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A theoretical conformational study of substituted *o*-anisamides as models of a class of dopamine antagonists

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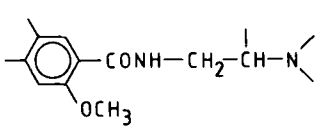
The quantum mechanical PCILO method has been used to investigate the conformational behaviour of *N*-(2-aminoethyl)- and *N*-(2-dimethylaminoethyl)-*o*-anisamide, two model molecules of substituted benzamides. The molecules are shown to have only limited conformational freedom due to the presence of two intramolecular hydrogen bonds acting as conformational locks. The molecules in their preferred conformation are characterized by a distance between the centre of the aromatic ring and the nitrogen atom of almost 6 Å, i.e. almost 1 Å longer than in the fully extended dopamine conformers. Some implications at the receptor level of this topographical dissimilarity are discussed.

Substituted *o*-anisamides (substituted *o*-methoxybenzamides) are a class of dopamine (DA) receptors antagonists having the general chemical structure I. Representative derivatives include metoclopramide, sulpiride, sultopride, and tiapride. These drugs display marked structural and pharmacological differences from 'classical' neuroleptics (e.g., phenothiazine and butyrophenone derivatives) (Jenner & Marsden 1979). A significant characteristic of these substituted *o*-anisamides is their selective action on a restricted population of DA receptors not linked to DA-sensitive adenylate cyclase (Jenner & Marsden 1979; Kebabian & Calne 1979). Furthermore, it has just been shown (Theodorou et al 1980) that the specific binding of [^{3}H]sulpiride is highly dependent on the presence of sodium ions, a feature not observed in the specific binding of [^{3}H]spiperone.

I



These effects may signify that the *o*-anisamides and the classical neuroleptics exert their effects at distinct receptor sites, and may explain the atypical properties of the former drugs.

Valuable rationalizations have been published on topographical properties of the DA receptors as deduced from the structure-activity relationships of rigid agonists, in particular apomorphine (Tedesco et al 1979) and 2-aminotetrahydronaphthalene derivatives (Horn & Rodgers 1980). Classical neuroleptics have also been actively investigated from a topographical viewpoint, allowing interesting considerations about their specific binding sites, and perhaps also DA receptors in general. In particular, butaclamol derivatives have led to the proposal (Humber et al 1979; Philipp et al 1979) that there exist on the DA receptors two adjacent sites for binding aromatic rings, the centres of which are located 5·1 and 6·4 Å away from the nitrogen binding site, respectively.

In contrast, little is known about the topography of the *o*-anisamide binding sites as deducible from the stereochemical properties (configurational and conformational) of these drugs. Relationships between the configuration and the activity of chiral substituted anisamides have been described (e.g. Jenner et al 1980), but little is known about their conformational behaviour.

The present study is an attempt, using theoretical means of investigation, to examine salient topographical properties of those DA receptors that bind the anisamide class of antagonists.

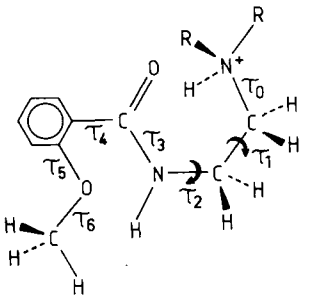
METHODS

Two model molecules were considered; the primary amine *N*-(2-aminoethyl)-*o*-anisamide (II, R = H) and the tertiary amine *N*-(2-dimethylaminoethyl)-*o*-anisamide (II, R = CH_3). The choice of these

* Correspondence.

molecules is dictated by the assumption that the conformation of the basic side-chain is influenced only negligibly by aromatic substituents in the 4- and 5-position. This assumption is proved correct by the identical H–H coupling constants seen in the n.m.r. spectra of the two model molecules and of metoclopramide (Anker, Testa & Lauterwein, to be published).

II



Only the amide forms of the molecules were considered. A tautomeric iminol form may be hypothesized, but its existence is not compatible with the high resolution ^{1}H-n.m.r. spectra of the molecules (Anker, Testa & Lauterwein to be published). The molecules were taken in their protonated form which is predominant under physiological conditions. Standard bond lengths and valency angles, as obtained from crystallographic work, were used (Sutton 1965).

Inspection of II reveals seven degrees of conformational freedom, the corresponding torsion angles being designated as τ_0 to τ_6 and defined according to Klyne & Prelog (1960; see also Testa 1979a). Diagram II displays the torsion angles in the following values: $\tau_0 = -60°$, $\tau_1 = \tau_2 = \tau_3 = 0°$, $\tau_4 = \tau_5 = 180°$, $\tau_6 = 60°$. For all torsion angles except τ_1 and τ_2, these values correspond to energy minima as assessed by preliminary calculations. In the final calculations reported here, τ_0 and τ_3 to τ_6 were blocked in their precalculated minimum energy values, while τ_1 and τ_2 were varied from 0° to 360° by 30° steps. However, in the regions of the conformational map where a better resolution was desirable (e.g., local and global minima), τ_1 and τ_2 were varied by 5° steps.

The quantum mechanical method used in this work is an all-valence-electron semi-empirical procedure, the PCILO method (perturbative configuration interactions using localized orbitals) (Diner et al 1969, and ref. therein). This method has been successfully used for several years in the theoretical conformational analysis of numerous biomolecules and drugs (e.g. Pullman 1976). The conformational energy maps were drawn by the DESNIV program (Bouberguig 1979). The pictorial representations of the molecules were drawn from the Cartesian coordinates of the atoms using a program written by Haselbach & Schmelzer (1971).

RESULTS AND DISCUSSION

The conformational energy map of *N*-(2-aminoethyl)-*o*-anisamide is given in Fig. 1 and shows interesting features. Two global energy minima are

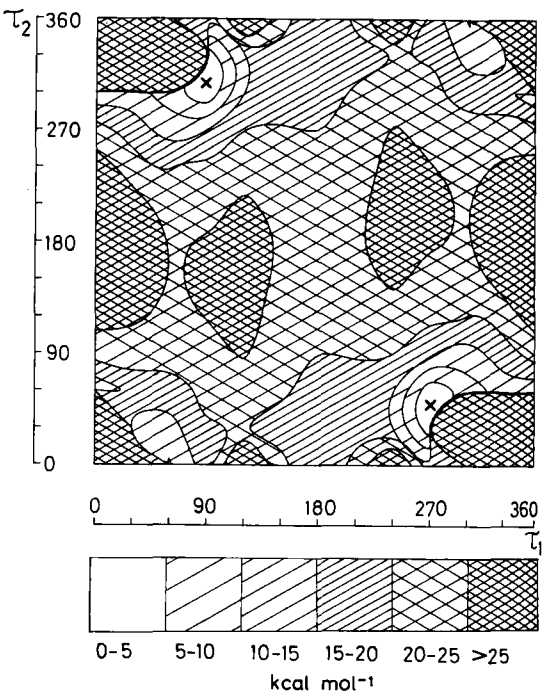


FIG. 1. The conformational energy map of *N*-(2-aminoethyl)-*o*-anisamide. The two enantiomeric global minima are marked with ×. For a definition of torsion angles see diagram II.

apparent at τ_1/τ_2 values of 90°/310° and 270°/50°, respectively. These two energy minima correspond to two enantiomeric conformations of the molecule. A particularly important relevation of Fig. 1 is the highly restricted conformational freedom of the molecule. Indeed, the two minima are at the bottom of two steep energy wells, and several kcal mol^{-1} (kJ mol^{-1}) are required for just a 10° rotation of the two dihedral angles. Less than 1% of the area of the conformational map corresponds to free energy values within 5 kcal mol^{-1} (21 kJ mol^{-1}) above the minimum, while less than 3% of the area

correspond to free energy values within 10 kcal mol^{-1} (42 kJ mol^{-1}) above the minimum.

The conformational energy map of the tertiary amine, *N*-(2-dimethylaminoethyl)-*o*-anisamide, is shown in Fig. 2. As opposed to Fig. 1, this map does not have a centre of symmetry, and shows only one global minimum corresponding to $\tau_1 = 90°$, $\tau_2 = 305°$. The fact that only one energy minimum is apparent in Fig. 2 is due to the loss of C_3 symmetry of the cationic head caused by disubstitution.

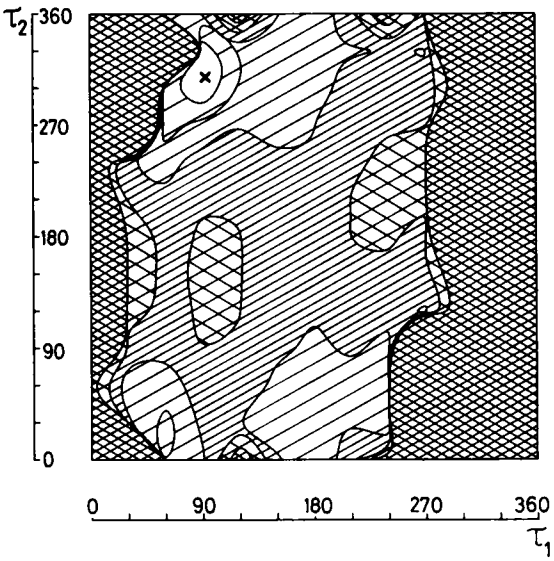


FIG. 2. The conformational energy map of *N*-(2-dimethylaminoethyl)-*o*-anisamide. For explanations see Fig. 1.

In fact, an enantiomeric conformation does exist on the energy hypersurface, characterized by $\tau_0 = 60°$, $\tau_1 = 270°$, $\tau_2 = 55°$. In Fig. 2 as in Fig. 1, the preferred conformer is located at the bottom of an energy well, indicating the molecule to have very little conformational freedom.

The two model molecules have preferred conformations which are practically identical. Salient topological features are compared in Table 1, and show that the disubstitution of the basic nitrogen atom has only a minor influence on the conformational behaviour of these molecules.

In the preferred conformations of both molecules, the *N*-adjacent proton is pointing toward the carbonyl oxygen atom, suggesting a possible intramolecular hydrogen bond. Of particular interest in Table 1 is the distance between the basic nitrogen atom and the carbonyl oxygen atom. In both

Table 1. Topological features of *N*-(2-aminoethyl)-*o*-anisamide (II; R = H) and *N*-(2-dimethylaminoethyl)-*o*-anisamide (II; R = CH_3) in their preferred conformation.

	Distance N$^+$-aromatic centre	Distance N$^+$-molecular plane	Distance =O N$^+$
II; R = H	5·94 Å	0·56 Å	2·41 Å
II; R = CH_3	5·95 Å	0·75 Å	2·46 Å

molecules, this distance corresponds to that seen in strong H-bonds (Testa 1979b). Such a strong intramolecular H-bond is consistent with the deep energy well found around the global minimum of the molecules, and it offers a reasonable explanation for their lack of conformational freedom. Another intramolecular H-bond exists in the substituted *o*-anisamides, that between the methoxy oxygen atom and the amide nitrogen atom. This is again a strong H-bond, the N–O distance being 2·40 Å. Thus this study offers theoretical evidence that substituted *o*-anisamides must be viewed as molecular systems made essentially rigid by two intramolecular H-bonds acting as conformational locks.

The preferred conformation of substituted *o*-anisamides having been determined, and the relative rigidity of these molecules having been established, a comparison of their topographical properties with those of dopamine remains to be made. This molecule in the crystal form (Bergin & Carlström 1968) exists in an extended conformation ($\tau_1 = 101°$, $\tau_2 = 186°$, τ_1 and τ_2 being the torsion angles along the C_ϕ-C_β and C_β–Cα bonds, respectively) which corresponds to a global minimum in a PCILO-computed conformational energy gap (Pullman et al 1972). Unlike the substituted *o*-anisamides, the side-chain of dopamine has considerable conformational freedom (Pullman et al 1972), but in its most extended conformation it cannot reach a N-centroid distance greater than approximately 5 Å (the exact figure is a function of the bond length and valency angle values being used in calculations, or found in the crystal). The crystalline structure of apomorphine (Gieseke 1973) suggests the active conformation of dopamine to be an extended ($\tau_2 = -178°$), but rather planar ($\tau_1 = 140°$) one, with a N-centroid distance of 5·10 Å and a height of the nitrogen atom above the aromatic ring of approximately 1 Å. At present, an almost ideal semi-rigid analogue of DA is considered to be 2-amino-6,7-dihydroxytetrahydronaphthalene (ADTN) in which τ_2 and τ_1 have values of 168° and 165°, respectively, resulting in a N-centroid distance of 5·15 Å and a

height of N over the aromatic ring of only 0·001 Å (Horn & Rodgers 1980).

In Fig. 3, the crystalline preferred conformation of DA is displayed together with *N*-(2-aminoethyl)- and *N*-(2-dimethylaminoethyl)-*o*-anisamide in their calculated preferred conformation. Using standard bond distances and valency angles (Sutton 1965), we calculate that for DA in its preferred conformation the distance between the nitrogen atom and the centre of the phenyl ring is 4·94 Å, i.e. 1 Å less than in the substituted *o*-anisamides. The difference is clearly apparent in Fig. 3.

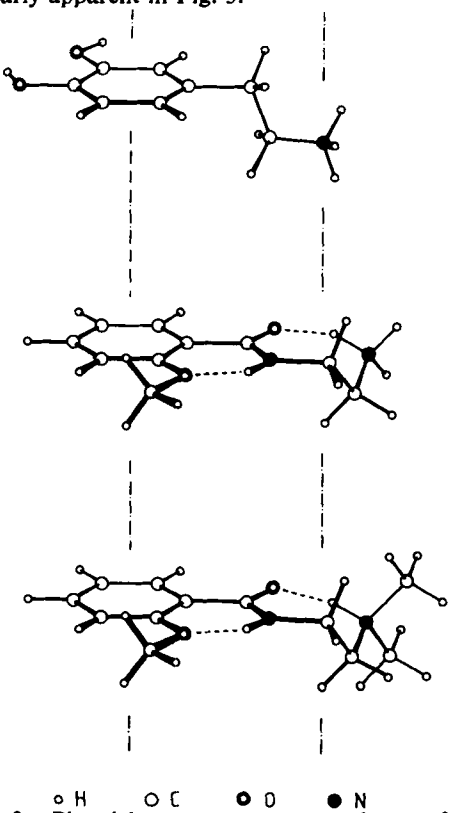


FIG. 3. Pictorial representations, redrawn from computer-generated drawings, of dopamine in its preferred crystalline conformation, and the model *o*-anisamides in their preferred calculated conformation. The left vertical axis marks the position of the centre of the aromatic rings, while the right axis corresponds to the position of the nitrogen atom in dopamine. The two intramolecular H-bonds in the substituted *o*-anisamides are shown by a broken line.

The main topographical difference between DA and the two model antagonists thus appears to be the *N*-centroid distance, which is approximately 18% longer in the latter molecules than in DA. Is this difference a significant one? Inspection of the conformational energy maps (Figs 1 and 2) and of molecular models reveals that in the substituted *o*-anisamides, the *N*-centroid distance cannot be shortened without reaching highly unfavourable or forbidden conformational regions, or without considerably bending valency angles. Shortening the *N*-centroid distance to a value close to 5 Å would thus require many kcal mol^{-1}, presumably 20 kcal mol^{-1} (84 kJ mol^{-1}) or more. This indicates that the difference in the *N*-centroid distances must truly be a significant one. Furthermore, an aqueous environment can be expected to favour more extended conformers due to competition between the intramolecular $=O\cdots H\text{-}N^+$ hydrogen bond and hydration of the cationic head.

The above discussion suggests that a key topographical feature, namely the *N*-centroid distance, is not the same for DA agonists and antagonists of the anisamide class. An explanation of this discrepancy can be found in the two-state model of many receptors including DA receptors (Ariëns 1979; Ariëns & Rodrigues de Miranda 1979). There is converging evidence that DA receptors exist in an activated, agonist-binding state, and in an antagonist-binding state. This two-state model is compatible with the present conformational studies if topographical differences are assumed between the two states of the DA receptors. Such an assumption, far from being unrealistic, must be viewed as reasonable since the two states of the receptor *must* show topographical differences if they are to discriminate between agonists and antagonists. In variance with the two-state model which assumes interconvertibility of the two states, some authors (Titeler & Seeman 1978; Köhler et al 1979) even propose that the agonist- and antagonist-binding sites are separate and non-interconvertible entities. As an alternative explanation of the different topographical properties of agonists and antagonists, the model of DA receptors discussed in the introduction (Humber et al 1979; Philipp et al 1979) can be evoked. This model could be postulated to apply not only to classical neuroleptics, but also to the atypical neuroleptics of the *o*-anisamide class.

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