The biologically active conformation of ergot alkaloids

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28 February 1985

Summary. Molecular mechanics and NMR studies of the D ring conformation of ergot alkaloids demonstrate that both D_1 and D_2 forms may exist in solution. The comparison of the geometric parameters defining the spatial relations between the aromatic moieties and the basic nitrogen of conformationally restricted dopamine analogs, and that of ergolene, shows the D_1 conformation to be the bioactive one.
Key words. Ergot alkaloids; bioactive conformation; dopamine receptors; NMR.

Ergolene[1] derivatives including natural and synthetic ergot alkaloids are partly flexible molecules acting on dopamine, serotonin and adrenaline receptors[1]. Conformationally variable are the D ring (D_1 and D_2 half chair conformations, fig. 1), the orientations of the N6 (axial, equatorial) and C8 substituents (β,α), and the peptide moiety. We shall mainly discuss the D ring conformation. Molecular mechanics calculations (QCFF/Pi method) show that the D_1 form of 9,10 ergolene with an equatorial N-methyl has the lowest energy[2] and this is also true of ergotamine if the intramolecular hydrogen bond (H-bond) between N20-H and N6 is not included in the calculation[3]. However, this H-bond stabilizes the D_2 form as revealed by NMR spectra of ergosine in $CDCl_3$. Characteristic of this form are the downfield position of the N20-H signal ($\delta = 9.36$ ppm) and the coupling constants $J_{(7\alpha,8)} = 3.1$ Hz, $J_{(7\beta,8)} = 4.1$ Hz, $J_{(8,9)} = 6.0$ Hz[4]. Similar results were also obtained with ergotamine[3]. H-bonding is not possible with N6 protonated and thus the D_1 form predominates. In DMSO-d_6 solution the H-bond of the ergosine base is disrupted and this also results in a favoring of the D_1 form. The coupling constants (in DMSO-d_6) $J_{(7\alpha,8)} = 4$ Hz, $J_{(8,9)} = 2$ Hz are characteristic of ergosine methanesulfonate and $J_{(7\alpha,8)} = 5$ Hz, $J_{(7\beta,8)} = 12.5$ Hz, $J_{(8,9)} = 2$ Hz of the free base. The details of the NMR conformational analysis will be published elsewhere.

Obviously the D ring may assume either the D_1 or the D_2 conformation depending on medium effects acting via protonation of N6 and H-bonding. This situation raises the question of which conformation is preferred by the receptor. In general, the problem of the bioactive conformation of ligands with several conformations of comparable energy is approached by considering geometrical parameters of conformationally restricted molecules which are active on the same receptor type. Since the requirements of the dopamine receptor for the spatial disposition of the catechol ring and the aliphatic nitrogen with its lone electron pair (or the N^+–H direction are rather well defined by a series of (semi) rigid dopamine analogs[5], we shall compare the key parameters of II and III with those of ergolene. These parameters are the distance r between the center of the aromatic ring and the projection of N on the ring plane, the height h of the N above the ring plane and the torsional angles θ and φ (fig. 2). We chose the ergolene ring B to correspond to the catechol one following the arguments of Nichols[6] and Bach et al.[7]. This is also in agreement with the similarities in the molecular electrostatic potential above the respective aromatic moieties[8]. The data presented in the table (QCFF/Pi calculated[2,5]) show the correspondence between the parameters of the catecholamine analogs and ergolene in the D_1 conformation. The difference between the parameters of D_1 and D_2 forms is only in the orientation of the N^+–H bond. Thus the D_1 conformation appears to be well suited for interaction with the dopamine receptor. This conformation also corresponds more closely to that of dihydroergotamine in the stable chair form[9].

Geometrical parameters computed by the QCFF/Pi method[2,5] defining the spatial relations between the aromatic moiety and the N6-lone pair of some dopaminergic agonists

	N-Me_{eq}	r	h	Θ	φ
Apomorphine		5.0 Å	0.9 Å	21°	154°
Octahydrobenzo[f] quinoline		5.2	0.3	17	131
9,10-ergolene	D_1	4.9	0.4	10	137
9,10-ergolene	D_2	4.9	0.4	160	−168

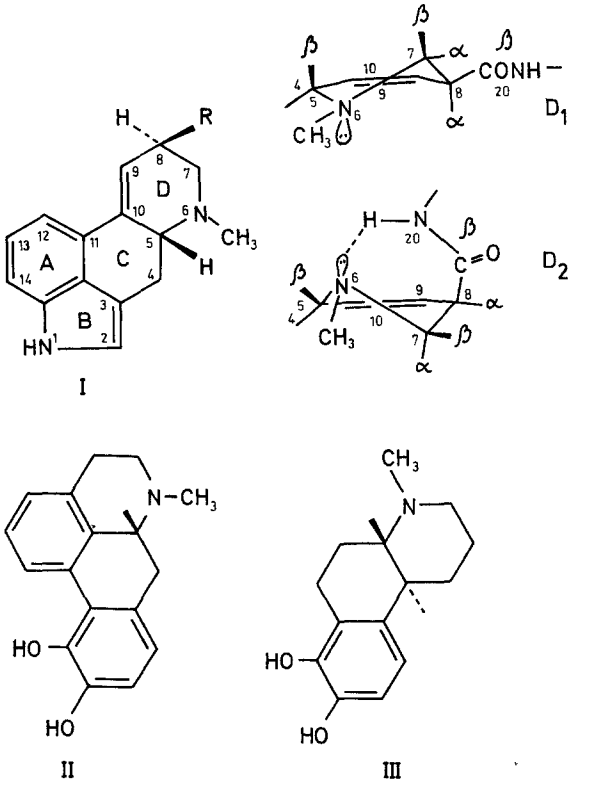

Figure 1. The molecular structures of I: 8-substituted 9,10-ergolene with the D ring conformations D_1 and D_2, II: apomorphine, and III: octahydrobenzo [f] quinoline.

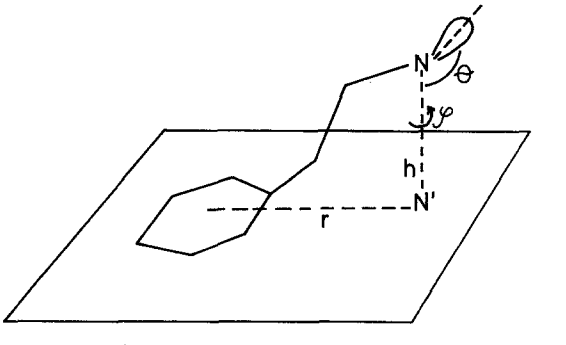

Figure 2. Geometrical parameters defining the spatial relations between the aromatic moiety and the N6-lone pair of some dopaminergic agonists.

The present conclusion opposes the one advanced by Pieri et al.[3], whose argument is based on the H-bond stabilization of the D_2 conformation. This implies that the ergot alkaloids interact in the nonprotonated form with the receptor, which would only be possible if the binding site definitely had non-polar properties. Quantum mechanical calculations on carboxylic acid-amine systems show, however, that a neighboring charge or dipole suffices to shift the bridging proton towards the amine[10,11].

Another argument against the D_2 form being the biologically active one can be drawn from the general conclusion that the DA receptor agonists must be rather flat[12]. The bulky peptide moiety bent towards N6 and the H-bond, if it persists, would sterically and electronically interfere with the interaction of N6 with the putative anionogenic group of the receptor. Thus we believe that the D_1 form of ergot alkaloids with its appropriate geometric parameters, relative flatness and greater flexibility is more suited for interaction with DA receptors.

The steric requirements of serotonin receptors are less well defined than those of the DA receptor. However, considering LSD as a rather rigid serotonin ligand, it is again the D_1 form that may be the one most likely to suit the serotonin receptor.

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0014-4754/86/030327-02$1.50 + 0.20/0

Correction

P. Baumann, A. N. Tchernitchin, G. Grunert and P. Ball: Effects of various doses of catecholestrogens on uterine eosinophilia in the immature rat, **Experientia 42 (1986) 165–167.** We regret that there was an error in the labeling of the figure; the final line should read: Hormone – C – Estradiol-17β – 4-OH-estradiol – 2-OH-estradiol.