Articles

Molecular Electrostatic Potential of Orthopramides: Implications for Their Interaction with the D-2 Dopamine Receptor

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The electronic properties of orthopramides, a group of selective D-2 dopamine receptor antagonists, were investigated by calculating molecular electrostatic potentials (MEP) of model compounds with the ab initio STO-3G MO method. The various substitution patterns of the aromatic ring are characterized by a positive region comprising the H-bonded 2-methoxy group and ring positions 2, 3, and 4 and a negative region comprising the CONH group, 5-substituent, and ring positions 5 and 6. The regions of positive and negative potential are separated by a "curtain" running along the longitudinal axis of the molecule. At shorter distances from the plane of the aromatic ring (1.75 and 2.0 Å), this "curtain" is quite sinuous, but at greater distances (2.5 and 3.0 Å) it tends toward rectilinearity. We postulate that this longitudinal separation, together with the single positive maximum and the three negative minima perceptible at 3.0 Å, constitute a *distance pharmacophore* responsible for the recognition and proper alignment of the ligand. The more complex MEP at 1.75 and 2.0 Å are equated with a *contact pharmacophore*. Comparison of the MEP of orthopramides and dopamine reveals some analogies and suggests a possible mode of binding of these antagonists to the D-2 receptor.

Substituted *o*-methoxybenzamides (substituted *o*-anisamides, orthopramides) and a number of closely related analogues are a group of dopamine (DA) receptor antagonists displaying neuroleptic, antipsychotic, thymoanaleptic, antidyskinetic, antimanic, antiemetic, and antiulcer effects, as well as being useful in some cases for nonhormonal therapy of menopause disorders.[1] The variety of active congeners is considerable, and a number of representative compounds are presented in Chart I.[2-4] The mechanisms of action of these drugs are complex and far from being fully elucidated. At the molecular level, it is accepted that they act selectively on a subpopulation of DA receptors not linked to adenylate cyclase, the so-called D-2 receptors.[5-7] However, pharmacological and clinical differences also suggest poorly understood selectivities at the level of tissue and organ distribution. Molecular structural properties such as electronic and stereochemical features must account for these various selectivities.

Lipophilicity plays an as yet poorly understood role in distribution and binding.[3,8,9] We believe that the conformational behavior of these compounds is a critical factor. Theoretical and experimental conformational analysis[10-12] of aminoethyl and pyrrolidine derivatives showed these to exist as mixtures of extended and folded conformers, while 4-piperidine derivatives are in the extended form[13] as must be the novel 3-nortropane derivatives (see Chart I). An intramolecular H bond between the amide H atom and the methoxy O atom is found to exist in the vacuum,[10] in the crystal,[14,15] and in nonpolar media but not in aqueous solution.[12] This H bond creates a virtual six-membered ring which we postulated[13] to bind to the α region of the receptor model topographically defined by Humber and colleagues.[16] As a consequence, we[13] and others[3] regarded the distance between the virtual cycle and the basic nitrogen atom as a major pharmacophoric element which could correspond to the distance existing in extended dopamine between the aromatic ring and the nitrogen atom. However, the postulated[13] correspondence between the virtual ring of orthopramides and the aromatic ring of dopamine implies that these regions show close analogies in their electronic structure.

Molecular electrostatic potentials (MEP) provide a highly informative means of assessing the electronic structure of molecules, particularly when biological recognition processes are involved. Thus one goal of the present MEP study is to examine the region of the virtual cycle in orthopramides and to compare it with the aromatic region of dopamine.[17]

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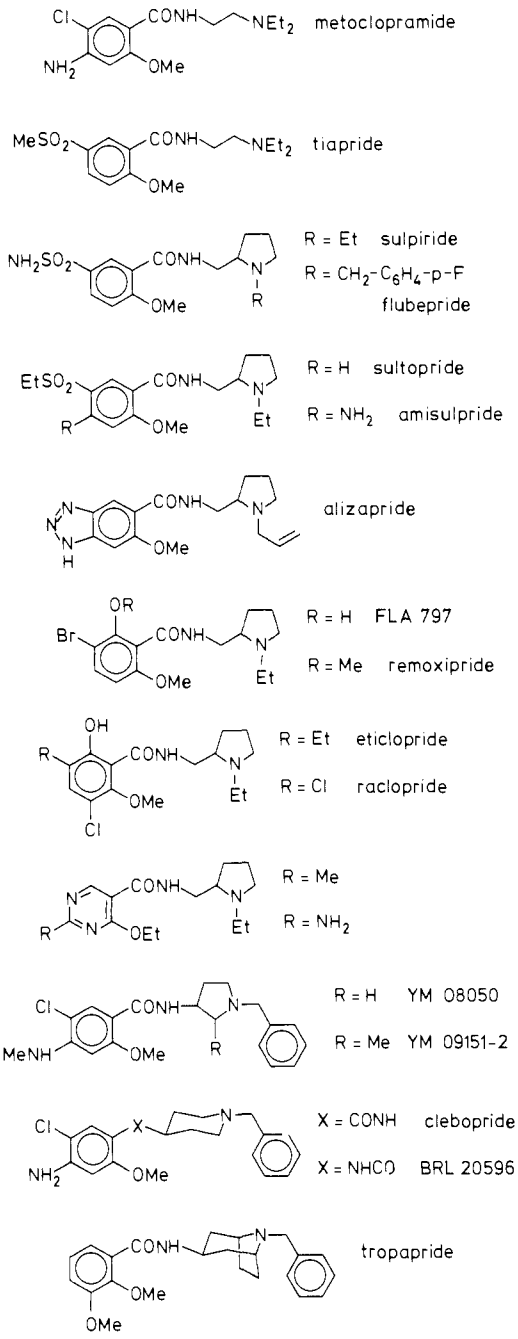
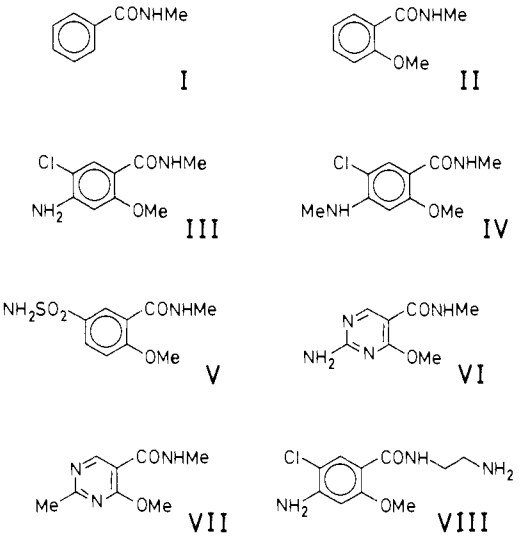
Chart I. Chemical Structure of Representative Orthopramides



Aromatic substituents are always present in orthopramides. The methoxy or 2-ethoxy group is indispensable for reasons already outlined, but other aromatic substituents are also necessary. This is evidenced by the complete lack of D-2 receptor affinity of metoclopramide analogues devoid of aromatic substituents except the 2-methoxy group.[18] Thus a second goal of the present study is to examine the role of aromatic substituents on the electronic structure of benzamides and to search for common elements in the electrostatic potential of variously ring-substituted derivatives.

The conclusion to emerge from this study is that the various ring substitution patterns of orthopramides generate comparable MEPs, but that the topographical analogy postulated between dopamine and these antagonists[13] is somewhat too simplistic.

Chart II. Model Compounds Investigated in the Present Study



Methods

The model compounds examined in this study are shown in Chart II. As in previous investigations,[10,11,13] standard bond lengths and valency angles from crystallographic data[19] were used. The geometric parameters for the pyrimidine ring in model compound VI were taken from a gas-phase electron-diffraction study.[20] X-ray crystallographic studies of benzenesulfonamides[21,22] and metoclopramide[14] afford the geometric parameters of the sulfamoyl group and of the side chain of model compound VIII. No geometrical optimizations were performed. Wave functions and electronic densities were calculated by using the ab initio MONSTERGAUSS program[23] operating in the STO-3G minimal basis set. MEPs were obtained with the VSS program (QCPE 245) and a modified version[24] of the program DENPOT (QCPE 360). As a general rule, the electrostatic potentials were taken in a parallel plane 1.75 Å above the plane of the aromatic ring, i.e., just above the region of the π-electrons. All calculations were performed on the CDC CYBER 170/720 and 170/855 computers of the Federal Institute of Technology in Lausanne.

Preliminary calculations performed using the semiempirical CNDO/2 method gave results differing significantly from those obtained with the STO-3G method. However, the former method is known to be less reliable than the latter for the calculation of MEP (see references listed in a previous study[17]). Additional calculations at the STO-5G and 4-31G levels (not shown) produced MEP patterns closely resembling those obtained at the STO-3G level.

Results

MEP of *N*-Methylbenzamide and *N*-Methyl-*o*-anisamide. The MEP of model compounds I and II (Chart II) were calculated in order to progressively assess the influence of ring substituents in orthopramides. The

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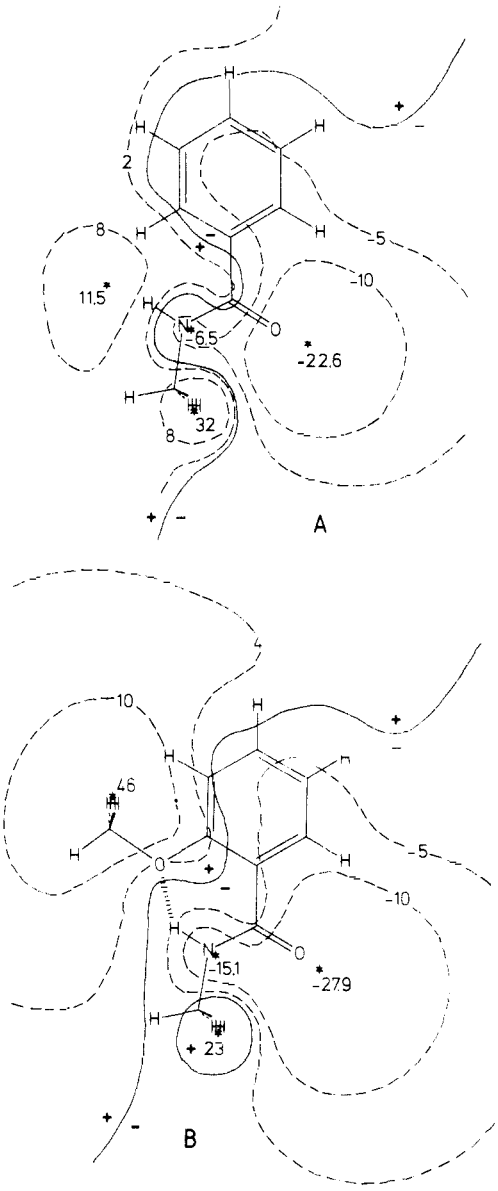

Figure 1. MEP (calculated by the STO-3G ab initio method) of A, compound I; and B, compound II. The isoenergy contours (in kilocalories/mole) are in a plane 1.75 Å above the plane of the aromatic ring.

compounds were set in their low-energy, planar conformation. The MEP as calculated by the STO-3G method are shown in Figure 1 for a plane 1.75 Å above the plane of the aromatic ring.

The MEP plot of *N*-methylbenzamide (Figure 1A) shows the entire ring and the heteroatoms to lie in regions of negative potentials. The methoxy group in *N*-methyl-*o*-anisamide (Figure 1B) is itself in a zone of positive potential, but the entire amide group is now surrounded by a negative potential. These effects reflect the influence of the intramolecular H bond.

MEP of Ring-Substituted *N*-Methyl-*o*-anisamides as Model Compounds of Medicinal Orthopramides. The MEP plots of compounds III–VII (Chart II) are shown in Figure 2 for a plane of 1.75 Å above the plane of the aromatic ring. In addition to the contributions of the amide and methoxy groups as assessed in Figure 1, all plots show a number of common features due to the 4- and 5-substituents which may be significant. Thus, a negative potential is found above all or most of the CONH moiety, with the carbonyl group generating a strong negative potential. The region above the aromatic ring is positive in part or in totality, the latter case (compound V, Figure 2C) being due to the marked electron-withdrawing effect of the sulfamoyl group. Of interest is the fact that the region above position 2, 3, and 4 of the aromatic ring is always positive and constitutes the positive edge of the ring. The methoxy group is always positive, including its oxygen atom, due to the influence of the intramolecular H bond, as noted earlier.

Positions 5 and 6 correspond to the negative edge of the aromatic ring. Here, the influence of the carbonyl group and of an electronegative substituent in position 5 are clearly felt. At same distance from the ring, compounds III, IV, and VI (parts A, B, and D of Figure 2, respectively) display two marked negative minima beyond positions 4 and 5. This is due to the amino and chloro groups, and for compound VI (Figure 2D) to a pyrimidine nitrogen and to the amino group. Compound V (Figure 2C) appears to behave differently. This difference however may be more apparent than real and due to conformational effects. Indeed, the sulfamoyl group in compound V was taken with the S and N atoms coplanar with the aromatic ring. Another low-energy conformation has the SO_2NH_2 group perpendicular to the ring, as found in the crystal structure of hydrochlorothiazide[21] and sulthiame.[22] Such a perpendicular conformation should project the negative potential of the two oxygen atoms in regions corresponding to those noted above for compounds III, IV, and VI.

Compound VII (Figure 2E) shows a somewhat different MEP pattern since the 2-methyl group is surrounded by a positive potential. This discrepancy needs further investigations, be they chemical, pharmacological, or metabolic.

MEP Plots of 4-Amino-5-chloro-*N*-(2-aminoethyl)-*o*-anisamide at Various Distances from the Molecule. Compound VIII, which is the primary amine analogue of metoclopramide, was investigated in an extended conformation believed to be the active one.[13] MEP plots were calculated for various distances away from the molecule. At 1.75 Å (Figure 3A), the frontier between the positive and negative potentials is quite sinuous. All heteroatoms except the methoxy oxygen produce marked negative potentials, while three hydrogen atoms (two in the side chain and one in the methoxy group) appear as strong positive potentials merely due to the fact that the plane cuts through their van der Waals volume. At 2.0 Å (Figure 3B), the frontier line is only slightly less sinuous, although all extrema of positive and negative potentials have lost intensity to variable degrees. At greater distances, namely, 2.5 and 3.0 Å (parts C and D of Figure 3, respectively), the frontier line shows only soft undulations. In the positive region, only one maximum remains (the methyl group), while three minima exist in the negative region due to the influence of the amino, carbonyl, and chloro groups. Noteworthy is the fact that the influence of the 4-amino group is practically lost even at 2.5 Å, suggesting that its role in the drug–receptor recognition process must be modest. This is of interest since the differences seen at 1.75 Å in the MEP plots of compounds III–VII tend to decrease at 2.5 and 3.0 Å (data not shown).

MEP of Protonated 4-Amino-5-chloro-*N*-(2-aminoethyl)-*o*-anisamide (Compound VIII). Compound VIII was also investigated as the protonated species which is the predominant form of orthopramides under physiological conditions.[13] The MEP plot for a plane 1.75 Å above the aromatic ring is shown in Figure 4. Analogous to the situation we reported for protonated dopamine,[17] protonated VIII is entirely surrounded by a very strong positive potential which almost erases the complex po-

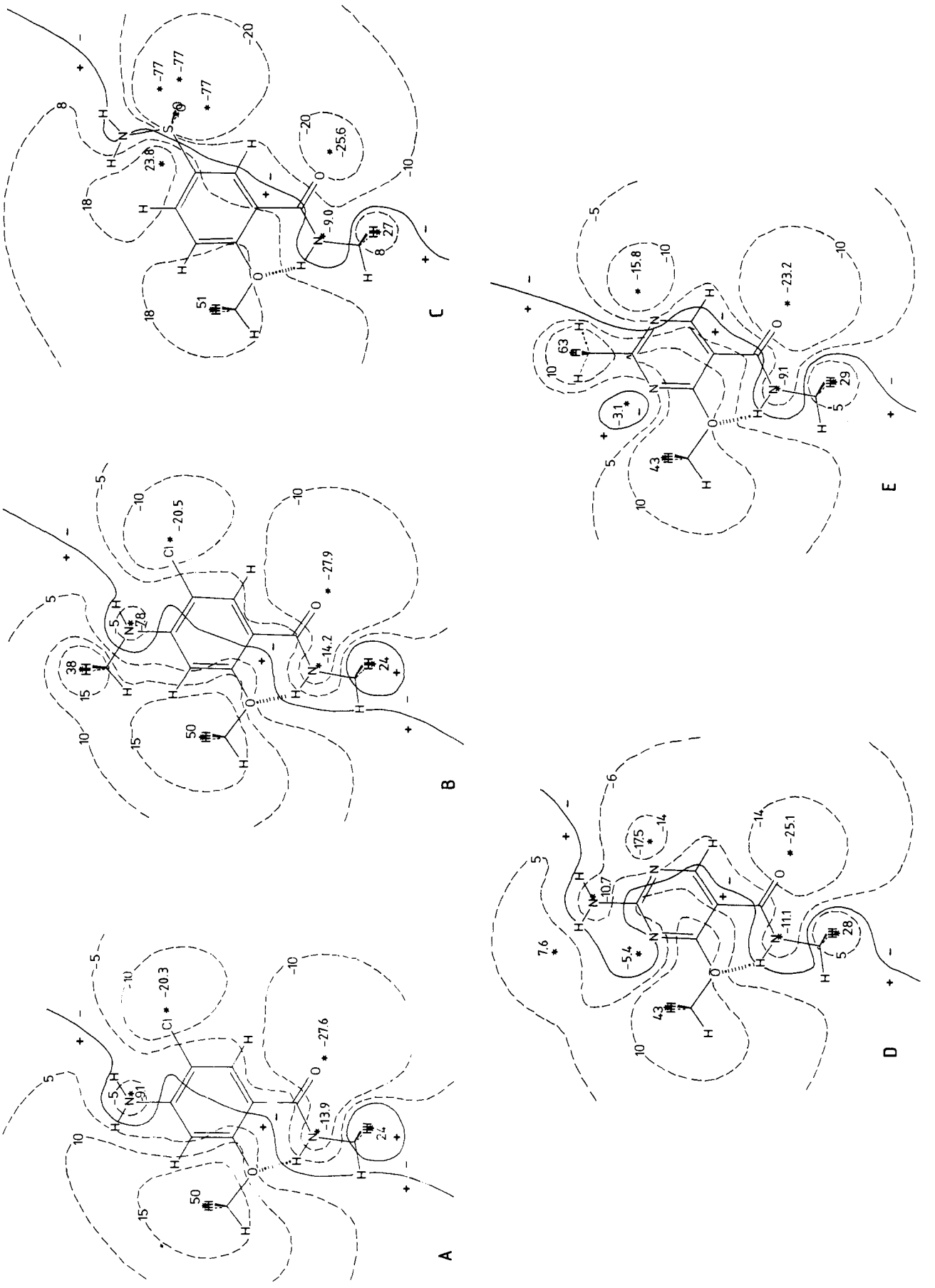

Figure 2. MEP (calculated by the STO-3G ab initio method) of A, compound III; B, coupound IV; C, compound V; D, compound VI; and E, compound VII. The isoenergy contours (in kilocalories/mole) are in a plane 1.75 Å above the plane of the aromatic ring.

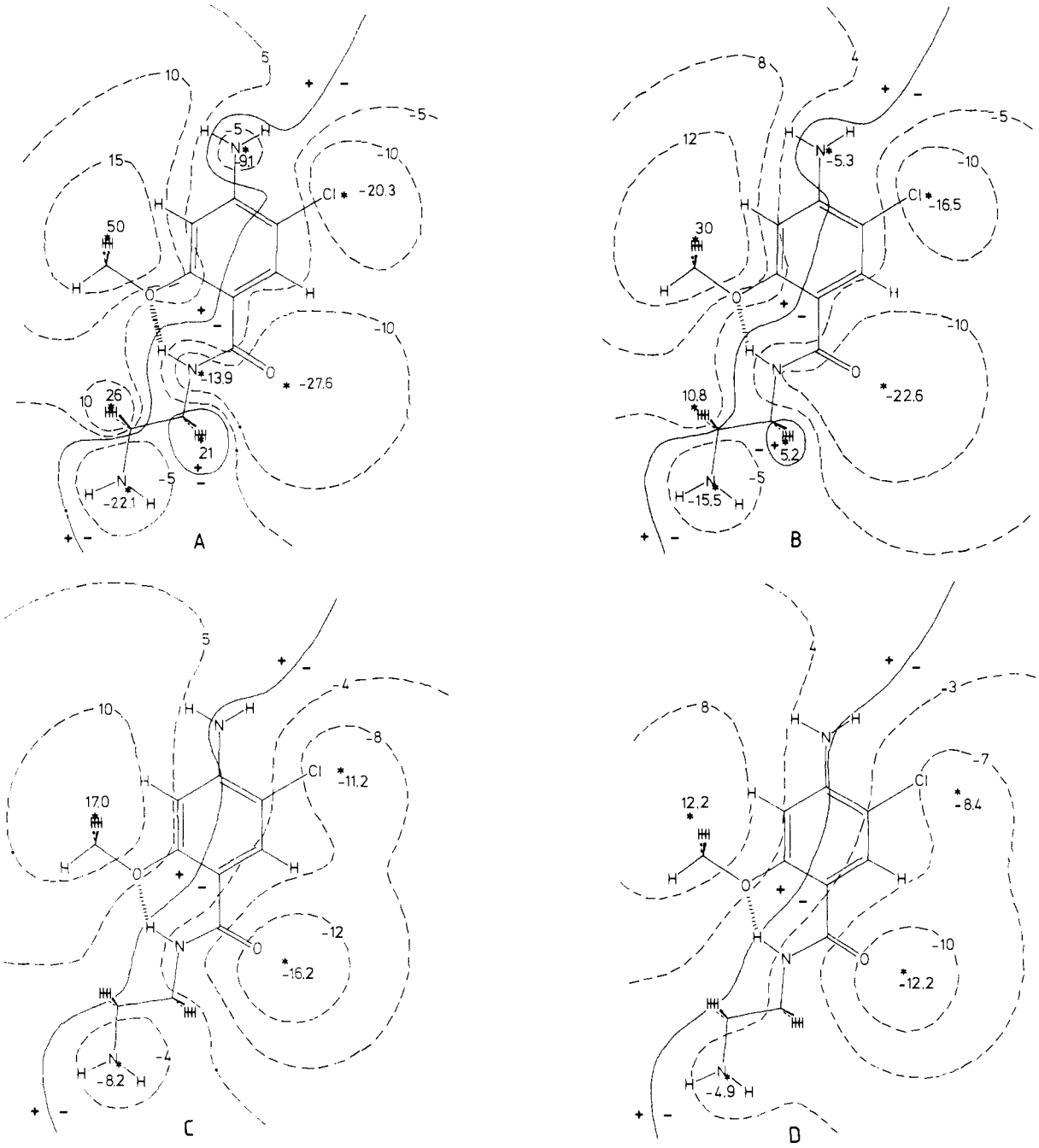

Figure 3. MEP (calculated by the STO-3G ab initio method) of compound VIII in neutral form. The isoenergy contours (in kilocalories/mole) are in planes: A, 1.75 Å; B, 2.0 Å, C, 2.5 Å; and D, 3.0 Å above the plane of the aromatic ring.

tential pattern noted around the aromatic region of model molecules (free bases, vide supra). In particular, the influence of the three strongly electronegative substituents (=O, Cl, NH_2) is detected only in the form of three local minima in the positive field. However, the relative monotony of the electrostatic potential around protonated compound VIII is more apparent than real, because as already noted for dopamine,[17] the difference in electrostatic potential between local minima and maxima is the same for the protonated and neutral molecule. There is only a shift to more positive values. Furthermore, the MEP of protonated VIII was calculated without its charge being balanced by a counterion. When this was done for protonated dopamine by adding a chloride counterion,[17] a global shift of the electrostatic potential toward less positive and even negative values was found to occur, the difference in potential between minima and maxima remaining the same.

Discussion

Orthopramides are basic compounds, the pK_a values of the *N*-alkyl and *N*-benzyl analogues being close to 9 and 8, respectively.[25] Many other dopamine antagonists have comparable basicity, while tricyclic piperazinyl derivatives have pK_a values of 7–7.5.[26] This and a number of other facts suggest, but do not prove conclusively, that the active form of dopamine agonists and antagonists is the cationic one.

This raises the question of the pharmacological relevance of electronic calculations involving uncharged dopamine antagonist molecules. As noted above, differences in

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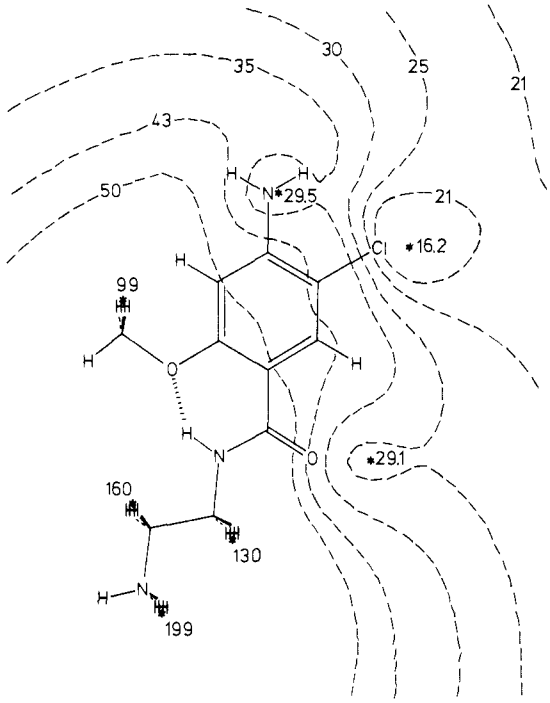

Figure 4. MEP (calculated by the STO-3G ab initio method) of compound VIII in the protonated form. The isoenergy contours (in kilocalories/mole) are in a plane 1.75 Å above the plane of the aromatic ring.

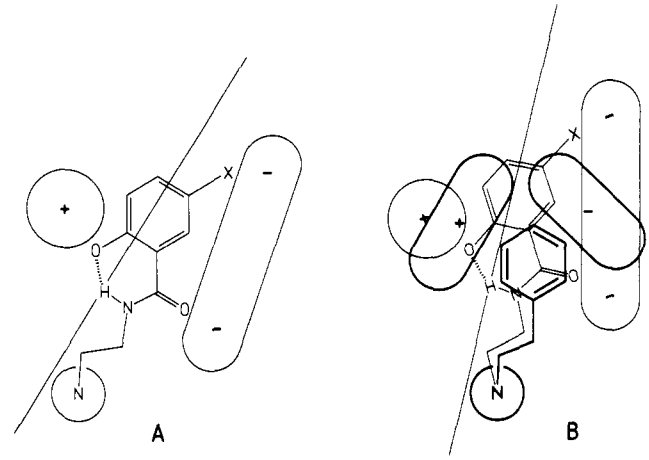

Figure 5. (A) Postulated main elements in the pharmacophore of orthopramides as deduced from MEP. (B) Superimposition of the simplified pharmacophore of orthopramides (this study) and dopamine (heavy lines) obtained from a previous study.[17] This superimposition suggests a possible mode of binding of orthopramides to the D-2 receptor.

electrostatic potential energies remain the same in neutral and protonated molecules, the change upon protonation being essentially a global shift toward positive values. Adding a counterion in the calculations results in partial charge compensation[27] which depends on the nature and relative position of the counterion. Thus, and in the absence of a definitive knowledge about the active form (neutral or protonated) of dopamine receptor ligands, the discussions to follow focus on the MEP of the neutral molecules. We believe that results from the present study may bring elements of understanding regarding (a) the recognition process, i.e., the approach of orthopramides toward the D-2 receptor, and (b) the mode of binding of orthopramides to a hypothetical topographical model of the D-2 receptor.

Figure 3 shows that, at a distance of 3 Å, the MEP of neutral orthopramides is divided into a positive and a negative region by an almost rectilinear frontier line which becomes more sinuous nearer the molecule. A curtain is a fit image for this frontier, the main characteristic of which is to run along the longitudinal axis of the molecule. This leads to the hypothesis that, at some distance from the receptor, the drug may be subjected to a proper longitudinal alignment, leaving little freedom of motion along the transversal axis. At a distance of 3 Å, four electrostatic singularities can be felt, namely, the influence of the basic nitrogen, a positive maximum (OMe), and two negative minima (=O and the 5-substituent). Together with the frontier line these four elements could constitute what we propose to call a *distance pharmacophore*, a MEP pattern which orthopramides project at a distance of ca. 3 Å (Figure 5A) and beyond and which could be responsible for the recognition and proper alignment of these D-2 antagonists.

At a shorter distance (ca. 2 Å) which is that of the actual binding to the receptor, the pharmacophoric pattern becomes more complex, with a more sinuous frontier, large extrema in the potential and, perhaps secondary, less important maxima and minima, also playing a role. The MEP at these short distances is equated with a *contact pharmacophore*. At this stage, it is tempting to search for similarities and differences in the pharmacophoric patterns of dopamine and antagonists with the idea of gaining some information on the mode of binding of the latter to the D-2 receptor. Before doing so, however, a word of caution is necessary.

Indeed, the D-2 dopamine receptor is believed to consist of a single antagonist binding site, which however exists in two interconverting states differing in agonist affinity.[28-30] The existence of two affinity states may be due to a conformational change in the receptor, resulting in a slight change in the topography of the dopamine-binding site, or involving the shift of a sterically hindering group. In the first case, looking for common elements in the pharmacophore of D-2 receptor agonists and antagonists could perhaps imply comparing partly uncomparable objects. Given the present limited state of our knowledge, however, attempting such a comparison may be of interest, whatever the restrictions.

That the aromatic ring of orthopramides and dopamine cannot be topographically equivalent has already been recognized by comparing the respective N/aryl distances[13] and the different structure–activity relationships of the aromatic substituents, e.g., replacing the catechol group of dopamine by the heterocyclic moiety found in alizapride (Chart I) suppresses dopaminergic activity.[31] We recently proposed[13] that the virtual six-membered ring of orthopramides, the presence of which is critical for activity, is topographically equivalent to the aromatic ring in dopamine. This model however has to be somewhat revised after comparing the MEP pattern of orthopramides with that of dopamine.[17] Indeed, the postulated topographical equivalence[13] does not permit an optimal correspondence between the regions of maximum positive and negative potential generated by both dopamine[17] and orthopramides. To allow the best possible correspondence of elec-

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trostatic potentials, one must abandon the rigourous topographical equivalence between the aromatic ring of dopamine and the virtual cycle in orthopramides and allow a slight and lateral displacement of the two rings relative to each other. This is illustrated in Figure 5B where the aromatic ring of dopamine is made to coincide with the amide group of a model orthopramide, allowing the best possible fit between the regions of maximum positive potential, as well as between the regions of maximum negative potential.

Such distinct modes of binding as postulated here for orthopramides and dopamine are not a novel proposal. Indeed, McDermed et al.[32] and Wikström et al.[33] have concluded from their studies that agonists of various chemical and stereochemical classes have different modes of binding to a hypothetical dopamine receptor model. While the nitrogen binding site is well defined, the aromatic ring can occupy a variety of positions, a situation also postulated here (see Figure 5B). These models should be challenged with MEP and other structural data of various D-2 receptor agonists and antagonists.

Figure 5 also suggests that orthopramides may interact with elements of the D-2 receptor not involved in dopamine binding. This is in particular the case of the aromatic substituents of orthopramides, which as mentioned earlier play a critical role in the D-2 receptor affinity of these compounds.[18] Understanding the role played by these substituents, as well as by other structural features of orthopramides, should help rationalize differences in therapeutic activities (see introduction). Indeed, these differences may be due to contrasting distribution of orthopramides and/or to selectivity for different subpopulations of D-2 receptors. More detailed studies of the electronic structure of substituted benzamides belonging to different therapeutic classes may reveal crucial differences. Additional pharmacological and physicochemical investigations have to verify or falsify hypotheses deduced from the results of quantum mechanical calculations. For example, it has been shown that the closely related benzamides sulpiride and sultopride (see Chart I) differ markedly in terms of crossing of the blood–brain barrier and intracerebral regional distribution.[34] Additionally, it may or may not be relevant that the receptor binding of orthopramides, in contrast to other dopamine antagonists, is strongly Na^+ dependent,[8] suggesting distinct D-2 binding sites or a distinct mode of binding. Work in progress (collaborative study with the Department of Neurology, Institute of Psychiatry, University of London) involves assessment of lipophilicity–activity relationships and thermodynamics of D-2 receptor binding.

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Analogues of Poison Ivy Urushiol. Synthesis and Biological Activity of Disubstituted *n*-Alkylbenzenes

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The total synthesis of different isomers and analogues of poison ivy urushiol is described. These include the positional isomers 1–**5** and the nitrogen-containing analogues **6** and **8** and their mesylamino derivatives **7** and **9**. 3,4-Dimethoxybenzaldehyde, *m*-dimethoxybenzene, resorcinol, and *p*-dimethoxybenzene were used as starting materials for compounds 1, **2**, 3, and 4, respectively. Compound **5** is prepared by catalytic hydrogenation of bilobol isolated from *Ginkgo biloba*. Compounds **6** and **7** were prepared from anacardic acid as the starting material while compounds **8** and **9** were prepared from phenol as the starting material. Compounds 1–**9** were tested for their ability to cross-react with poison ivy urushiol in sensitized guinea pigs. Compounds **6** and **8** were reactive at the 10-μg dose level when applied topically, while compound 1 was a skin irritant at that dose. On the other hand, compounds **2**–**5**, **7**, and **9** showed no cross-reactivity up to the 30-μg dose level. Structural requirements for cross allergenicity are discussed.

Contact dermatitis, a widespread problem in the United States, is caused by many members of the family Anacardiaceae of which poison ivy (*Toxicodendron radicans*) is the most common. The chemicals responsible for this allergenic reaction are commonly referred to as urushiols. These are mixtures of 3-*n*-pentadec(en)yl- or 3-*n*-heptadec(en)ylcatechols.[1,2]

Studies from our laboratory showed that intravenous administration of the product urushiol acetate was effective in producing immune tolerance in naive guinea pigs and desensitization or hyposensitization in already sensitized animals.[3] However, these compounds were less effective by the oral route.[4] As part of our continuing efforts to

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