rad^{-1}, for bond stretches and angle bends, respectively. In order to ensure that the conformations resulting from the minimisation procedure correspond to true minima in the PES, the nature of all critical point structures was systematically checked by inspection of the correspondent Hessian matrices. Molecular graphics were generated from the final optimised geometries with the WebLab Viewer (version 1.1) or MolWin (version 2.3) programs [33].

3. Results and discussion

3.1. Neutral dopamine

The existence of a large number of possible conformational states for dopamine is easily predicted on the basis of simple stereochemical principles, when the five relevant internal axes of rotation of the molecule (H–O1–C5–C6, H–O2–C6–C7, C1–C2–C3–C8, C3–C2–C1–N and C2–C1–N–lp) are taken into account. In the case of the dopamine cation, there is one less relevant conformational degree of freedom, as internal rotation around the C–N bond does not lead to different rotational isomers.

In order to perform a detailed examination of the PES of dopamine and identify the relevant regions of the configurational space of this molecule that should be submitted later to a higher level theoretical treatment, a series of systematic calculations were first undertaken on this compound using the semiempirical PM3 Hamiltonian. The semiempirical PES mapping was performed by varying

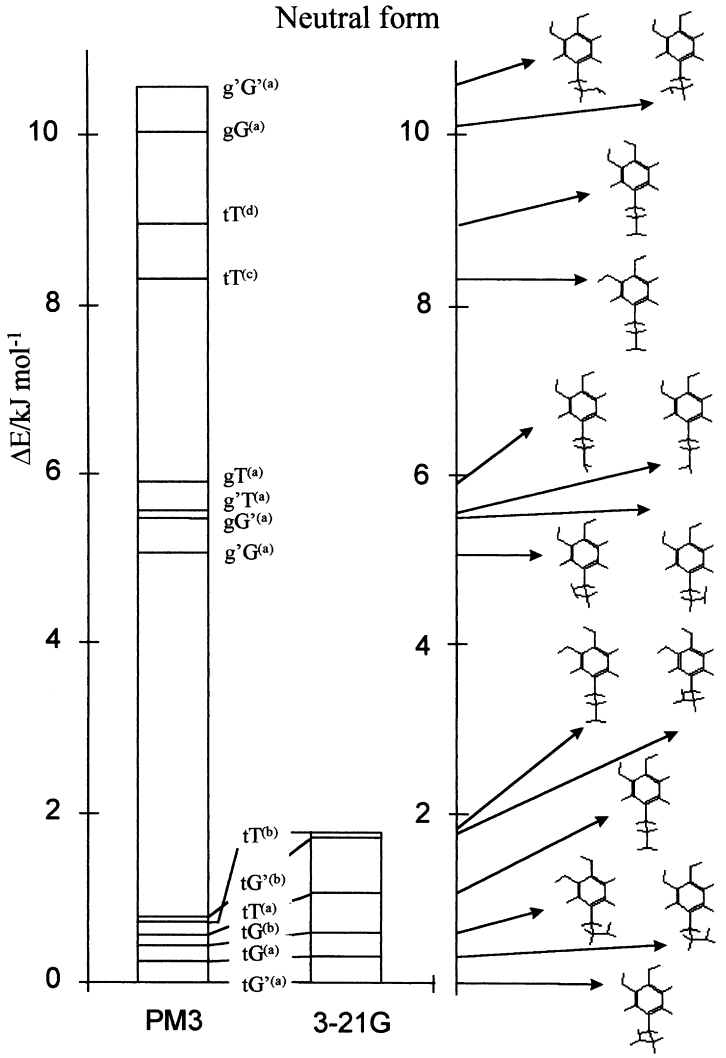


Fig. 4. Calculated (3-21G and PM3) relative energies of the relevant lower energy conformers of neutral dopamine. Other conformers were predicted by the preliminary semiempirical PM3 calculations reported here, but all of them have high energies. Indeed, some of these high energy forms could be plotted in the graph shown in this figure; however, this would just make it unreadable, while no relevant information would be added (see text).

systematically the relevant dihedral angles and performing full geometry optimisation for each starting configuration. The main conclusions obtained from these preliminary calculations can be summarised as follows:

(i) For all minimum energy structures, the C1–C2–C3–C8 dihedral angle was predicted to be close to 90°, i.e., this axis adopts geometry where the CH_2–CH_2 chain and the aromatic ring are nearly perpendicular to each other (Fig. 4). No stable forms corresponding to other values of the C1–C2–C3–C8 dihedral were found in the PES. Thus, the present calculations do not confirm the previously reported INDO results that suggested the existence of two additional stable conformations for C1–C2–C3–C8 dihedral angles of 40° and 140° [26].

(ii) The two hydroxyl groups were found to lie in the aromatic ring plane. Four possible arrangements

Table 1
Ab initio (3-21G) and semiempirical (PM3) calculated optimized geometrical parameters, energies and electric dipole moments for the most stable forms of dopamine (neutral form)[a]

Parameter	tT[(a)]		tG[(a)]		tG′[(a)]		tT[(b)]		tG[(b)]		tG′[(b)]	
	3-21G	PM3	**3-21G**	PM3	**3-21G**	PM3	**3-21G**	PM3	**3-21G**	PM3	**3-21G**	PM3
C–N	**146.8**	147.3	**146.6**	147.3	**146.5**	147.3	**146.8**	147.3	**146.5**	147.3	**146.5**	147.3
C1–C2	**155.1**	153.0	**155.3**	153.0	**155.3**	153.0	**155.1**	153.0	**155.3**	153.0	**155.3**	153.0
C2–C3	**151.4**	149.4	**151.4**	149.5	**151.4**	149.5	**151.4**	149.4	**151.4**	149.5	**151.4**	149.5
C3–C4	**139.1**	139.4	**139.2**	139.6	**139.1**	139.4	**139.1**	139.4	**139.3**	139.6	**139.2**	139.4
C4–C5	**137.3**	139.9	**137.3**	139.8	**137.4**	140.0	**137.2**	139.7	**137.1**	139.6	**137.2**	139.8
C5–C6	**138.7**	141.2	**138.8**	141.3	**138.6**	141.2	**138.6**	141.2	**138.7**	141.3	**138.5**	141.2
C6–C7	**137.1**	139.8	**137.0**	139.7	**137.1**	139.8	**137.3**	140.0	**137.2**	139.9	**137.4**	140.0
C7–C8	**138.9**	138.9	**139.0**	139.0	**138.8**	138.9	**138.7**	138.9	**138.8**	138.9	**138.6**	138.8
C3–C8	**138.3**	139.6	**138.3**	139.5	**138.0**	139.6	**138.3**	139.5	**138.3**	139.5	**138.4**	139.6
C5–O1	**137.1**	136.9	**137.0**	136.8	**137.1**	136.8	**138.7**	137.5	**138.6**	137.4	**138.7**	137.5
C6–O2	**138.9**	137.5	**138.8**	137.4	**138.8**	137.5	**137.2**	136.8	**137.2**	136.8	**137.2**	136.8
O1–H	**96.7**	94.9	**96.8**	94.9	**96.8**	94.9	**96.3**	94.8	**96.3**	94.8	**96.3**	94.8
O2–H	**96.3**	94.8	**96.3**	94.8	**96.3**	94.8	**96.7**	94.9	**96.7**	94.9	**96.7**	94.9
C–C–N	**114.4**	114.4	**115.0**	115.2	**115.5**	115.3	**114.5**	114.5	**115.0**	115.2	**115.1**	115.2
C1–C2–C3	**111.1**	110.5	**111.3**	112.2	**111.3**	112.2	**111.2**	110.5	**111.4**	112.3	**114.4**	112.3
C2–C3–C4	**119.6**	119.7	**119.6**	119.6	**121.5**	120.2	**119.6**	119.7	**120.2**	119.7	**121.9**	120.3
C2–C3–C8	**120.0**	119.8	**121.0**	120.1	**120.0**	119.8	**120.0**	120.3	**121.5**	120.5	*120.2*	119.9
C6–C5–O1	**119.9**	122.9	**120.0**	122.9	**120.0**	122.9	**114.2**	115.9	**114.3**	115.9	**114.3**	115.9
C4–C5–O1	**120.5**	117.2	**120.5**	117.2	**120.5**	117.2	**125.0**	124.7	**125.0**	124.6	**125.0**	124.7
C7–C6–O2	**125.4**	124.6	**125.5**	124.7	**125.5**	124.6	**120.8**	117.1	**120.8**	117.1	**120.7**	117.1
C5–C6–O2	**114.4**	115.7	**114.3**	115.8	**114.3**	115.7	**120.0**	122.7	**120.1**	122.8	**120.3**	122.8
C5–O1–H	**110.1**	107.3	**110.2**	107.4	**110.4**	107.4	**113.6**	108.6	**113.7**	108.6	**113.7**	108.7
C6–O2–H	**113.6**	108.6	**113.6**	108.7	**113.6**	108.6	**110.1**	107.4	**110.2**	107.4	**110.2**	107.4
C4–C5–O1–H	**180.0**	180.0	**− 179.2**	− 179.5	**180.0**	− 179.8	**− 0.1**	− 0.2	**− 0.1**	− 1.1	**− 5.2**	− 0.9
C7–C6–O2–H	**0.2**	1.3	**1.5**	0.9	**0.3**	0.9	**179.9**	178.8	**179.7**	179.6	**179.6**	179.9
C1–C2–C3–C4	**− 89.1**	− 96.6	**− 84.0**	− 72.9	**− 92.9**	− 107.4	**− 90.7**	− 84.8	**− 84.0**	− 71.9	**− 94.9**	− 108.4
C1–C2–C3–C8	**90.9**	83.4	**96.0**	107.1	**87.1**	72.6	**89.3**	95.2	**96.0**	108.1	**85.1**	71.6
C3–C2–C1–N	**179.6**	− 179.6	**− 61.8**	− 66.6	**61.8**	66.5	**180.0**	179.4	**− 61.4**	− 66.0	**61.4**	66.1
C2–C1–N–1p	**179.4**	179.3	**− 179.9**	− 177.8	**179.9**	178.8	**− 179.4**	− 179.8	**− 179.2**	− 178.8	**179.6**	177.8
ΔE	**1.050**	0.552	**0.315**	0.248	**0.000**	0.000	**1.772**	0.716	**0.603**	0.421	**1.709**	0.785
$\lvert\mu\rvert$	**3.25**	2.31	**3.60**	2.73	**3.14**	2.24	**3.27**	1.95	**2.80**	1.73	**3.23**	2.28

[a] Bond lengths in pm, angles in degrees, energies in kJ mol^{-1}, dipole moments in Debye (1 D = 3.33564×10^{-30} cm); see Fig. 1 for atom numbering. Only the relevant structural parameters are presented; the complete set of optimized structural parameters may be obtained from the authors. Energies relative to the most stable conformer, the total calculated energies for the most stable form are − 510.6560337 E_h.(ab initio 3-21G); − 0.1170185 E_h (PM3)

of these two groups are then possible, and these were here analysed in detail (see Fig. 4): forms (a) and (b) show intramolecular O–H…O hydrogen bonds (O1–H…O2 and O2H…O1, respectively), and were found to be the most stable forms, having similar energies ($\Delta E < 1$ kJ mol^{-1}); form (c) has the two hydroxyl groups with the hydrogen atoms pointing to each other and, because of the unfavourable H…H repulsion, has an energy ca. 7 kJ mol^{-1} higher than forms (a) and (b); finally, form (d) exhibits a considerably strong repulsive interaction between the lone electron pairs of the two oxygen atoms and corresponds to the highest energy form ($\Delta E \approx 8$ kJ mol^{-1}).

(iii) The preferred conformation of the C2–C1–N–lp axis is *trans*. The gauche forms are predicted to be ca. 5 kJ mol^{-1} higher in energy than the *trans* forms. Notable exceptions are those conformers where the lone electron pair of the nitrogen atom is directed towards the π system of the aromatic ring (e.g., conformers g′G$^{(a)}$ and gG$^{(a)}$; see Fig. 4), which have much higher energies. The preference of the C2–C1–N–lp axis for the *trans* arrangement in primary amines has been studied in detail previously [34,35], being associated with the greater electron delocalization from the nitrogen lone-pair electron to the molecular skeleton in the *trans* conformation. This electronic transfer changes the hybridisation state of the carbon atom to closer an sp^2 state and this can also be noticed by looking at the relative values of the C–C–N angle in *trans* and gauche forms: as it could be anticipated, this angle is considerably larger in conformers where the C2–C1–N–lp axis is *trans* (ca. 115°) than in gauche forms (ca. 111°).

(iv) Finally, as already pointed out before [21–25], the internal rotation about C2–C1 gives rise to three different conformers, corresponding to C3–C2–C1–N dihedral angles of 180° (*trans*) and in the $\pm$ 60° regions (gauche forms). The semiempirical calculations yield similar energies for these three conformations ($\Delta E < 1$ kJ mol^{-1}), with the *trans* form being slightly less stable than the gauche forms (comparing conformers where the conformations adopted by the remaining axes are equal; e.g., forms tT$^{(a)}$, tG$^{(a)}$ and tG′$^{(a)}$ or forms tT$^{(b)}$, tG$^{(b)}$ and tG′$^{(b)}$ in Fig. 4).

It is clear from the semiempirical results that dopamine has a considerably high conformational flexibility, as the relative energies of the different conformers are relatively close and some of the energy barriers for conformer interconversion must also be low. However, it can also be concluded from these results that the relevant conformational states of this molecule (those which should be mostly populated under normal conditions) are those where the C2–C1–N–lp axis is *trans* and the configuration of the OH groups is either (a) or (b), i.e., the six conformers here referred to as tT$^{(a)}$, tG$^{(a)}$, tG′$^{(a)}$, tT$^{(b)}$, tG$^{(b)}$ and tG′$^{(b)}$ (see Fig. 4).

Thus, higher level 3-21G ab initio calculations were performed on these six forms. The structural and energetic results obtained at this level of theory show a general agreement with the semiempirical data (see Fig. 4 and Table 1).

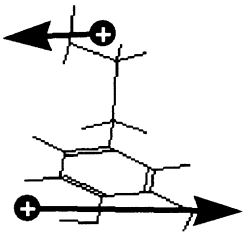
The ab initio results enable us also to explain the relative stability of the most stable conformers of dopamine in terms of the main intramolecular interactions that are operating in the various forms:

(i) As a general trend, the conformers having the hydroxyl groups adopting the (a) configuration are more stable than those where these groups adopt the (b) configuration (providing the remaining axes of internal rotation assume the same conformation; see Fig. 4). This may be correlated with the well known greater acidity of the dopamine *meta*-hydroxyl group substituent [16], that is also on the basis of its greater ability to participate in intramolecular hydrogen bonding. The relative stabilisation of the (a) configuration with respect to the (b) structure can be evaluated by the relative stability of the *trans* conformers (tT$^{(a)}$, tT$^{(b)}$), whose relative energy is essentially determined by this interaction, and thus may be estimated as ≈ 0.72 kJ mol^{-1}.

(ii) However, in all gauche forms of dopamine now considered (tG$^{(a)}$, tG′$^{(a)}$, tG$^{(b)}$ and tG′$^{(b)}$), one of the NH_2 hydrogen atoms is directed towards the π system of the aromatic ring (see Fig. 4). This stabilising interaction explains the lower energy of the gauche forms with respect to the *trans* forms: $E\{tG^{(a)}\}$ and $E\{tG'^{(a)}\} < E\{tT^{(a)}\}$; $E\{tG^{(b)}\}$ and $E\{tG'^{(b)}\} < E\{tT^{(b)}\}$. Despite it is not possible to evaluate precisely the energy reduction associated with this interaction because other effects simultaneously operate in all gauche forms, a higher limit for this may be estimated as the difference between the energy of the tT$^{(a)}$ conformer and the relative energy between forms tG$^{(a)}$ and tG′$^{(a)}$ (ca. 0.74 kJ mol^{-1}). In fact, the relative energy of these two gauche forms (where the

NH_2/π-system interactions must be very similar) is essentially determined by the relative orientation of the NH_2 and $\overline{HO\ldots HO}$ fragments, the higher energy $tG^{(a)}$ form being destabilised by this effect by an amount of energy that must be slightly smaller than the stabilisation produced by the same effect on the most stable $tG'^{(a)}$ form, as explained in detail later. By using a similar reasoning, a lower limit of 0.67 kJ mol^{-1} may be estimated for the energy reduction associated with the NH_2/π-system interaction from the relative energies of the three (b) conformers.

(iii) Finally, it is important to explain the relative energies of the gauche forms, which assume the same arrangement of the hydroxyl groups. The molecule of dopamine has essentially two regions of electron charge concentration, besides that related with the π system of the aromatic ring: one associated with the nitrogen lone electron pair, and the second associated with the two oxygen atoms. These two regions of electron charge concentration is compensated by regions of electron charge depletion that stay in their vicinity. The first of these corresponds to the two hydrogen atoms bound to the nitrogen atom; the second, to the hydroxylic hydrogen atom that is not involved in the hydrogen bond established between the two hydroxyl groups. In fact, the topology of the charge distribution in the molecule enables to associate to each one of the NH_2 and $\overline{HO\ldots HO}$ fragments group dipoles, the first pointing from the NH_2 hydrogens towards the nitrogen lone pair, and the second pointing from the hydroxyl hydrogen atom not involved in the hydrogen bond towards the lone electron pairs of the oxygen atom which acts as a hydrogen-bond donor:



The relative orientation of these two dipoles plays an important role in determining the relative energy of the gauche forms of dopamine now considered ($tG^{(a)}$, $tG'^{(a)}$, $tG^{(b)}$ and $tG'^{(b)}$), leading to a stabilisation of forms $tG'^{(a)}$ and $tG^{(b)}$, where the dipoles are nearly antiparallel and to an increase of energy of forms $tG'^{(b)}$ and $tG^{(a)}$, where they point to the same direction. This effect is relatively more important when the amino group is in the gauche' position (i.e., the amino group is in the same side of the *meta*-hydroxyl group; see Fig. 4) than when it is in the gauche position. This may be easily correlated with the fact that the distance between the interacting intramolecular dipoles is shorter when the amino group occupies the gauche' than the gauche position. In addition, it also appears that the intramolecular dipolar interaction is more important when the configuration of the two hydroxyl groups is (b) than when it is (a) (the ab initio calculated relative energy of the two (a) forms is 1.71 kJ mol^{-1}, while that of the two (b) forms is only 0.32 kJ mol^{-1}). On the whole, and together with the effect of hydrogen bonding associated with the hydroxyl groups discussed earlier, these dipolar interactions can account for the predicted relative energies of the gauche forms of dopamine.

Looking now at the structural changes in bond lengths and angles associated with conformation, the following main conclusions may be drawn (see Table 1):

(i) The C–N bond is slightly shorter in the gauche conformers than in the *trans* forms, whilst the C1–C2 bond length follows the opposite trend. These changes lead to a better contact between the NH_2 hydrogen atom pointing towards the π-system of the aromatic ring, in the gauche forms, and are certainly related with the stabilising NH_2/π-system interactions mentioned before (that are absent in the *trans* conformers). The slightly larger C–C–N and C1–C2–C3 angles in the gauche forms may also be related with this effect. Further, the relative values of the C2–C3–C4 and C2–C3–C8 angles can also be correlated with the position of the NH_2 group with respect to the aromatic ring. In particular, C2–C3–C4 increases when the NH_2 group is directed to C4 (in $tG'^{(a)}$ and $tG'^{(b)}$) while C2–C3–C8 when the amino group is closer to C8 ($tG^{(a)}$ and $tG^{(b)}$); indeed, these angles are similar in gauche and *trans* forms when the NH_2 group is directed to the other side of the molecule (i.e.,C2–C3–C4 in $tG^{(a)}$ and $tG^{(b)}$, and C2–C3–C8 in $tG'^{(a)}$ and $tG'^{(b)}$).

(ii) The C1–C2–C3–C4 and C1–C2–C3–C8 dihedral angles also reflect the effect of the NH_2/π-system interactions. In fact, these angles are very close to 90° in the *trans* forms, while C1–C2–C3–C4 increases in

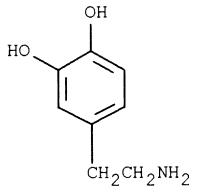
Table 2
3-21G ab initio calculated Mulliken atomic charges for the most stable forms of dopamine (neutral form)[a]

Atom	$tT^{(a)}$	$tG^{(a)}$	$tG'^{(a)}$	$tT^{(b)}$	$tG^{(b)}$	$tG'^{(b)}$
N	− 0.792	− 0.791	− 0.792	− 0.792	− 0.791	− 0.793
H	0.294	0.309	0.292	0.296	0.311	0.289
H	0.296	0.289	0.311	0.294	0.291	0.310
C1	− 0.167	− 0.172	− 0.169	− 0.166	− 0.170	− 0.169
H	0.224	0.214	0.218	0.218	0.214	0.222
H	0.220	0.223	0.214	0.224	0.216	0.214
C2	− 0.456	− 0.455	− 0.455	− 0.454	− 0.454	− 0.454
H	0.215	0.218	0.216	0.208	0.212	0.209
H	0.211	0.212	0.215	0.215	0.216	0.219
C3	− 0.059	− 0.053	− 0.053	− 0.062	− 0.056	− 0.056
C4	− 0.227	− 0.226	− 0.238	− 0.248	− 0.247	− 0.258
H	0.260	0.262	0.258	0.232	0.234	0.230
C5	0.384	0.385	0.384	0.325	0.326	0.324
O1	− 0.757	− 0.757	− 0.757	− 0.764	− 0.764	− 0.764
H	0.418	0.418	0.418	0.405	0.406	0.404
C6	0.307	0.307	0.307	0.369	0.369	0.369
O2	− 0.764	− 0.764	− 0.764	− 0.756	− 0.756	− 0.755
H	0.404	0.404	0.405	0.416	0.417	0.416
C7	− 0.250	− 0.251	− 0.250	− 0.231	− 0.233	− 0.231
H	0.238	0.239	0.239	0.266	0.266	0.267
C8	− 0.236	− 0.247	− 0.236	− 0.233	− 0.243	− 0.232
H	0.236	0.234	0.238	0.237	0.236	0.239

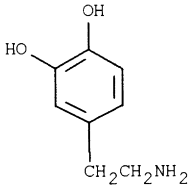
[a] Atomic charges in units of e ($e = 16021892 \times 10^{-19}$ C). See Fig. 1 for atom numbering.

both $tG'^{(a)}$ and $tG'^{(b)}$ and C1–C2–C3–C8 increases in $tG^{(a)}$ and $tG^{(b)}$.

(iii) The C–C bonds in the ring were found not to vary significantly with the conformation. Resulting from a repulsive interaction between the lone-pair electrons of the oxygen atoms, the electron distribution within the π system favours canonical form I instead of canonical form II. Such effect gives rise to longer C3–C8, C4–C5 and C6–C7 bonds and alternate shorter C3–C4, C5–C6 and C7–C8 bonds.



(I)



(II)

(iv) Conformers where the hydroxyl groups are in the (a) configuration ($tT^{(a)}$, $tG^{(a)}$ and $tG'^{(a)}$) exhibit an O1–H…O2 intramolecular hydrogen bond, while those having these groups in the (b) configuration ($tT^{(b)}$, $tG^{(b)}$ and $tG'^{(b)}$) show an O2–H…O1 intramolecular hydrogen bond. Accordingly, (a) conformers have a longer O1–H bond and (b) forms a longer O2–H bond.

(v) The intramolecular hydrogen bonding does also affect the relative length of the two C–O bonds. These bonds have bond lengths that are typical of C–O bonds with a substantial double bond character (a typical C–O single bond in alcohols and ethers has a bond length within the range 141–144 pm; a typical C=O double bond measures ca. 120 pm; the partially double C–O bonds in carboxylic compounds and phenols have bond lengths respectively in the ranges 133–136 and 136–139 pm [36,37]), indicating that mesomerism involving these bonds and the aromatic ring is operating. Taking also into consideration the calculated Mulliken atomic charges shown in Table 2, it can clearly be concluded that besides canonical form Ia (see Fig. 5), canonical form IIa also contributes significantly to the electronic structure of (a)-like conformers, leading to a C–O1 bond shorter than C–O2, a less negative charge on O1 and to an increased negative charge on C4. However, in (b)-like

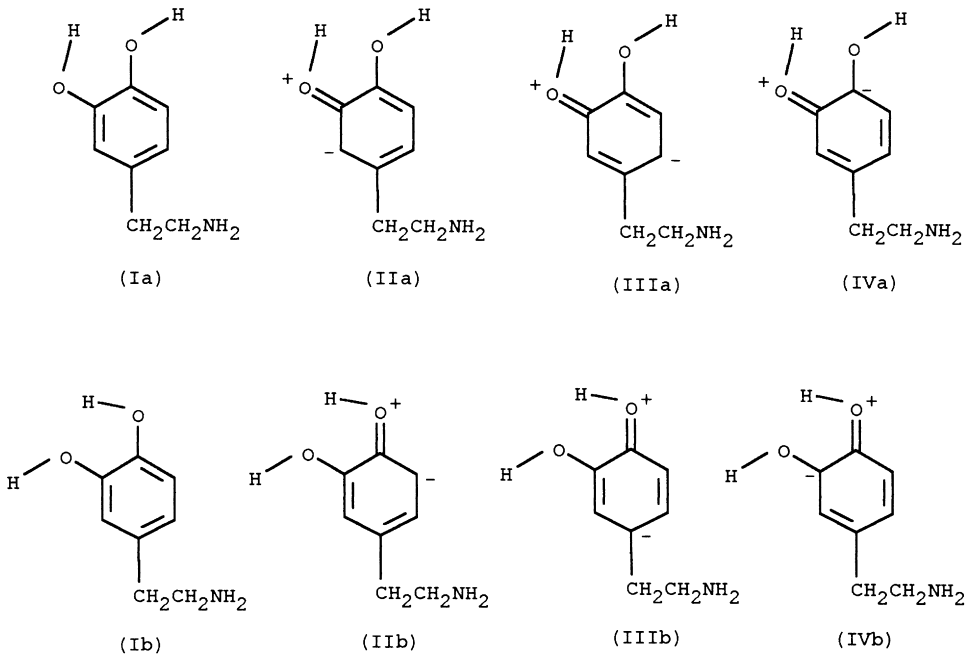


Fig. 5. Relevant canonical forms showing the mesomerism associated with the hydroxyl groups and the aromatic ring. Upper structures were found to be important in (a)-like conformers, while bottom structures are important in (b)-like conformers.

conformers, besides canonical form Ib, canonical form IIb must also play an important role, leading to a longer C–O2, a less negative O2 and a more negative C7. Canonical forms IIIa, IVa and IIIb, IVb, are of minor importance, although they are responsible for the slightly more negative (or less positive) charges on C6 and C8 in (a)-like conformers and more negative (or less positive) charges on C3 and C5 in (b) conformers (comparison shall be made between conformers with an identical conformation of the C1–C2–C3–C4 axis). It is also worth mentioning that the causes of the extra negative charge on C4 and C7 in (a) and (b)-like conformers are different: for (a) conformers, the extra charge on C4 comes essentially from the mesomerism associated with canonical form IIa, while the extra charge on C7 is because of a π-system electronic charge migration from the attached H atom that, in these conformers are close to the hydroxylic hydrogen atom bound to O2 (the relative values of the calculated charges on the hydrogen atom bound to C7 for (a) and (b) conformers clearly reflect this effect; see Table 2); for (b) conformers, the mechanisms of intramolecular electron charge migration now discussed work precisely in the opposite direction and the extra negative charge on C7 is because of mesomerism (canonical form IIb shown in Fig. 5) whilst the extra negative charge in C4 results from the π-system electronic charge migration from the H attached to this atom.

(vi) The relative values of the C–O–H and C–C–O angles are also determined by the intramolecular hydrogen bonding involving the two hydroxyl groups. The C–O1–H and C–O2–H angles assume their larger values respectively in (a) and (b)-type conformers, i.e., when the corresponding hydrogen atom is not participating in the hydrogen bond and is suffering the electrostatic repulsion because of the close proximity of the hydrogen atom bound to the vicinal aromatic ring carbon atom (C4 and C7, respectively). In turn, as can be easily understood, these interactions also determine why the C–C–O angle *syn*-periplanar to the C–O–H fragment whose hydrogen atom is not involved in the intramolecular hydrogen bond is considerably larger (ca. 4° by the 3-21G calculations; Table 1) than the *syn*-periplanar C–C–O angle associated with the second hydroxylic group.

3.2. Dopamine cation

When compared with neutral dopamine, dopamine cation is a much simpler system. Firstly, it has one degree less of conformational freedom (internal rotation about the C–N bond does not give rise to conformational isomers). In addition, in this case, there is an intramolecular interaction that strongly dominates, making much easier to understand the trends followed by the molecular properties upon changing the conformation. This is, naturally, coulombic charge attraction between the positively charged NH_3 group and the negatively charged hydroxyl groups.

The relevant results obtained for dopamine cation are presented in Tables 3 and 4 and in Figs. 6 and 7.

As referred to before, it is possible to associate to the HO...HO fragment a group dipole pointing from the hydroxyl hydrogen atom not involved in the hydrogen bond towards the lone electron pairs of the oxygen atom which acts as hydrogen-bond donor. In practical terms, this means that the negative charge in this fragment, for an (a)-like configuration of the hydroxyl groups, is located near O1 and closer to C4

Table 3
3. Ab initio (3-21G) calculated optimized geometrical parameters, energies and electric dipole moments for the most stable forms of dopamine cation[a]

Parameter	$T^{(a)}$	$G^{(a)}$	$G'^{(a)}$	$T^{(b)}$	$G^{(b)}$	$G'^{(b)}$
C–N	156.6	155.1	155.1	156.7	155.0	155.1
C1–C2	153.5	153.9	154.0	153.5	154.1	154.0
C2–C3	151.8	151.8	151.7	151.8	151.7	151.9
C3–C4	139.2	139.5	139.6	139.3	139.6	139.3
C4–C5	137.1	137.1	137.5	137.1	137.0	137.5
C5–C6	139.3	139.6	139.2	139.2	139.5	138.8
C6–C7	137.0	136.8	137.1	137.4	137.2	137.9
C7–C8	139.0	139.4	139.0	138.6	139.0	138.2
C3–C8	137.9	138.2	138.1	138.1	138.4	138.7
C5–O1	136.1	135.7	135.8	139.2	137.5	138.3
C6–O2	137.5	137.4	137.4	135.8	135.6	135.6
O1–H	96.9	96.9	96.9	96.4	96.4	96.6
O2–H	96.4	96.4	96.4	96.8	96.9	96.9
C–C–N	110.4	108.4	108.9	110.6	108.6	108.6
C1–C2–C3	107.7	110.6	110.4	107.6	110.5	110.7
C2–C3–C4	119.4	119.6	119.7	120.3	120.2	120.5
C2–C3–C8	121.0	121.1	121.0	120.4	120.9	120.7
C6–C5–O1	120.4	120.3	120.6	113.8	113.7	114.8
C4–C5–O1	120.1	120.1	119.9	125.5	125.6	124.6
C7–C6–O2	125.9	126.1	126.1	120.3	120.4	120.0
C5–C6–O2	113.7	113.6	113.7	120.4	120.4	120.8
C5–O1–H	111.3	111.6	111.5	115.2	115.5	114.7
C6–O2–H	115.1	115.4	115.3	111.6	111.8	111.6
C4–C5–O1–H	− 178.5	− 177.1	− 176.2	− 12.7	− 16.5	− 37.3
C7–C6–O2–H	4.1	10.2	10.0	178.9	177.4	179.2
C1–C2–C3–C4	95.6	− 70.9	− 98.4	− 93.5	− 78.1	− 109.7
C1–C2–C3–C8	84.4	109.1	81.6	86.4	101.9	70.3
C3–C2–C1–N	178.4	− 54.9	56.2	178.8	− 55.5	60.4
ΔE	19.980	1.523	0.000	28.418	7.670	10.577
$\lvert\mu\rvert$	15.67	11.54	10.34	18.18	12.66	12.52

[a] Bond lengths in pm, angles in degrees, energies in kJ mol^{-1}, dipole moments in Debye (1 D = 3.33564×10^{-30}C m); see Fig. 1 for atom numbering. Only the relevant structural parameters are presented; the complete set of optimized structural parameters may be obtained from the authors. Energies relative to the most stable conformer, the total calculated energy for the most stable form is − 511.0481904 E_h. PM3 relative energies and dipole moments are: $T^{(a)}$ (13.633; 16.26), $G^{(a)}$ (1.727; 11.79), $G'^{(a)}$ (0.000; 11.21), $T^{(b)}$ (18.970; 17.98), $G^{(b)}$ (5.749; 12.84), $G'^{(b)}$ (6.586; 12.76).

Table 4
4. 3-21G ab initio calculated Mulliken atomic charges for the most stable forms of dopamine cation[a]

Atom	$T^{(a)}$	$G^{(a)}$	$G'^{(a)}$	$T^{(b)}$	$G^{(b)}$	$G'^{(b)}$
N	− 0.836	− 0.838	− 0.840	− 0.837	− 0.839	− 0.837
H	0.439	0.458	0.435	0.439	0.460	0.433
H	0.439	0.433	0.462	0.438	0.434	0.461
H	0.442	0.439	0.438	0.442	0.438	0.439
C1	− 0.244	− 0.250	− 0.248	− 0.243	− 0.248	− 0.249
H	0.312	0.300	0.302	0.308	0.299	0.302
H	0.309	0.306	0.298	0.311	0.300	0.300
C2	− 0.477	− 0.462	− 0.466	− 0.476	− 0.463	− 0.459
H	0.260	0.302	0.266	0.253	0.294	0.258
H	0.256	0.260	0.297	0.260	0.265	0.301
C3	− 0.071	− 0.121	− 0.100	− 0.078	− 0.115	− 0.136
C4	− 0.228	− 0.233	− 0.291	− 0.241	− 0.241	− 0.266
H	0.265	0.279	0.270	0.241	0.255	0.254
C5	0.408	0.414	0.417	0.342	0.349	0.328
O1	− 0.751	− 0.747	− 0.750	− 0.756	− 0.755	− 0.750
H	0.433	0.437	0.437	0.417	0.423	0.419
C6	0.340	0.340	0.337	0.404	0.405	0.407
O2	− 0.759	− 0.757	− 0.758	− 0.745	− 0.743	− 0.742
H	0.422	0.425	0.426	0.431	0.435	0.432
C7	− 0.242	− 0.241	− 0.237	− 0.226	− 0.226	− 0.226
H	0.268	0.254	0.278	0.296	0.301	0.304
C8	− 0.234	− 0.272	− 0.234	− 0.227	− 0.279	− 0.230
H	0.248	0.275	0.261	0.245	0.251	0.259

[a] Atomic charges in units of e ($e = 1.6021892 \times 10^{-19}$ C). See Fig. 1 for atom numbering.

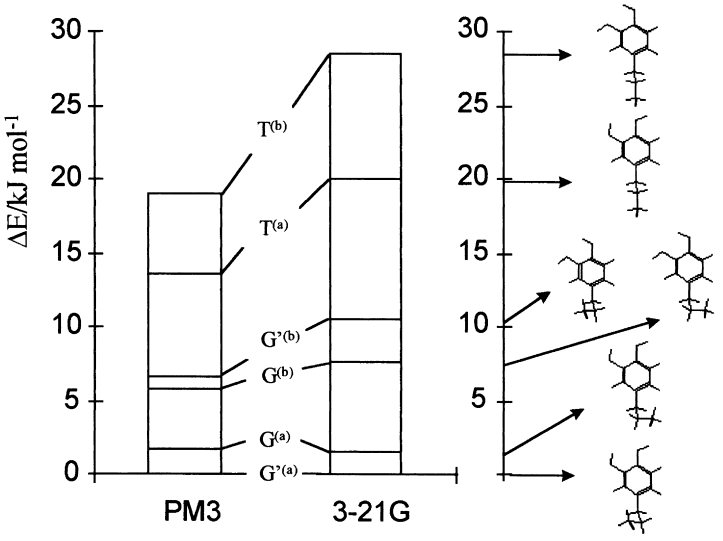


Fig. 6. Calculated (3-21G and PM3) relative energies of the relevant lowest energy conformers of dopamine cation.

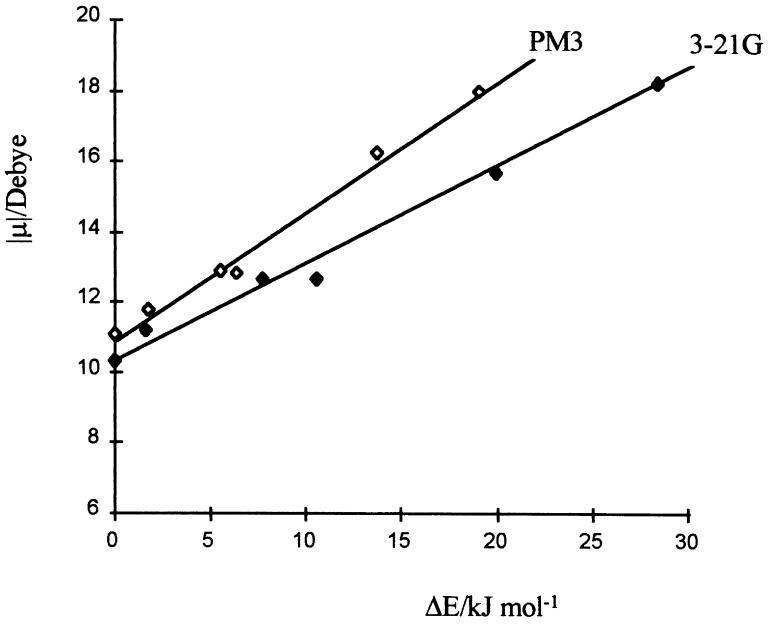


Fig. 7. Plot of calculated (3-21G and PM3) electric dipole moments, $|\mu|$, vs. relative energies, ΔE, of the lowest energy forms of dopamine cation.

than to C6, while for a (b)-like configuration of these groups, it is located near C6, but closer to C7 than to C5. Hence, it is not surprising that the most stable conformer is $G'^{(a)}$, where the distance between the NH_3 group and the negative charge centre of the $\overline{HO\ldots HO}$ fragment is the smallest one. In addition, the order of stability of the remaining conformers of low energy is also determined by this distance, as can be easily noticed by looking at the data shown in Fig. 6. Note also that in this molecule (a) like conformers are also more stable than the (b) forms (assuming that the C1–C2–C3–N axes are in the same configuration), but the effect of the different strengths of the intramolecular hydrogen bonds (O1–H…O2 or O2–H…O1) corresponds just to a minor contribution to the energy differences of the various conformers of dopamine cation, as it is easy to conclude taking into consideration the relative magnitude of these differences in dopamine cation and neutral dopamine.

The fact that conformer relative energies correlate well with dipole moments (Fig. 7) gives further support to the earlier interpretation. Such correlation does not hold for neutral dopamine where, as discussed earlier, various intramolecular interactions play relevant roles in determining the relative energy of the different conformers.

Despite their relatively reduced importance in determining the energies of the various conformers of dopamine cation, it is possible to conclude, from the changes in both geometrical parameters and atomic Mulliken charges with conformation, that most of the intramolecular interactions present in the neutral form of dopamine, discussed earlier, are also operating in this molecular system.

Thus, the conformational dependence of the C–N and C1–C2 bond lengths (which are respectively larger and smaller in gauche than in *trans* forms), as well as that of the C1–C2–C3, C2–C3–C4 and C2–C3–C8 angles and C1–C2–C3–C4 and C1–C2–C3–C8 dihedrals, follow the same trends as in neutral dopamine, clearly evidentiating the presence in the gauche conformers of the cation of stabilising interactions between the NH_3^+ group and the π-system of the aromatic ring that are similar to the NH_2/π-system interactions found in neutral dopamine. Indeed, these interactions are even stronger in the cation, as the charge of the NH_3^+ hydrogen atom involved in this interaction is more positive than that of the NH_2 hydrogen atom that participates in this interaction in

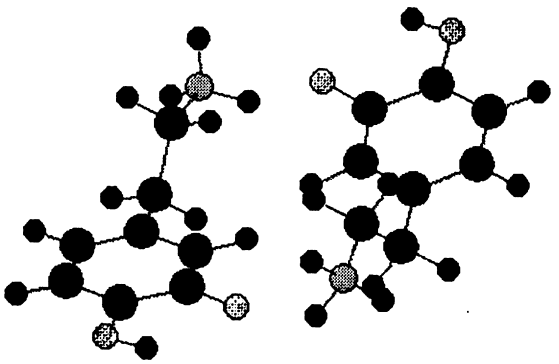


Fig. 8. Lowest energy dimmer of zwitterionic dopamine as predicted by the PM3 method.

neutral species (ca. 0.46 vs. 0.31 *e*; see Tables 2 and 4). The effect of this interaction on the charge of C4 (in gauche' forms) or C8 (in gauche forms) atoms, that become considerably more negative than in the conformers where they are not involved in this kind of interaction, is easily noticeable from the data shown in Table 4. Note that a similar effect is also evident in neutral dopamine, but it is much less pronounced (see Table 2)

The repulsive interaction between the lone-pair electrons of the oxygen atoms and the π system associated with the aromatic ring, discussed in detail above for neutral dopamine, is also on the basis of the observed longer C3–C8, C4–C5 and C6–C7 and shorter C3–C4, C5–C6 and C7–C8 bonds for dopamine cation.

Finally, as observed for neutral dopamine, the intramolecular hydrogen bonding within the HO…HO fragment, the mesomerism involving the hydroxyl groups and the aromatic ring, and repulsive charge interactions between the hydroxyl hydrogen atom not involved in the intramolecular hydrogen bond and the nearest hydrogen of the aromatic ring, are important in determining the changes with conformation observed in the O–H and C–O bond lengths, C–O–H and C–C–O angles and relative charges on the ring carbon atoms and hydroxyl groups, which, in fact, follow the same general trends in both molecules.

It is also worth noting that the C–N bond becomes longer upon protonation of the NH_2 group, while the C1–C2 bond length and the C–C–N and C1–C2–C3 angles decrease, thus following the general trend previously found for similar systems [38,39].

3.3. Zwitterionic dopamine

As it was mentioned in Section 1, in solution at pH 7.4, besides the neutral molecule and the amine protonated cation, the zwitterionic form of dopamine also exists, corresponding to ca. 3% of the population. However, zwitterionic dopamine was found not to correspond to a minimum energy state for the isolated molecule situation, either when the semiempirical (PM3) or the ab initio (3-21G) Hamiltonians were considered.

It is very interesting that, concerning this property, dopamine behaves like aminoacids, whose zwitterionic forms have also been shown not to be stable structures as isolated species [38,40].

As the semiempirical PM3 calculations here carried out for both neutral dopamine and dopamine cation were found to provide structural results in good general agreement with the higher level 3-21G ab initio calculations, the preferred structure of dopamine zwitterion dimmer was investigated by this method. The lowest energy species found is depicted in Fig. 8 and corresponds to a centrosymmetrical (C_i point group) dimmer where the conformation adopted by the individual molecules is similar to that observed in crystalline dopamine hydrochloride [20], i.e., the monomeric units have a C3–C2–C1–N axis nearly assuming the *trans* conformation. The NH_3^+ group of each monomeric unit is hydrogen-bonded to the unprotonated *meta*-hydroxyl group of the second molecule (the predicted O…N distance is 259.3 pm), which in turn also participates in an intramolecular hydrogen bond involving the *para*-hydroxyl group of the same molecule as donor (predicted O…O distance: 280.5 pm).

4. Conclusion

Neutral dopamine and dopamine cation have a considerably high degree of conformational flexibility and may exist as a mixture of several conformers of similar energies differing by the relative orientation of the aromatic ring with respect to the alkylamine chain or of the hydroxyl groups. For both molecules, the conformational ground state corresponds to a form where the *meta*-hydroxy group has its hydrogen atom directed towards the *para*-hydroxy group,

forming an intramolecular hydrogen bond, the aromatic ring and the alkylamine axis are nearly perpendicular and the C–C–C–N axis assumes a gauche geometry, with the amine group in the same side of the *meta*-hydroxy group (conformers $tG'^{(a)}$ and $G'^{(a)}$, respectively). In the case of neutral dopamine, the higher level ab initio 3-21G calculations predict that five additional conformers have energies within the energy range of 2 kJ mol^{-1} with respect to the most stable form, their relative energies depending on a delicate balance of several intramolecular interactions (HO…HO hydrogen bonding, NH_2/aromatic ring π system attraction, oxygen lone electron pairs/aromatic ring π system repulsion, NH_2/HO…HO group dipolar interactions, free O–H/vicinal aromatic H–C repulsion). However, relative conformational energies in dopamine cation are substantially larger and mainly determined by electrostatic repulsions between the NH_3^+ group and the HO…HO fragment. The 3-21G calculations predict that within a range of 5 kJ mol^{-1} relative to the most stable conformer, only a second conformer exists ($G^{(a)}$). For both molecules, mesomerism involving the two hydroxyl groups and the aromatic ring was found to be responsible for the relative bond lengths of the aromatic C–C bonds.

The results now obtained clearly show that, for the isolated molecule, the C–C–C–N axis in both neutral dopamine and dopamine cation adopts preferentially a gauche arrangement. On the contrary, in the crystalline state, dopamine cation was previously found to exhibit a *trans* conformation about this axis [20]. In addition, previous NMR studies also point to a larger population of the *trans* forms in aqueous solution [21]. Considering that the *trans* forms are more polar than the gauche conformers, it is not surprising that these forms are stabilised by polar solvents, such as water (or D_2O), or become more stable in condensed phases (in this case, more efficient packing forces related with geometrical effects may also play an important role in selecting a particular conformation of the individual molecules to form the crystal).

The results of a previous variable temperature NMR experiment [21] revealed a small but significant increase in the mole fraction of the *trans* conformer with temperature. As the authors of that study had predicted by EHT calculations the *trans* form as the most stable form, this result was unexpected, considering that the Boltzmann law predicts increased population of the higher energy conformers with increased temperature, providing that energy levels and intermolecular interactions with solvent remain constant over a temperature range. However, this observation may be easily understood, without requiring further assumptions, considering that the *trans* form has in fact a higher intrinsic energy than the gauche forms (its stabilisation in solution relatively to the gauche forms is because of stronger interactions with the solvent molecules) and knowing that an increase in temperature over the range covered in the NMR study (30°–90°) might not change appreciably the solvent–solute interactions (e.g., the Reaction Field Model [41] predicts a ratio of the relative energy of stabilisation because of interaction with solvent at 30° and 90°, $\Delta E^{30^\circ}/\Delta E^{90^\circ} = (k^{30^\circ} - 1)(2k^{90^\circ} + 1)/(k^{90^\circ} - 1)(2k^{30^\circ} + 1)$, smaller than 0.1%, using the dielectric constants for D_2O at these temperatures and assuming that the dipole moments and molecular volume of the conformers do not change with temperature).

Zwitterionic dopamine was found not to correspond to a minimum in the PES for the isolated molecule situation, following the same trend previously observed for aminoacids [48,40]. However, in the zwitterion dimmer, the conformation assumed by the individual molecules is predicted to be similar to that previously observed in crystalline dopamine hydrochloride [20], which very probably indicates that the conformational preferences of these two species should not differ considerably.

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References

[1] L. Farde, E. Ehrin, L. Erikson, T. Grietz, H. Hall, C.-G. Hedstrom, J.-E. Litton, G. Sedvall, Proc. Natl. Acad. Sci. 82 (1985) 3863.
[2] D.F. Benson, Alzheimer's disease: A review of progress in research, in: S. Corkin (Ed.), Aging, 19, Raven, New York, 1982.
[3] H.N. Wagner Jr, H.D. Burns, R.F. Dannals, D.F. Wong, B. Langstrom, T. Duelfer, J.J. Frost, H.T. Ravert, J.M. Links,

S.B. Kosenbloom, S.E. Lukas, A.V. Kramer, M.J. Kuhar, Science 221 (1983) 1264.
[4] J. Mukherjee, K.E. Luh, N. Yasillo, B.D. Perry, D. Levy, C.-T. Chen, C. Ortega, R.N. Beck, M. Cooper, Europ. J. Pharmacol. 175 (1990) 363.
[5] T.D. Reisine, Life Sci. 21 (1977) 335.
[6] C. Baron, J. Cereb. Blood Flow Metab. 1 (Suppl. 1) (1981) S500.
[7] N.C. Andreasen, R. Carson, M. Diksic, A. Evans, L. Farde, A. Gjedde, A. Hakim, S. Lal, N. Nair, G. Sedvall, L. Tune, D. Wong, Schizophr. Bull. 14 (1988) 471.
[8] E.D. Bird, E.G.S. Spokes, L.L. Iversen, Brain 102 (1979) 347.
[9] K.L. Davis, R.S. Kahn, G. Ko, M. Davidson, Am. J. Psychiatry 148 (1991) 1474.
[10] D.R. Burt, I. Creese, S.H. Snyder, Science 326 (1977) 326.
[11] D.F. Wong, A. Gjedde, H.N. Wagner Jr, J. Cereb. Blood Flow Metab. 6 (1986) 137.
[12] E.Q. Adams, J. Am. Chem. Soc. 38 (1916) 1503.
[13] J.T. Edsall, R.B. Martin, B.R. Hollingwooth, Proc. Natl. Acad. Sci. 44 (1958) 505.
[14] J. Granot, FEBS Lett. 67 (1976) 271.
[15] B. Grgas-Kuznar, V. Simeon, O.A. Weber, J. Inorg. Nucl. Chem. 36 (1974) 2151.
[16] J. Granot, FEBS Lett. 67 (1976) 271.
[17] S.G. Stepanian, I.D. Reva, E.D. Radchenko, M.T.S. Rosado, M.L.T.S. Duarte, R. Fausto, L. Adamowicz, J. Phys. Chem. 102 (1998) 1041.
[18] I.D. Reva, S.G. Stepanian, A.M. Plokhotnichenko, E.D. Radchenko, G.C. Sheina, Yu.P. Blagoi, J. Mol. Struct. 318 (1994) 1 and references therein.
[19] A. Kulbida, M.N. Ramos, M. Rasanen, J. Nieminen, O. Schrems, R. Fausto, J. Chem. Soc. Faraday Trans. 91 (1995) 1571.
[20] R. Bergin, D. Carlstrom, Acta Cryst. B24 (1968) 1506.
[21] T.M. Bustard, R.S. Egan, Tetrahedron 27 (1971) 4457.
[22] R. F. Rekker, D.J.C. Engel, G.S. Nijs, J. Pharm. Pharmacol. 24 (1972) 589.
[23] L.B. Kier, J. Theor. Biol. 40 (1973) 211.
[24] R. Katz, S.R. Heller, A.E. Jacobson, Molec. Pharm. 9 (1973) 486.
[25] B. Pullman, J.L. Conseils, Ph. Couriére, J.P. Grevois, J. Med. Chem. 15 (1972) 17.
[26] C.J. Grol, H. Rollema, J. Pharm. Pharmacol. 29 (1977) 153.
[27] J.J.P. Stewart, J.Comput.Chem. 10 (1989) 221, 209
[28] J.S. Binkley, J.A. Pople, W.J. Hehre, J. Am. Chem. Soc. 102 (1980) 939.
[29] R. Fausto, J.J.C. Teixeira-Dias, P.R. Carey, J. Am. Chem. Soc. 113 (1991) 2471.
[30] J.S. Binkley, J.A. Pople, W.J. Hehre, J. Am. Chem. Soc. 102 (1980) 939.
[31] M.J. Frisch, G.W. Trucks, H.B. Schlegel, P.M.W. Gill, B.G. Johnson, M.W. Wong, J.B. Foresman, M.A. Robb, M. Head-Gordon, E.S. Replogle, R. Gomperts, J.L. Andres, K. Raghavachari, J.S. Binkley, C.R. Gonzalez, L. Martin, D.J. Fox, D.J. Defrees, J. Baker, J.J.P. Stewart, J.A. Pople, Gaussian 92/DFT, Revision G.3, Gaussian Inc., Pittsburgh PA, 1993.
[32] H.B. Schlegel, Ph.D. Thesis, Queen's University, Kingston, Ontario, 1975.
[33] WebLab Viewer (version 1.1), MSI Inc., San Diego, USA, 1996; MolWin (version 2.3), P.V. Ganelin, Department of Chemistry, Catholic University of America, Washington DC, USA, 1994.
[34] L.A.E. Batista de Carvalho, J.J.C. Teixeira-Dias, R. Fausto, Struct.Chem. 1 (1990) 533.
[35] P.J. Krueger, J. Jan, Can. J. Chem. 48 (1970) 3229.
[36] R. Fausto, A. Matos-Beja, J.A. Paixão, J. Mol. Struct. 435 (1997) 207.
[37] J.J.C. Teixeira-Dias, R. Fausto, J. Mol. Struct. 144 (1986) 199.
[38] M.T. Rosado, M.L.T.S. Duarte, R. Fausto, Vibrat. Spectrosc. 16 (1998) 35.
[39] M.T. Rosado, Ph.D. Thesis, Departamento de Química e Bioquímica, Universidade de Lisboa, Portugal, 1998.
[40] Y. Ding, K. Krogh-Jesperssen, Chem. Phys. Lett. 199 (1992) 261.
[41] B.J. van der Veken, Low temperature molecular spectroscopy, in: R. Fausto (Ed.), NATO ASI Series C, 483, Kluwer Academic Publishers, Dordrecht, 1996, pp. 371.