Computational study on the conformations of dopamine, its α- and *ortho*-methylated derivatives and their *N*-protonated forms

Marcela P. Aliste * and Bruce K. Cassels

Department of Chemistry and Millennium Institute for Advanced Studies in Cell Biology and Biotechnology, Faculty of Sciences, Universidad de Chile, Casilla 653, Santiago, Chile

Received (in Cambridge, UK) 17th January 2001, Accepted 27th March 2001
First published as an Advance Article on the web 10th May 2001

A comparative theoretical study of the conformational profiles of dopamine, its α-, 2-, and 6-methyl derivatives, for which D_1-dopaminergic activities have been recorded, and their *N*-protonated forms, which predominate strongly at physiological pH, was carried out using the AM1 approximation and the COSMO model to evaluate the effects of an aqueous medium on intramolecular rotations. In the gas phase, for the neutral and *N*-protonated molecules, the perpendicular rotamers are generally more stable than the coplanar rotamers. In the *N*-protonated molecules, the *gauche* rotamers tend to be more stable than the *trans* forms, but in aqueous medium the *trans* rotamers are preferred. Taken together, our results support the contention that agonist activity at the D_1 dopaminergic receptor involves the *trans*-β rotamer. For this set of compounds, activity is associated with a stable *trans*-β rotamer lying less than 1 kcal mol^{-1} above the global energy minimum, and lack of activity is a consequence of this conformation being inaccessible at body temperatures.

Introduction

Dopamine (DA), the endogenous ligand of dopaminergic neurotransmission systems involved in a broad range of both central and peripheral physiological responses, may be expected to quite freely adopt many conformations, differing only slightly in energy and separated by low potential energy barriers, which interconvert rapidly at body temperatures. This behaviour has militated against any definite conclusions being reached regarding which rotamer(s) is (or are) involved in the elicitation of its pharmacologic actions, in spite of a fair number of X-ray,[1,2] NMR,[3,4] and theoretical studies.[5–9] Experimental data on the free energy, enthalpy and entropy of the DA–receptor interaction show that receptor binding is dominated by a favourable enthalpy change and that the entropic change is unfavourable.[10] These results indicate that an enthalpically favoured binding mode could help the DA molecule to populate relatively energy-rich conformations. The use of semirigid DA analogues has led to the conclusion that one or both of the *trans*-coplanar rotamers (*cf*. Fig. 1) appear to be involved in the activation of different types of DA receptors, but the possible rôle of each of these conformers is not yet clear.[11]

Studies on structure–activity relationships in open-chain DA analogues and in phenylethylamines generally as dopaminergic ligands have shown that all *N*-monosubstituted analogues are less active than DA at D_1 receptors, with the exception of *N*-methyldopamine (epinine), which is equipotent with the endogenous neurotransmitter.[12] In contrast, in these and in the *N*,*N*-disubstituted derivatives, the well-known "*N*-*n*-propyl phenomenon"—an increase in affinity for the D_2 receptor when the nitrogen atom bears an *n*-propyl group—is apparent.[13] A hydroxy group *meta* to the amine side chain, but not a catechol system, is widely believed to be essential for agonist activity.[14] Ring fluorination of DA at C-2 or C-5 affords analogues which differ little, if at all, from DA as dopaminergic agonists, while 6-fluorodopamine seemed to be somewhat less potent in a dog renal vascular assay.[15] In binding studies, all three fluorodopamines are as potent as dopamine in displacing [^{3}H]spiperone (a selective D_2 receptor antagonist) but the 2- and 6-fluoro analogues are less potent than DA or 5-fluorodopamine in displacing [^{3}H]apomorphine (a relatively unselective agonist which is equipotent with DA at D_1 receptors and several times more so at D_2 receptors).[16] The uptake of these analogues into synaptic vesicles has led to the use of [^{18}F]-fluorinated DAs as false neurotransmitters for positron emission tomographic imaging.[17] It therefore seems that introduction of the small, strongly electronegative fluorine atom at C-6 (and possibly C-2, but not C-5) interferes with the ability of DA to activate one or both of its major receptor types, but has little effect upon the recognition of the DA molecule by its neuronal receptors or transporters.

The introduction of the sterically more demanding, but electronically less disruptive, methyl group yields 2-methyldopamine (2-methylDA), equipotent with the parent molecule, and 6-methyldopamine (6-methylDA), two orders of magnitude less active in stimulating DA-sensitive adenylate cyclase from rat caudate nucleus, a clear reflection of D_1 receptor activation (see Fig. 2).[11] This different behaviour may be tentatively attributed to a direct steric effect of the C-6 (but not C-2) methyl group hindering the drug–receptor interaction, or to an indirect effect arising from destabilization of the pharmacophoric conformation. α-Methyldopamine (α-methylDA) has greatly decreased dopaminergic agonist effects or is quite inactive in some assays.[18] This has been explained as either a steric effect forcing the side chain into a presumably unfavourable perpendicular relationship with the catechol ring,[18] or a direct steric hindrance to interaction with the receptors,[19] but neither of these hypotheses has been examined with quantitative tools. The issue is further confused by the fact that several hydroxylated 2-amino-1,2,3,4-tetrahydronaphthalene (2-aminotetralin) derivatives, which incorporate an α-methyl group into a semirigid ring system, are potent dopaminergic agonists.[11,14]

We have now addressed this problem in terms of a conformational analysis of DA, its α-, 2- and 6-methyl derivatives and their *N*-protonated conjugate acids, using the AM1 semiempirical method[20] and COSMO (conductor-like screening model)[21] to evaluate the effects of an aqueous medium on conformational preferences. A study of the *N*-protonated forms is

 DOI: 10.1039/b100614m

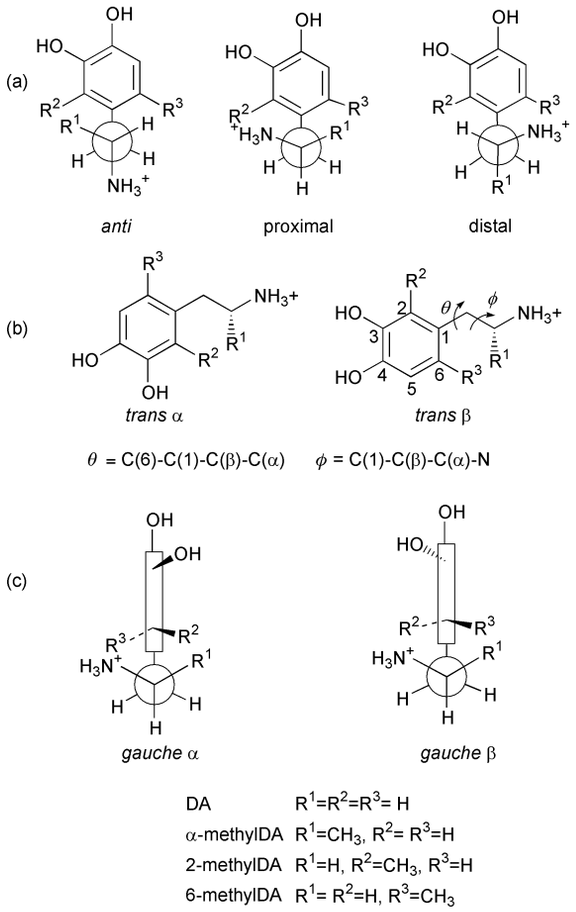

Fig. 1 The different rotamers for the *N*-protonated forms of the compounds: numbering and definition of the dihedral angles (θ and ϕ) used in the conformational study. (a) Perpendicular rotamers correspond to the staggered conformations resulting from rotation about ϕ with $\theta = 90°$, (b) *trans*-coplanar rotamers, (c) *gauche*-coplanar rotamers.

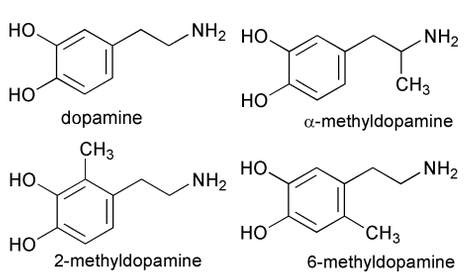

Fig. 2 Structures of the compounds studied.

justified by the fact that DA exists as its conjugate acid to an extent exceeding 95% at physiological pH.[22] Both polar and apolar media are relevant to the conformational profiles of ligands interacting with biological targets such as dopaminergic receptors, because drug molecules must go from an aqueous extracellular environment to a relatively apolar binding site in the receptor protein. Fig. 1 depicts the rotamers of the *N*-protonated forms of the compounds studied in this paper and the dihedral angles θ and ϕ that define the aminoethyl chain conformations.

Results and discussion

Gas-phase calculations

Inspection of Fig. 1 allows the ready identification of steric clashes between the methyl groups and the ammonium or the benzylic methylene group. The AM1 relative energy profiles in the gas phase are shown in Figs. 3 (for the neutral molecules) and 4 (for the *N*-protonated molecules), and the relative energy values for the optimised minima are collected in Table 1. In addition, in Table 2 are gathered the values for the dihedral angles θ and ϕ obtained for the fully optimised rotamers of the compounds.

Table 1 Relative gas-phase energies for optimised structures (kcal mol^{-1}) of dopamine, α-methyldopamine, 2-methyldopamine and 6-methyldopamine

Rotamer[a]	DA	α-MethylDA[b]	2-MethylDA	6-MethylDA
Neutral form				
Distal	0.0	0.0	0.0	0.6
Proximal	0.0	0.2	0.8	0.0
anti	0.3	0.8	0.3	0.4
trans-α	1.2	2.9	5.9	0.9
trans-α frozen	1.3	4.8	9.9	0.9
gauche-α	1.2	1.4 (3.3)	7.1	1.4
trans-β	1.1	2.7	1.1	6.6
trans-β frozen	1.2	4.3	1.2	9.2
gauche-β	1.2	1.4 (3.7)	0.5	7.9
N-Protonated form				
Distal	0.0	0.0	0.0	1.1
Proximal	1.1	0.2	0.6	0.0
anti	3.8	3.7	0.5	3.9
trans-α	2.5	4.7	12.7	5.1
trans-α frozen	2.5	7.3	13.9	5.2
gauche-α	1.2	1.5 (4.0)	8.0	3.0
trans-β	5.1	5.7	5.4	10.5
trans-β frozen	5.1	8.4	5.4	14.2
gauche-β	3.0	3.0 (4.9)	2.0	7.1

[a] The relative energies for the *trans*-coplanar rotamers correspond to the optimised conformations; in the *trans* frozen rotamers the dihedral angles were held fixed at their idealised values. [b] The relative energies for the *gauche* coplanar rotamers are for $-\phi$ (or $+\phi$ in parentheses).

In most cases our calculations allowed full geometry optimisation for each conformer. For both *trans*-coplanar rotamers, however, we performed two kinds of calculations: one with full geometry optimisation and the other with constraint of two dihedral angles (θ and ϕ) which we call the *trans* frozen conformations. The values for the *trans*-α frozen conformation are $\theta = 180°$ and $\phi = 180°$, while the values for the *trans*-β conformation are $\theta = 0°$ and $\phi = 180°$.

In the case of neutral DA, the proximal and distal *gauche* perpendicular rotamers ($\theta \approx 90°$) are the most stable and are isoenergetic, separated from each other by a barrier of less than 2 kcal mol^{-1} and separated from the very slightly less stable *anti* perpendicular form by a similarly low barrier [Table 1, Fig. 3(a)]. Both *trans*-coplanar rotamers and both *gauche*-coplanar rotamers ($\theta \approx 0°$ and 180°) are also practically isoenergetic, and less stable than the perpendicular forms by approximately 1 kcal mol^{-1}, with low (3 kcal mol^{-1}) barriers between the *trans* and *gauche* forms, and a rather higher barrier to rotation through $\phi = 0°$ (≈8 kcal mol^{-1}). The profiles indicate that rotation about ϕ is less hindered when the aromatic ring is perpendicular to the aminoethyl chain.

Of the neutral rotamers of α-methylDA [Fig. 3(b)], the distal *gauche* perpendicular form, which has the C-α methyl group oriented away from the aromatic ring, is the most stable followed closely by the proximal. The *anti* rotamer with the C-α methyl group in a proximal orientation with respect to the *meta*-hydroxy group is the least stable perpendicular form. The barriers remain below 3 kcal mol^{-1}, the highest occurring between the proximal and *anti* rotamers due to approach of the α-methyl group to the aromatic ring. The maximum barrier in the perpendicular profile thus corresponds to a conformation in which the methyl group and the aromatic ring are eclipsed. The coplanar profiles are practically isoenergetic, as in the neutral form of DA. The α-methyl group does not affect the relative energy trends of both coplanar profiles, but it strongly distorts the symmetry of the profiles, producing two different regions.

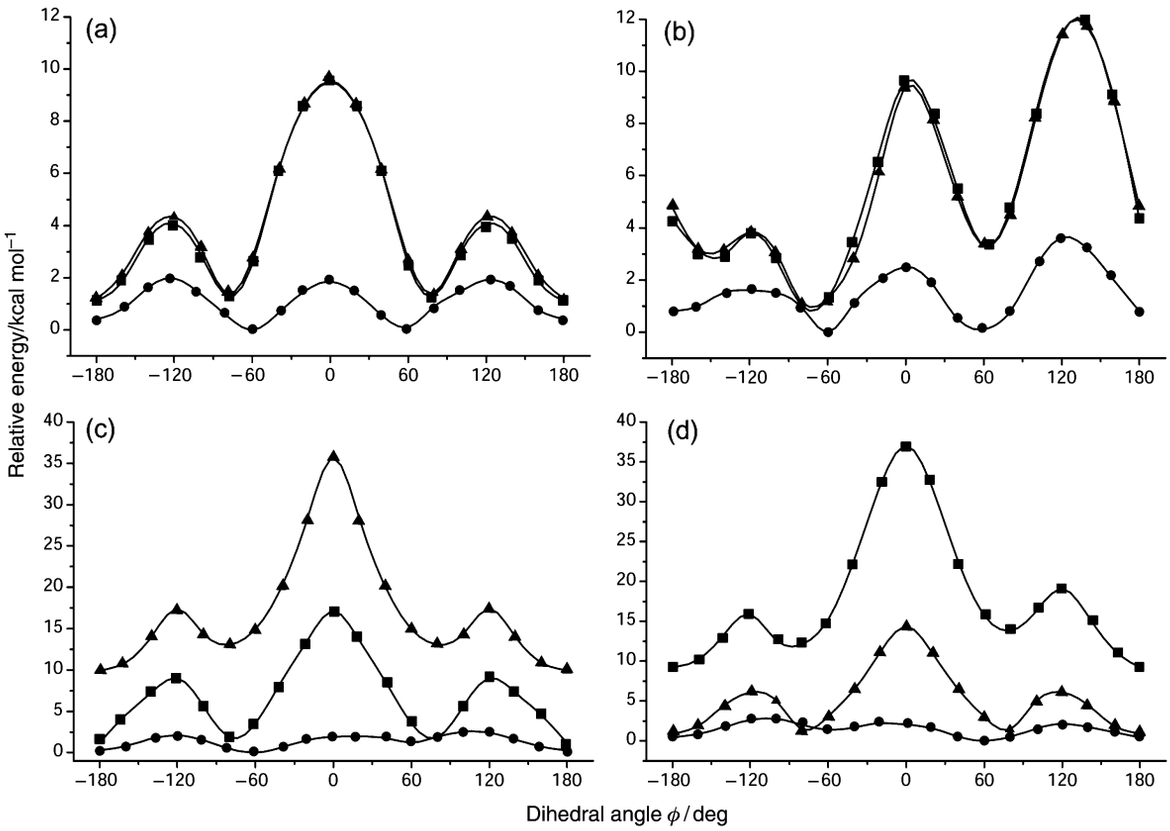

Fig. 3 Energy profile for rotation about dihedral angle ϕ for the neutral forms of the compounds: (a) dopamine, (b) α-methyldopamine, (c) 2-methyldopamine and (d) 6-methyldopamine. The energy of the lowest minimum was used as a reference value for each compound, with θ fixed at 0° (■) for the β conformation, 90° (●) for the perpendicular conformation and 180° (▲) for the α conformation.

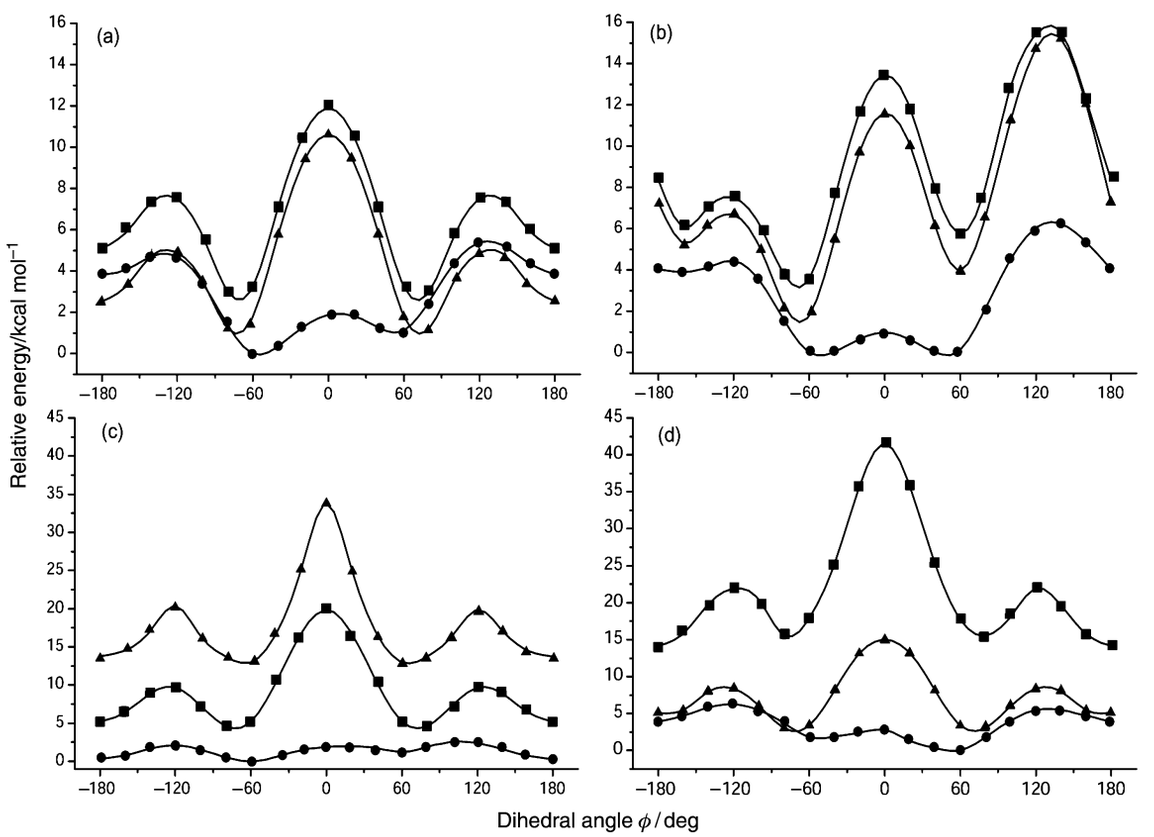

Fig. 4 Energy profile for rotation about dihedral angle ϕ for the *N*-protonated forms of the compounds: (a) dopamine, (b) α-methyldopamine, (c) 2-methyldopamine and (d) 6-methyldopamine. The energy of the lowest minimum was used as a reference value for each compound, with θ fixed at 0° (■) for the β conformation, 90° (●) for the perpendicular conformation and 180° (▲) for the α conformation.

Table 2 Optimised[a] dihedral angles (θ and ϕ in degrees) for the rotamers of the neutral and *N*-protonated forms of compounds in the gas phase

	DA		α-MethylDA		2-MethylDA		6-MethylDA	
Rotamer	θ	ϕ	θ	ϕ	θ	ϕ	θ	ϕ
Distal	94.0	−63.4	91.8	−58.5	88.9	−60.1	102.8	−62.5
	90.3	−56.3	94.9	−60.6	92.7	−50.9	110.4	−50.1
Proximal	90.1	62.3	92.7	51.7	87.9	60.2	92.4	60.4
	95.2	53.5	88.5	45.1	90.3	46.6	92.2	53.3
anti	73.9	−178.7	89.9	−160.8	88.8	−179.1	92.2	178.9
	107.2	176.3	92.0	−178.2	88.5	−177.2	96.1	175.7
trans-α	−179.6	179.7	173.1	−153.8	−168.2	168.0	−179.9	179.9
	−179.5	−179.9	−170.7	−165.0	−172.4	174.5	−175.7	178.0
gauche-α	−177.9	72.3	176 (172)	−68.9 (68.6)	−167.5	73.8	165.8	82.8
	177.6	71.4	180 (170)	−77.6 (67.6)	−162.0	56.1	178.0	71.0
trans-β	3.7	179.7	3.5	−160.2	0.0	−179.8	−3.3	−162.4
	5.1	175.6	2.1	−165.1	1.9	179.7	−12.1	−167.7
gauche-β	4.0	72.2	0.6 (5.6)	−72.7 (58.7)	27.7	56.8	13.3	−101.4
	3.9	68.2	5.6 (3.4)	−73.5 (57.5)	20.6	57.7	22.3	55.6

[a] First row: parameters for the neutral form; second row: parameters for the *N*-protonated form.

The lower energy region in the profiles ($\phi = -180°$ to 0°) corresponds to rotation of the C-α methyl group with regard to the aromatic ring, with the methyl group moving from a *gauche* through a *trans* orientation as the amino group approaches the ring. The other area in the profiles ($\phi = 0°$ to $+180°$) includes the highest energy conformation, with the methyl group eclipsing the ring. The energies of the optimised *trans*-coplanar and the frozen conformations differ by about 2 kcal mol^{-1}, showing that neither of the *trans* rotamers is strictly coplanar due to compression between the methyl group and the aromatic ring (see Table 2). One of the most outstanding characteristics of these profiles is that α-methyldopamine does not present a local minimum at $\phi = -180°$ or $+180°$. Both profiles show a local minimum at $\phi = -160°$ corresponding to a *trans*-pseudo-coplanar rotamer, whereas in the fully optimised conformation this lies at −153° or −161°, with the methyl group in a *gauche* orientation. On the other hand, the most stable conformer in these profiles is a *gauche*-coplanar rotamer ($\phi = -70°$), where the methyl group is in a *trans* position with regard to the aromatic ring, and this conformation only lies 1.4 kcal mol^{-1} above the global minimum that corresponds to the distal perpendicular rotamer. Meanwhile, the other *gauche* coplanar rotamer shown in Fig. 1 ($\phi \approx +70°$) is less stable due to compression between both the methyl and the amino groups with the aromatic ring, and lies 3.3 and 3.7 kcal mol^{-1} above each local minimum. The barrier between both *gauche*-coplanar rotamers is approximately 9 kcal mol^{-1}.

Among the perpendicular rotamers of neutral 2-methyldopamine [Fig. 3(c)] the distal form is the most stable, followed quite closely by the *anti* rotamer, while the proximal form is slightly unfavoured relative to the distal one as a result of the interaction between the methyl group at C-2 and the amino group. The barriers to rotation remain close to 2 kcal mol^{-1}. When the side chain carbon atoms are coplanar with the ring, the *trans*-β and *gauche*-β rotamers are practically identical in energy to the perpendicular forms, but the barrier separating them is about 7 kcal mol^{-1}, and the barrier to rotation through $\phi = 0°$ is considerably higher (≈14 kcal mol^{-1}). With regard to the coplanar α rotamers, either *trans* or *gauche,* the values obtained for the dihedral angle defining the conformation of the aminoethyl chain deviate from coplanarity by values in excess of 10°. This is reflected in an energy difference of 4 kcal mol^{-1}. When the coplanar α rotamers are considered, they are found to be 6–7 kcal mol^{-1} (for the fully optimised conformations) or 9–11 kcal mol^{-1} (for the frozen conformations) less stable than their β counterparts, again owing to steric compression between the methyl and amino groups, with a 7 kcal mol^{-1} barrier between the *trans*-α and *gauche*-α forms and a very high barrier (≈23 kcal mol^{-1}) to rotation through $\phi = 0°$.

For 6-methylDA [Fig. 3(d)] the pattern for the perpendicular conformations is similar to that found for the 2-methyl isomer, but now the proximal rotamer is the most stable. Among the coplanar forms, the α conformations are more stable than the β ones, since here the situation is determined by compression between the C-6 methyl and side chain C-α or amino group hydrogens. The most important difference between the conformational profiles of 2- and 6-methylDA is the relatively low potential energy barrier between the *trans*- and *gauche*-β forms in the latter compound, which is about 4 kcal mol^{-1} (*vs.* 7 kcal mol^{-1} for the former).

On going to the *N*-protonated molecules, the most striking change in the energy profiles is the relative stabilization of the *gauche* forms of the molecules studied which may be attributed to an intramolecular cation–π interaction.[23] In the cases of DA and α-methylDA, the proximal and distal perpendicular rotamers become more stable than their *trans* counterparts by 3–4 kcal mol^{-1}, with smaller changes for the coplanar forms of DA. However, 2-methylDA constitutes an exception in which the *anti* rotamer is practically isoenergetic with both *gauche* perpendicular conformations.

For the *N*-protonated form of DA in the perpendicular profile [Fig. 4(a)], the proximal and distal rotamers are separated by a barrier of less than 2 kcal mol^{-1} and lie about 4 kcal mol^{-1} below the *anti* form. The symmetry shown for the neutral molecule in the perpendicular arrangement is somewhat distorted, but there is a wide potential energy well spanning the region between $\phi = -60°$ to 60° corresponding to a range of energetically similar conformations in which the ammonium group approaches the aromatic ring. Moreover, the *gauche*-α coplanar rotamer is isoenergetic with the proximal perpendicular rotamer. The coplanar profiles are dissociated by *N*-protonation, with the least stable profile for $\theta = 0°$ corresponding to the *trans*-β rotamer. These results are in agreement with the experimental evidence for *gauche* conformers predominating in solution at low pH values.[4]

It should be noted that dopamine is the only compound in this series for which there are no differences in energy between the optimised and frozen or idealised *trans*-coplanar conformations for both coplanar rotamers. In the more stable *trans*-coplanar conformations of the *ortho*-substituted derivatives, *trans*-α for 6-methylDA and *trans*-β for 2-methylDA, the values of the dihedral angles are almost identical in the optimised and idealised forms. In the less stable rotamers, however, these angles differ by more than 10°. In contrast, the optimised *trans* conformations of α-methylDA never reach values close to those for the frozen forms. We will discuss later the consequences of this behaviour on the pharmacophoric conformations.

Table 3 Relative energies (kcal mol^{-1}) of dopamine, α-methyldopamine, 2-methyldopamine and 6-methyldopamine in aqueous medium

Rotamer[a]	DA	α-MethylDA[b]	2-MethylDA[b]	6-MethylDA[b]
Neutral form				
Distal	0.2	0.0	0.2	1.2
Proximal	0.2	1.2	0.7	0.2
anti	0.0	1.5	0.0	0.0
trans-α	0.7	2.4	4.8	1.2
trans-α frozen	0.7	4.9	8.4	1.3
gauche-α	1.4	1.4 (3.9)	6.5	2.2
trans-β	0.7	2.3	0.5	6.2
trans-β frozen	0.7	4.6	1.0	8.1
gauche-β	1.3	1.8 (4.1)	1.1	7.7
N-Protonated form				
Distal	1.3	0.3	0.7	1.9
Proximal	1.2	1.5	2.0	1.3
anti	0.0	0.0	0.0	0.0
trans-α	0.9	1.4	8.8	1.3
trans-α frozen	0.9	3.8	9.2	1.4
gauche-α	1.7	1.5 (3.6)	6.4	3.3
trans-β	0.9	1.5	0.3	6.0
trans-β frozen	0.9	4.4	0.3	8.3
gauche-β	2.0	1.8 (3.9)	1.3	8.9

[a] The relative energies for the *trans*-coplanar rotamers correspond to the optimised conformations; in the *trans* frozen rotamers the dihedral angles were held fixed at their idealised values. [b] The relative energies for the *gauche*-coplanar rotamers are for $-\phi$ (or $+\phi$ in parentheses).

Aqueous medium calculations

There is some controversy regarding the most appropriate methodology to study the influence of the medium on the conformational properties of biologically active molecules, especially for charged species. Using *in vacuo* calculations, the importance of intramolecular electrostatic interactions is likely to be overestimated for charged molecules. On the other hand, an analysis of solvent effects is important to ascertain the distribution and relative energies of the possible solution conformations, where gas-phase stabilizing interactions lose relevance. However, the drug–receptor interaction is believed to occur in highly non-polar microenvironments,[24,25] and this justifies gas-phase calculations even for charged molecules.

Solvent influence on the conformations of dopamine has been analysed using different levels of theory. Urban *et al*.,[7a] using AM1-SM1 methodology, found that the principal influence of the solvent on the neutral and *N*-protonated forms of DA is the stabilization of the *trans* rotamers, especially the *anti* perpendicular conformation which becomes the most stable one in solution, while the proximal and distal perpendicular rotamers are about 1 kcal mol^{-1} less stable. Furthermore, the *trans*-coplanar rotamers are almost isoenergetic with respect to the *anti* perpendicular form. Recently, Nagy *et al*.[8] studied the *N*-protonated perpendicular rotamers of dopamine using a high level of *ab initio* theory (MP2), and Free Energy Perturbation methods through Monte Carlo simulations. The free energy difference calculated at the *ab initio* level shows that the proximal and distal perpendicular conformers (designated as G2 and G1, respectively, by these authors) are isoenergetic, and the *anti* conformation (designated as T) lies about 3.2–5.6 kcal mol^{-1} above them. The calculated total free energy differences between the *anti* and distal conformers is only 0.6 ± 0.3 kcal mol^{-1} in aqueous solution, but the proximal and distal conformations are still more stable than the *anti* form. It may be pointed out that these authors did not consider the coplanar rotamers in their calculations. Although these methods show a preference for the proximal and distal conformations in solution, regardless of the solvent being modelled as a continuum or considering explicit molecules, none of them accounts for the experimentally determined similar populations of *trans* and *gauche* conformers.[4]

While it is important to know which are the most stable rotamers in solution, the main question to be answered is that of which conformation is associated with a particular biological activity, and this may not be the preferred form in aqueous medium or *in vacuo*. Knowledge of the more stable structures allows us to evaluate relative energies and changes in some quantum chemical descriptors. Recently, one of us studied the different rotamers of *N*-protonated DA in the framework of the Hard and Soft Acid and Base (HSAB) Principle as applied to the drug–receptor interaction.[9] That study related the pharmacophoric conformation to chemical hardness, as a global reactivity parameter, and pointed to the relevance of the *trans*-coplanar rotamers to the agonist activity of DA in spite of experimental and theoretical indications that the *gauche* and perpendicular conformations are more stable, both in solution and *in vacuo*.[4,7,8]

In the present investigation the COSMO[21] model implemented in the AM1 semiempirical framework was used to evaluate the influence of the aqueous medium on the intramolecular rotation of the compounds. The relative energies for the optimised rotamers are summarised in Table 3, and the values for the dihedral angles θ and ϕ are presented in Table 4 for the neutral and *N*-protonated species. Fig. 5 shows the energy profiles for the *N*-protonated forms. The profiles for the neutral forms are not shown because there is little difference between the aqueous medium and gas-phase results.

In the case of neutral DA, the most stable rotamer in solution is the *anti* perpendicular, and the proximal and distal perpendicular forms have practically the same energy. The barrier between them remains below 3 kcal mol^{-1}, resembling the gas-phase results. The principal difference between the calculations for the gas phase and the aqueous medium is the relative stabilization of the *trans*-coplanar forms which lie only 0.7 kcal mol^{-1} above the *anti* perpendicular rotamer, while the *gauche*-coplanar forms have similar relative stabilities to those found for the gas phase.

For neutral α-methyldopamine, the distal perpendicular rotamer is not only the most stable, but the proximal and *anti* forms become relatively more energetic than in the gas phase. Also, the coplanar profiles show the same general trends as the gas-phase results, the only difference being the local minimum at $\phi \approx -160°$ that corresponds to a *trans*-pseudocoplanar rotamer, shifted from strict coplanarity by steric compression between the methyl group and the aromatic ring. This conformation shows similar stability to that of the most stable *gauche*-coplanar conformation ($\phi \approx -60°$).

Table 4 Optimised dihedral angles[a] (θ and ϕ in degrees) for compounds in their neutral and *N*-protonated forms in aqueous medium

	DA		α-MethylDA		2-MethylDA		6-MethylDA	
Rotamer	θ	ϕ	θ	ϕ	θ	ϕ	θ	ϕ
Distal	85.5	−60.9	86.2	−61.3	93.6	−62.7	88.3	−63.3
	90.3	−61.7	95.3	−61.2	93.4	−61.8	110.0	−62.8
Proximal	85.7	62.2	94.5	62.3	88.2	60.4	85.3	64.8
	81.3	63.0	94.5	62.3	88.7	50.3	90.0	62.6
anti	90.0	180.0	91.2	−174.9	97.0	−178.5	90.2	179.7
	90.4	180.0	85.9	−165.7	80.3	−179.8	90.0	179.9
trans-α	−179.5	180	174.5	−154.1	−167.5	170.2	−179.8	179.9
	−179.9	−179.6	−170.7	−165.0	−172.3	170.6	−179.6	−179.9
gauche-α	−172.4	78.1	176 (170)	−71.1 (−77.6)	−166.9	74.5	169.1	83.5
	−168.1	66.1	180 (170)	69.5 (70.1)	−161.0	61.7	169.4	82.1
trans-β	0.9	179.7	3	−165.0	0.0	−179.3	−3.4	−160.3
	0.8	179.9	7.9	−164.0	1.9	179.7	−10.0	−167.7
gauche-β	3.9	72.7	1.8 (4.1)	−81.9 (62.4)	22.7	60.1	13.6	−101.9
	11.3	69.1	−3.9 (1.8)	−68.9 (60.1)	7.6	70.3	10.8	−84.4

[a] First row: parameters for the neutral form; second row: parameters for the *N*-protonated form.

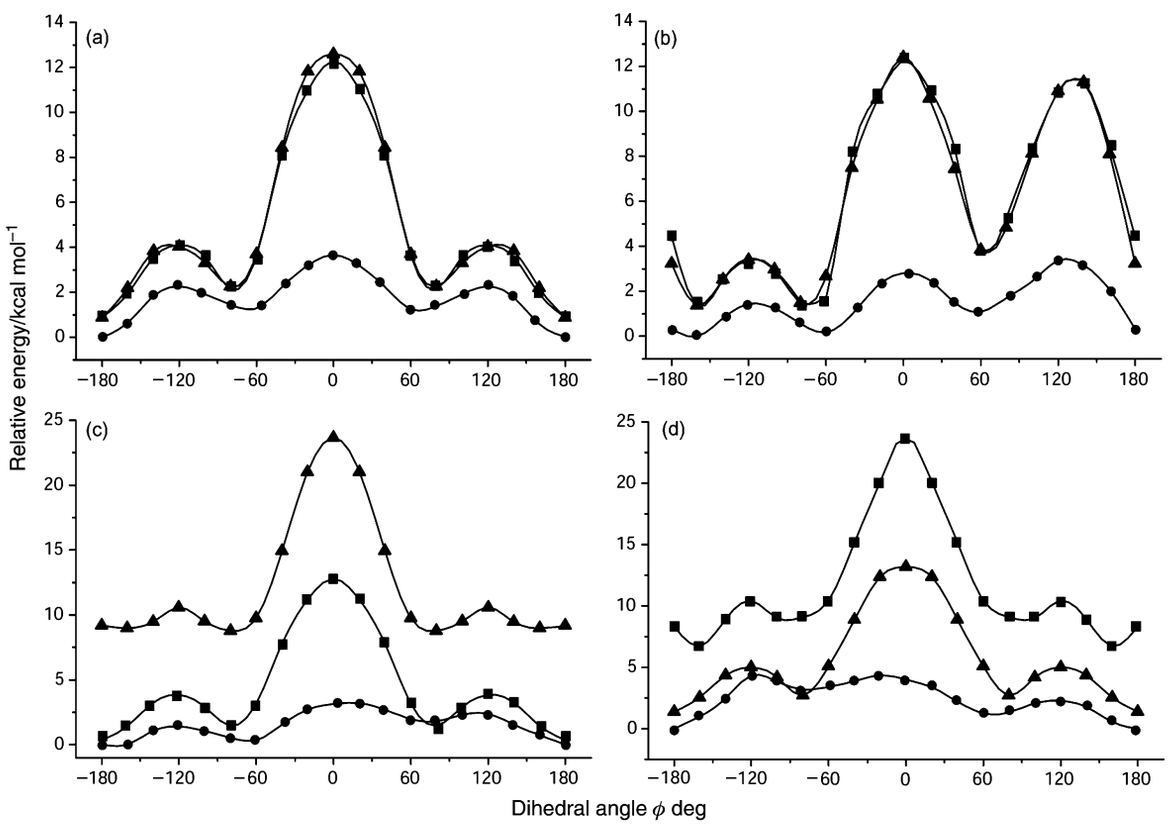

Fig. 5 AM1-COSMO energy profile for rotation about dihedral angle ϕ for the *N*-protonated forms of the compounds: (a) dopamine, (b) α-methyldopamine, (c) 2-methyldopamine and (d) 6-methyldopamine. The energy of the lowest minimum was used as a reference value for each compound, with θ fixed at 0° (■) for the β conformation, 90° (●) for the perpendicular conformation and 180° (▲) for the α conformation.

The *ortho*-methylated compounds in the neutral form again show the same trends in aqueous medium as the gas-phase results. The only significant differences occur in the coplanar conformational profiles. For both compounds, the less stable profiles (α for 2-methylDA and β for 6-methylDA) are less energetic than their gas-phase counterparts, but they are still quite unstable compared to their perpendicular companions. The local minima for the *trans*-α coplanar rotamers are shifted again from $\phi = \pm 180°$ to $-160°$, and lie about 6 kcal mol^{-1} above the energy of the most stable rotamer of each compound.

In the case of the *N*-protonated molecules, the intermolecular solvation process and the intramolecular interaction between the aromatic ring and the positively charged ammonium group compete. The most outstanding differences between the gas-phase results and the aqueous medium calculations are for the conjugate acids of DA and α-methyl-DA. The results obtained here with the AM1-COSMO model for *N*-protonated DA are similar to those obtained by Urban *et al*. using the AM1-SM1 model.[7a]

In *N*-protonated DA the aqueous medium stabilizes the *anti* rotamer with regard to the distal and proximal conformers [see Fig. 5(a)]. The relevance of the solvation process is clearly shown in the perpendicular profile, particularly in the region between $\phi = -60°$ and $+60°$. In the gas-phase results this area is a fairly flat, wide valley of potential energy where the intramolecular interaction stabilizes the distal and proximal conformers in which the ammonium group faces the aromatic ring. On the contrary, when the solvation process dominates, a barrier of about 3 kcal mol^{-1} arises between the proximal and distal conformers, which are 1.3 kcal mol^{-1} less stable than the *anti* rotamer. Another difference is that in aqueous medium the perpendicular profile is symmetrical, with identical relative

energies for the proximal and distal conformers. The coplanar profiles are also quite symmetrical and practically identical, while in the gas phase the α profile is lower in energy than the β. It is also noteworthy that the preferred *trans*-coplanar rotamer lies only 0.9 kcal mol^{-1} above the *anti* conformation. It should be borne in mind that the *trans*-coplanar conformations approximate the postulated pharmacophoric conformations for the different receptor subtypes. Our results show the accessibility of these conformations from the global minimum in the gas phase and even more so in the aqueous medium calculations.

Our results for *N*-protonated α-methylDA in aqueous medium [Fig. 5(b)] show similar trends to those observed for *N*-protonated DA. The perpendicular profile is the most stable, and the coplanar profiles become isoenergetic. The *anti* form is the most stable rotamer, and the proximal becomes the least stable rotamer in the perpendicular profile, with rotational barriers below 4 kcal mol^{-1}. In the overlapping coplanar profiles (α and β) the lowest energy region lies between $\phi = -180°$ and $-60°$ with a barrier of about 2 kcal mol^{-1} between the practically isoenergetic *trans* (shifted to $\phi = -160°$) and the more favoured *gauche* rotamers. To reach the less favoured *gauche* rotamers considerable barriers (in excess of 10 kcal mol^{-1}) must be overcome, as in the gas phase.

For *N*-protonated 2-methylDA [Fig. 5(c)], the perpendicular energy profile in aqueous medium is almost identical to that seen for the gas phase. The β-coplanar profile is lowered to the extent that the *trans* and *gauche* rotamers become isoenergetic with the *anti* and the proximal perpendicular rotamers, and the barriers separating them are also reduced to about 3 kcal mol^{-1}. On the other hand, while the α relative energy profile in aqueous solution indicates greater stability than the gas-phase results, the practically identical minima corresponding to the *trans*-α and *gauche*-α rotamers remain more than 9 kcal mol^{-1} above the global minimum.

N-Protonated 6-methylDA in aqueous medium [Fig. 5(d)] presents similar trends to those seen in the gas-phase results, but the *anti* perpendicular conformer becomes the most stable by about 2 kcal mol^{-1}. As in the gas phase, the α rotamers differ from their perpendicular counterparts by not more than 2 kcal mol^{-1}, with the *gauche*-α conformer slightly more stable than the distal form. Interestingly, the relatively energetic β-coplanar profile exhibits two equivalent minima which lie about 7 kcal mol^{-1} above the *anti* conformation.

The results in aqueous solution show that the energies of the *trans*-β rotamers of DA and 2-methylDA differ by less than 1 kcal mol^{-1}, and furthermore the *trans*-β conformation of 2-methylDA is isoenergetic with the global minimum of the *N*-protonated form in aqueous solution. For the inactive compounds α- and 6-methylDA the corresponding rotamers lie about 4 and 8 kcal mol^{-1} above the global minimum.

It is worth pointing out that while in the perpendicular conformations the proximal and distal energy minima occur at $\phi \approx -60°$ and $+60°$, in the coplanar conformations the *gauche* minima are shifted to appreciably larger ϕ values, even approaching 90° in DA and its *ortho*-methyl derivatives (see Table 4).

When these results are viewed in the light of the equipotency of 2-methylDA and DA at D_1 receptors and the very low activity of 6-methylDA, it seems clear that the most significant distinguishing feature is the high relative energy of the whole β-coplanar rotational profile of the latter compound, both in its neutral and protonated forms and regardless of the polarity of the medium. This makes the *trans*-β and *gauche*-β-coplanar rotamers practically inaccessible in the 6-methylDA molecule. Consequently, one of these conformations may be presumed to be the one which leads to D_1 receptor activation in the cases of DA and its 2-methyl derivative, which may easily adopt either. Our results, therefore, support the contention—based on the comparison *in vitro* of the dopaminergic activities of 5,6-dihydroxy- (α-like) and 6,7-dihydroxy- (β-like) 2-amino-1,2,3,4-tetrahydronaphthalenes (aminotetralins)—that the pharmacophoric conformation of DA and dopaminergic agonists at the D_1 receptor approximates the *trans*-β rotamer.

The fact that (*R*)-(+)-6,7-dihydroxyaminotetralin (6,7-DHAT) is four times more potent than DA itself would seem to indicate not only that its molecular shape is best able to mimic the active conformation of DA at the D_1 receptor, but also that there may be a favourable lipophilic or hydrophobic interaction of the CH_2–CH_2 bridge of the tetralin ring with the active site of this receptor. When this bridge is cut, leaving the methyl group either of 6-methylDA (a mimic of the C-4 CH_2 group of the tetralin ring system) or of α-methylDA (a mimic of the C-3 CH_2 group), the *in vitro* efficacy is lost, and this may now be explained by the loss in both cases of the ability of the ethylamine side chain to adopt a favourable conformation similar to that of the semirigid 6,7-DHAT. Such a conformation in the case of α-methylDA corresponds to $\theta = 0°$ and ϕ values between 100° and 140°, the region of highest energy for this compound both in the gas phase and in aqueous solution. In 6-methylDA, although this conformational range corresponds to a region of relative stability in the β-coplanar profile, it still lies 5–7 kcal mol^{-1} above the preferred α and perpendicular profiles. Unlike the former cases, the methyl group on the ring of 2-methylDA does not interfere at all with the adoption of this presumably pharmacophoric conformation. It may be pointed out that in this conformation of 2-methylDA the methyl group at C-2 occupies a similar position to a substituent at C-8 in 6,7-DHAT derivatives. In this regard, it is significant that the 8-chloro- and 8-fluoro analogues of 6,7-DHAT are selective D_1 agonists.[11,12,26]

The pharmacophoric model of the D_2 receptor subtype has been postulated to coincide with the *trans*-α rotamer.[11,12,27] 6-MethylDA shows the same trends in the relative stabilities of its α- and β-coplanar rotational energy profiles as 2-methylDA exhibits for its β and α profiles, respectively, both in the gas phase and in aqueous solution. Therefore, if the former hypothesis is true, our results predict that 6-methylDA should be an agonist at the D_2 receptor and that 2-methylDA should be inactive, based on the relative stabilities found for their *trans*-α and *trans*-β rotamers.

Nagy *et al.* have suggested quite recently that *N*-protonated DA, bonded to a chloride ion through a bridging water molecule, may constitute an ion pair with an increased probability of adopting a *gauche* conformation, and that this cluster might be stable in a receptor cavity or when penetrating a biomembrane.[8] We propose that most DA molecules in the synaptic cleft, whether *N*-protonated or not, presumably adopt a distal or proximal perpendicular conformation (G1 or G2, respectively, in the cited paper) most of the time, with a smaller solvent-accessible surface than the *anti* conformation (T in the reference). This compact *gauche* rotamer may be in a better position to cross the receptor's extracellular loops, enter the active site or cross a lipid membrane. Analysis and multiple alignment of the amino acid sequences of G-protein coupled receptors indicate that the extracellular loops contain hydrophilic side chains, with many charged ones.[24,25] These may act as counterions and provide a path for the *N*-protonated DA molecule on its way to the interior of the receptor macromolecule, making it unnecessary to drag a chloride counterion and a water molecule through this relatively apolar microenvironment. When the DA molecule arrives at less polar regions, *i.e.* in a receptor cavity, it may be expected to spontaneously adopt a conformation allowing it to maximise its interactions with the receptor binding site, with the restrictions discussed in the foregoing paragraphs.

Pharmacophoric analysis

The process of pharmacophoric recognition involves a three-dimensional interaction between the ligand (an endogenous

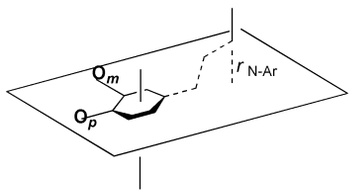

Fig. 6 Pharmacophore map for D_1 and D_2 agonists.

substance or a drug molecule) and the receptor binding site. The topography of the binding site must be complementary to the shape of the ligand molecule, with particular regard to the distribution of electron density in three-dimensional space around the (usually small) ligand and its binding site. These ideas are implicit in the proposals of the D_1-dopaminergic agonist pharmacophore to include the *trans*-β rotamer of DA,[28] and the D_2 pharmacophore to include the *trans*-α rotamer.[27]

There are many topographical models of the binding site of the dopaminergic receptors.[11,12,14,27,28] Initially these were based exclusively on analyses of structure–activity relationships, to which CoMFA (comparative molecular field analysis) and molecular modelling have contributed in the last few years.[27,28] Based on structure–activity relationships, and before different types of DA receptors were recognized, Goldberg *et al.* suggested that a *trans*-coplanar rotamer of the neurotransmitter is the active conformer for vascular DA receptors, postulating hydrogen bonds between the receptor on one hand and the amino group and the catechol moiety of DA on the other.[29] Shortly thereafter McDermed *et al.* put forth their model accounting for the enantioselectivity of dopaminergic agonists.[30] These authors suggested that the two most important binding sites in the DA receptor interact with the amino group and the hydroxy group *meta* to the aminoethyl side chain in an orientation corresponding to the *trans*-α rotamer of DA. Nichols described a model similar to that of McDermed, which included enantioselective–stereoselective nitrogen and *meta*-hydroxy binding sites.[31] Recently, Mottola *et al.* proposed their model of the D_1 receptor pharmacophore based on DA in its *trans*-β conformation and on adding an accessory ring system.[28] Wilcox *et al.*, using CoMFA methodology, stressed the importance of the distance between the *meta*-hydroxy group and the amine nitrogen atom, as well as the elevation of the quaternary nitrogen centre above the mean plane of the catechol ring.[27] These distances are different for the postulated pharmacophores of both main DA receptor types.

In general, the pharmacophoric map for dopaminergic agonists may be said to involve four main points: the nitrogen atom, the *meta*- and *para*-hydroxy oxygen atoms, and the centroid of the aromatic ring (see Fig. 6). The three latter points define the ring plane, and the distance of the nitrogen atom from this plane is also relevant. This description may be simplified specifying the distances between the nitrogen atom and each oxygen atom ($r_{N\text{–}Om}$ and $r_{N\text{–}Op}$), and the distance of the nitrogen from the plane of the aromatic ring ($r_{N\text{–}Ar}$). Fig. 7 shows the dependence of $r_{N\text{–}Om}$, $r_{N\text{–}Op}$ and $r_{N\text{–}Ar}$ on the value of ϕ, with θ fixed at 0°, 90° and 180°, in the aqueous medium calculations for the *N*-protonated form of DA.

The results of the aqueous medium and the gas-phase calculations are similar regarding molecular geometries, because the molecules show more significant changes in their relative energies than in their interatomic distances. There is little change in bond lengths, bond angles and dihedral angles, and consequently there is no great effect on the pharmacophoric distances for these rotamers comparing gas-phase and aqueous medium calculations. The greatest differences are seen for the (ideally) *trans*-coplanar conformations where the aminoethyl side chain is not actually coplanar with the ring. In Table 5, we have summarised the results for the $r_{N\text{–}Om}$ and $r_{N\text{–}Op}$ distances for the *trans* rotamers of the *N*-protonated form of DA and its derivatives. The distances found for the fully optimised and the

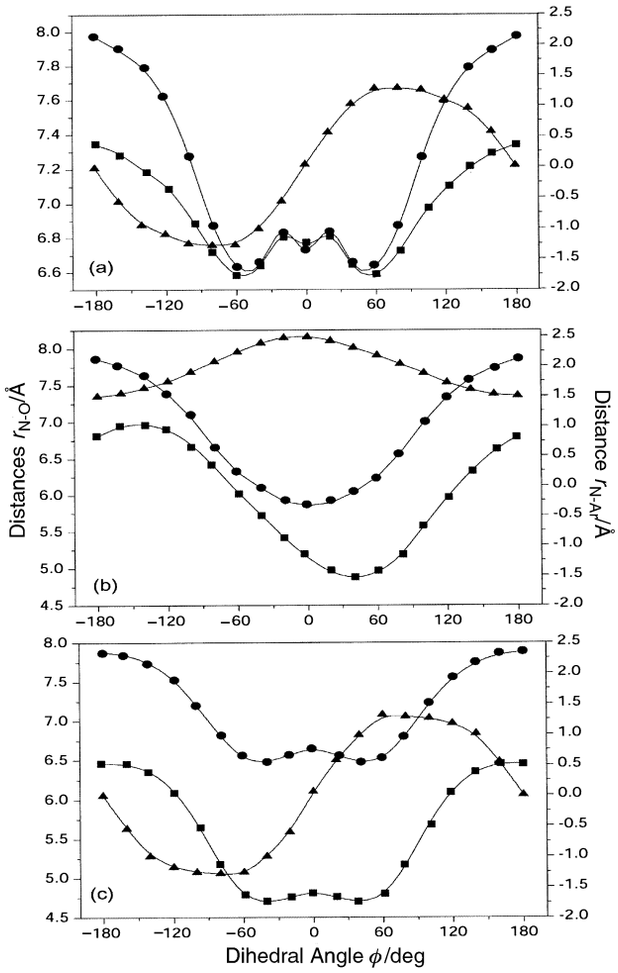

Fig. 7 Distance profiles (Å) for the *N*-protonated form of dopamine, (a) β conformation profile ($\theta = 0°$), (b) perpendicular conformation profile ($\theta = 90°$) and (c) α conformation profile ($\theta = 180°$). $r_{N\text{–}Om}$ (■), $r_{N\text{–}Op}$ (●) and $r_{N\text{–}Ar}$ (▲).

frozen, idealised conformations are shown for the *trans*-coplanar rotamers. It may be clearly seen that the these distances behave differently for the coplanar and the perpendicular profiles. In addition, we included results from the paper by Mottola *et al.*[28] Our definitions of the interatomic distances differ from those published in that study, but the trends are similar.

For the active compounds DA and 2-methylDA, the distances found are in good agreement with the pharmacophoric structure postulated by Mottola *et al.*[28] Moreover, the presumed pharmacophoric conformation is accessible both in solution and in the gas phase. In the case of the inactive compounds, there is agreement in the distances for the corresponding rotamers, but these are less stable and are separated by considerable barriers from neighbouring conformers.

Moreover, we suggest that 6-methylDA should be an agonist at D_2-dopaminergic receptors. Our analysis of the pharmacophoric distances agrees with this hypothesis, which also predicts that 2- and α-methylDA should be inactive. In addition, we conclude that the $r_{N\text{–}Op}$ distances for the *trans* perpendicular and coplanar rotamers remain constant for all the compounds, while the $r_{N\text{–}Om}$ distance varies between 6.3 and 7.4 Å. The structure-activity relationship data[11,12,14,26] for DA agonists show the importance of the catechol ring for the D_1 receptor, while for the D_2 receptor only one hydroxy group, congruent with the *m*-hydroxy group of DA, appears to be necessary. This is the case of 5- or 7-hydroxy-2-amino-1,2,3,4-tetrahydronaphthalenes, from which some of the most selective D_2 agonists are derived. Conversely, pharmacological studies of aryl-3-benzazepines show that two hydroxy groups are

Table 5 Selected distances[a] (Å) between the nitrogen atom and the catechol ring oxygen atoms from optimised structures for the compounds

Compound	*anti*		*trans*-α		*trans*-β	
	r_{N-Om}	r_{N-Op}	r_{N-Om}	r_{N-Op}	r_{N-Om}	r_{N-Op}
DA	6.84	7.81	6.5	7.9	7.3	7.9
DA[b]	—	—	—	—	7.4	7.8
α-MethylDA	7.01	7.82	6.9	8.1	7.5	8.0
			6.5	7.9	7.3	8.1
2-MethylDA	7.02	7.82	7.0	8.0	7.4	7.9
			6.6	8.1	7.4	7.9
6-MethylDA	6.81	7.80	6.4	7.9	7.2	8.1
			6.4	7.9	7.3	8.0
DHX[b]	—	—	—	—	7.4	7.9
SFX89629[b]	—	—	—	—	7.1	7.9
A70108[b]	—	—	—	—	7.4	8.0

[a] For the *trans*-coplanar rotamers, the first row corresponds to the aqueous medium optimised rotamers and the second row to the frozen or idealised rotamers. [b] From ref. 28 and structures in Fig. 8.

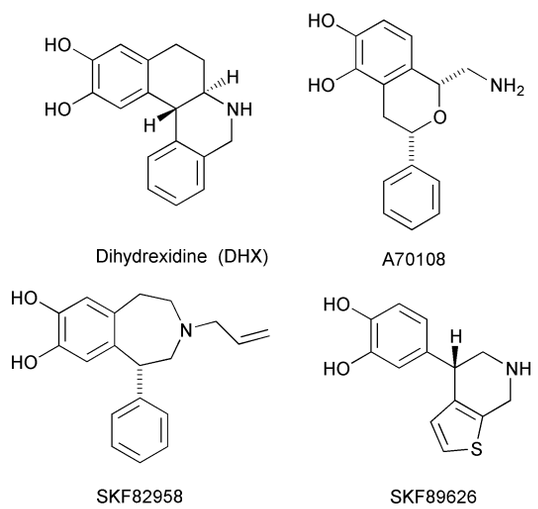

Fig. 8 Structures of some selective D_1 dopaminergic agonists.

essential for D_1-dopaminergic agonist activity (*cf.* SFK-82958 in Fig. 8).

Analysing Fig. 7, an immediate conclusion is that the r_{N-Ar} distances show the same trends for both coplanar profiles, while the perpendicular profile shows relatively small variations with the highest elevation of the nitrogen atom above the aromatic plane for the unstable, eclipsed synclinal conformation and the lowest for the *anti* conformation.

If we compare the homologous regions in the α and β profiles between $\phi = \pm 140°$ and $\pm 180°$, where the *trans*-coplanar rotamers lie, we note that the differences in the N–O distances are quite small and the most important change is in the nitrogen–*meta*-hydroxy group distance. A small difference may have a strong effect on the drug–receptor interaction energy, however. Wilcox *et al.*[27] have pointed out the importance of the height to which the charged nitrogen atom rises above the plane of the aromatic ring. While in their model for the D_1 receptor this deviation from planarity is 1.25 to 1.4 Å, for the D_2 receptor it is less than 0.5 Å. Our work shows that small departures from coplanarity of the aminoethyl chain with respect to the aromatic ring have a strong effect on r_{N-Ar} for both coplanar profiles. Still, the β-coplanar profile is the one where the three descriptors are most sensitive to variations in the dihedral angles used in this study.

An analysis of the hardness variation for the coplanar and perpendicular conformations of the *N*-protonated form of dopamine has shown that the α and β hardness profiles remain constant throughout the $\phi = \pm 140°$ to $\pm 180°$ region corresponding to the *trans*-coplanar rotamers.[9] Hardness is a parameter which may be associated with electrostatic interactions. Consequently, in this region relatively large conformational changes should not cause any important changes in the overall reactivity of the compound, although they should produce significant variation in the structure of the pharmacophore, and consequently in its ability to interact with the receptor.

Conclusions

Although previous studies have emphasised the conformational preferences of DA in aqueous or non-aqueous media, our analysis of DA and some of its methylated congeners with known activity at the D_1 receptor leads to the conclusion that accessibility and not absolute stability of the pharmacophoric conformation determines the power of some of these compounds to activate the receptor. When the potential energy difference separating the pharmacophoric (in this case, *trans*-β) conformation from an energetically preferred (perpendicular) rotamer is small enough, of the order of 1 kcal mol^{-1}, the molecule is able to bind effectively to the receptor binding site. This is true for DA and 2-methylDA. When such an energy difference is greater, as in α-methyl- and 6-methylDA, activation cannot occur. Previous pharmacophoric analyses of D_2 receptor ligands have indicated that the *trans*-α conformation may be relevant to receptor activation. On the basis of the energy profiles shown here, we predict that 6-methylDA may be a D_2 receptor agonist, but that neither 2-methyl- nor α-methylDA should activate this receptor.

Earlier work indicating that the perpendicular rotamers of DA are preferred to the coplanar ones has now been extended to the methylated congeners of DA. In all these compounds, *in vacuo* calculations indicate that the proximal and distal forms are almost isoenergetic with or more stable than the *anti* form, for both the neutral and the *N*-protonated molecules. In a simulated aqueous medium this situation is reversed, with the *anti* form being generally preferred. Nevertheless, even in a polar environment, the proximal and distal perpendicular rotamers appear to be readily accessible. Considering the abundance of anionic sites in the extracellular loops and in the interior of the putative seven transmembrane domain of DA receptors, which may act as counterions and provide a path for the charged ligand molecules, presumably in one of their more compact, harder, and thus less reactive conformations,[9] the close protonated DA–chloride ion pair separated by a water molecule (which has been suggested to exist in a receptor cavity)[8] does not seem to be a necessary arrangement for DA to reach its site of action.

Details of calculations

All calculations were performed with the AM1 Hamiltonian[20] as a part of the MOPAC 97[32] program implemented in the WinMopac v2.0 program.[33] The relative energies were

calculated from the difference between the total energy for each rotamer with respect to the lowest minimum found for each compound. The structures were optimised using the EF minimisation algorithm and the PRECISE and GNORM keywords.

Two dihedral angles were used to describe the conformations: θ and ϕ (defined in Fig. 1). Dihedral angle θ was set at three different values corresponding to the *trans*-coplanar [$\theta = 0°$ (β) or 180° (α)] and perpendicular ($\theta = 90°$) conformers. In each case, dihedral angle ϕ was varied in 20° increments from −180° to +180°. At each point a complete geometry optimisation was performed with θ and ϕ frozen at their respective values. The water solution simulations were carried out using COSMO with the keywords NSPA = 42 and EPS = 78.4.[21]

Acknowledgements

This work was supported by a CONICYT fellowship and grant PG/038/1997 from the Departamento de Postgrado y Postítulo, Universidad de Chile (M. P. A.) and by the Presidential Chair in Sciences (Chile, B. K. C.). We are grateful to Dr M. A. Leiva for use of the WinMopac software.

References

1 R. Bergin and D. Carlström, *Acta Crystallogr.*, *Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1968, **24**, 1506.
2 J. Giesecke, *Acta Crystallogr.*, *Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1980, **36**, 178.
3 T. M. Bustrad and R. S. Egan, *Tetrahedron*, 1971, **27**, 4457.
4 P. Solmajer, D. Kocjan and T. Solmajer, *Z. Naturforsch.*, *C: Biosci.*, 1983, **38**, 758.
5 B. Pullman, J. L. Coubeils, Ph. Courrière and J.-P. Gervois, *J. Med. Chem.*, 1972, **15**, 17.
6 R. Katz, S. R. Heller and A. E. Jacobson, *Mol. Pharmacol.*, 1973, **9**, 486.
7 (*a*) J. J. Urban, C. J. Cramer and G. R. Famini, *J. Am. Chem. Soc.*, 1992, **114**, 8226; (*b*) J. J. Urban and G. R. Famini, *J. Comput. Chem.*, 1993, **14**, 353.
8 P. I. Nagy, G. Alagona and C. Ghio, *J. Am. Chem. Soc.*, 1999, **121**, 4804.
9 M. P. Aliste, *THEOCHEM*, 2000, **507**, 1.
10 G. J. Kilpatrick, N. El Tayar, H. van der Waterbeemd, P. Jenner, B. Testa and C. D. Marsden, *Mol. Pharmacol.*, 1986, **30**, 226.
11 A. S. Horn, in *Comparative Medicinal Chemistry. The Rational Design*, *Mechanistic Study and Therapeutic Application of Chemical Compounds*, ed. C. Hansch, P. G. Sammes and J. B. Taylor, Pergamon, Oxford, 1990, vol. 3, p. 229.
12 C. Kaiser and T. Jain, *Med. Res. Rev.*, 1985, **5**, 145.
13 M. E. Goldman and J. W. Kebabian, *Mol. Pharmacol.*, 1984, **25**, 18.
14 J. G. Cannon, *Prog. Drug Res.*, 1985, **29**, 303.
15 L. I. Goldberg, J. D. Kohli, D. Cantacuzène, K. L. Kirk and C. R. Creveling, *J. Pharmacol. Exp. Ther.*, 1980, **213**, 509.
16 Y. Nimit, D. Cantacuzène, K. L. Kirk, C. R. Creveling and J. W. Daly, *Life Sci.*, 1980, **27**, 1577.
17 G. Eisenhofer, D. Hovevey-Sion, I. J. Kopin, R. Miletich, K. L. Kirk, R. Finn and D. S. Goldstein, *J. Pharmacol. Exp. Ther.*, 1989, **248**, 419.
18 J. G. Cannon, Z. Perez, J. P. Long, D. B. Rusterholz, J. R. Flynn, B. Costall, D. H. Fortune and R. J. Naylor, *J. Med. Chem.*, 1979, **22**, 901.
19 P. W. Erhardt, *Acta Pharm. Suec.*, 1983, suppl. 2, 56.
20 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
21 A. Klamt and G. Schüürmann, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 799.
22 C. R. Ganellin, *J. Med. Chem.*, 1977, **20**, 579.
23 J. C. Ma and D. A. Dougherty, *Chem. Rev.*, 1997, **97**, 1303.
24 D. Donnelly, J. B. C. Findlay and T. L. Blundell, *Recept. Channels*, 1994, **2**, 61.
25 J. A. Bikker, S. S. Trumpp-Kallmeyer and C. Humblet, *J. Med. Chem.*, 1998, **41**, 2911.
26 H. E. Katerinopoulos and D. I. Schuster, *Drugs Future*, 1987, **12**, 223.
27 R. E. Wilcox, T. Tseng, M. Y. K. Brusniack, B. Ginsburg, R. S. Pearlman, M. Teeter, C. DuRand, S. Starr and K. A. Neve, *J. Med. Chem.*, 1998, **41**, 4385.
28 D. M. Mottola, S. Laiter, V. J. Watts, A. Tropsha, S. D. Wyrick, D. E. Nichols and R. Mailman, *J. Med. Chem.*, 1996, **36**, 285.
29 L. I. Goldberg, J. D. Kohli, A. N. Kotake and P. V. Volkman, *Fed. Proc.*, 1978, **37**, 2396.
30 J. D. McDermed, H. S. Freeman and R. M. Erris, in *Catecholamines: Basic and Clinical Frontiers*, ed. E. Usdin, L. J. Kopin and J. Barchas, Pergamon Press, New York, 1979, vol. 1, p. 568.
31 D. E. Nichols, in *Dopamine receptors*, ed. C. Kaiser and J. W. Kebabian, ACS Symposium Series 224, American Chemical Society, Washington DC, 1983, p. 201.
32 MOPAC 97, Quantum Chemistry Program Exchange (QCPE), Program Number 455, Bloomington, IN, 1984.
33 WinMopac v2.0, Fujitsu 1998, Japan.