Dopaminergic Pharmacophore of Ergoline and Its Analogues. A Molecular Electrostatic Potential Study

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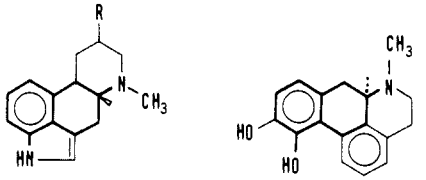
Spatial correspondence between apomorphine, a prototype dopaminergic (DA) drug, and ergoline and some of its (partial) analogues were derived by matching their molecular electrostatic potential (MEP) patterns surrounding the aromatic moieties with respect to the coincident aliphatic N atoms. The MEP patterns were calculated from ab initio wave functions of model molecules. The congruent superimpositions of the molecular frameworks obtained between apomorphine and DA active ergoline analogues might corroborate the hypothesis that they bind with the same receptor sites when activating certain subtypes of the DA receptor.

Ergoline derivatives exhibit complex pharmacological effects; in addition to serotonergic and α-adrenergic effects, they exert dopaminergic (DA) agonist activity in the central and peripheral nervous system.[1] The structural feature of most dopaminergic agonists is, however, a dopamine (DA) fragment as exemplified by a variety of dihydroxy derivatives of phenylethylamine, aminotetralin, aporphine, and octahydrobenzo[*f*]- and -[*g*]quinolines.[2] The assumption that ergoline derivatives induce a dopaminergic response by activating the same receptor sites as DA analogues is supported by pharmacological and direct receptor-binding data.[3] Structure–activity relationship (SAR) studies on the semirigid DA analogues established that the near-coplanar conformation of the catechol ring with the fully extended ethylamine chain is generally required for DA-like activity.[4] The marked dependence of drug action upon chirality[5,6] and conformation justifies the search for a precise three-dimensional relation between the ergoline and the semirigid DA analogues.

Up to now, various correlations giving steric relations between the ergoline derivatives and the DA analogues were invoked in order to delineate the "dopaminergic portion" of the ergoline skeleton that confers DA activity upon the molecule. Several authors have proposed the correspondence of the indole NH with the *m*-OH of the DA fragment.[7,8] The "*m*-OH" function has been shown to be important for DA activity of monohydroxy derivatives of aminotetralin, aporphine, and phenylethylamine.[2] Two different correlations emerge from fitting the "acidic" functions with respect to the aliphatic N atoms, schematically shown in the examples of ergoline (**1**) and apomorphine (**2**):



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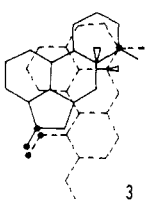

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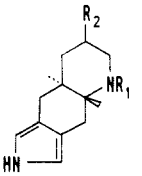
(i) the correspondence of the aminotetralin fragments with the opposing chiralities at the asymmetric centers (bold lines of **1** and **2**). (ii) superimposition **3** with congruent chiralities, its characteristic being the spatially mismatched positions of the aromatic rings (full circles represent the N, O, and H atoms).[9,10]

In view of the high stereoselectivity of DA receptors, Nichols has earlier suggested the correspondence of the pyrroleethylamine with DA fragment by giving priority to the congruent stereochemistry at the chiral centers.[11] In the respective superimposition the bulk of the two structures occupies approximately the same spatial area,[12] but it should be noted that the important 11-OH of **2** corresponds to the edge of the benzene ring in **1**.

The Eli Lilly group has reported the synthesis of several bicyclic and tricyclic ergoline partial structures, their 2-aza analogues,[13] and 2-azaergolines.[14] The pyrrole and pyrazole analogues (**4** and **5**) have been shown to be potent DA agonists, whereas 2-azaergolines (**6**) are devoid of any significant DA activity. Crystallographic analysis of octahydropyrazolo[3,4-*g*]quinoline (**5**) has proven that the absolute configuration of the active enantiomer corresponds to that of the natural ergolines.[15]



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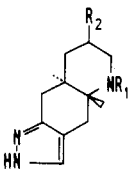

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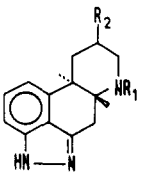

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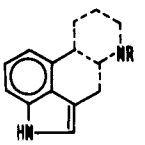
Such a series of rigid molecular structures with high DA agonist activity is well suited for a study of stereochemical requirements for binding with DA receptor sites and receptor activation. The pharmacophore—the three-dimensional disposition of functional groups essential for recognition and receptor activation—is assumed to be the arylethylamine moiety, on the basis of SAR studies.[2] However, in order to examine the spatial correspondence of the arylethylamine fragments, it is necessary to apply a physically acceptable criterion for correlating the chemically diverse aromatic systems.

Stereochemical similarity of structurally different drugs has been frequently estimated by molecular electrostatic potential (MEP) maps generated around selected fragments of the molecule. In a series of β-adrenergic drugs, the spatial correspondence between molecular regions surrounding the aromatic moieties with a characteristic potential in common to agonists and antagonists has been correlated with the affinities for the β-receptor. An attempt has been additionally made to rationalize the intrinsic activity with the MEP of another region of the aromatic moieties.[16-19] Weinstein et al. have shown that the affinity differences between serotonin (5-HT) and other hydroxy congeners for 5-HT/LSD receptor site correlate well with the difference between the optimal electrostatic orientation of the indole ring of 5-HT and that of the congeners.[20-22] The relative success of SAR studies based on MEP originates from the nature of the drug–receptor interaction. Its early stages, drug recognition and binding, have been claimed to be driven by long-range, electrostatic forces.[20] Otherwise, the MEP is generally a reliable reactivity index for noncovalent interactions of a series of structurally related, polar molecules with a common reactant. The validity and the limits of this approach are well documented.[16,23] The MEP calculations on numerous aromatic compounds have demonstrated the superiority of the potential over an electron-population analysis in accounting for the reactivity toward the electrophilic reagents.[23] The aromatic moiety of a drug might be involved in a stacking type of interaction with another aromatic ring located at the receptor site. In the stacking complexes of the nucleic acid bases, for example, the electrostatic component is not necessarily a dominant term of the interaction energy, yet it has a decisive effect on the mutual orientation of the aromatic rings.[24,25]

These results encouraged us to examine the applicability of the MEP for a definition of the DA pharmacophoric pattern of ergoline analogues. We evaluated the spatial correspondence of the MEP patterns surrounding the aromatic moieties of the molecules **1**, **2**, and **4–6**, with respect to the coincident N atoms taken as a reference. The MEP patterns used were calculated on model molecules. The MEP patterns of apomorphine (**2**), which was chosen as a prototype of DA analogues, matched the MEP patterns of the ergoline analogues. The resulting superimpositions of the active compounds show satisfactory matching of the overall molecular volumes, but not that of **6**, which might account for its DA inactivity.

Methods

The ab initio SCF computations of ergoline-like molecules are impractical because of the high computer time requirements. Therefore, we had to resort to calculations of reasonably chosen model molecules in order to retain the ab initio quality of wave functions. Semiempirical calculations of the MEP, based on zero-differential overlap approximation, yield erroneous results with aromatic molecules.[26] In our calculations we neglected the contribution of the saturated part of the ergoline analogues to the MEP. Comparative calculations on hydroxy derivatives of tryptamine[27] and β-adrenergic phenylethylamine derivatives[17] have indicated that the ethylamine side chain has a negligible influence on the MEP characteristics in the surroundings of the aromatic moieties. The actual calculations were performed on model compounds 3,4-dimethylindole (**7**), 3,4-dimethylpyrrole (**8**), and their 2-aza analogues, **10** and **9**, respectively.



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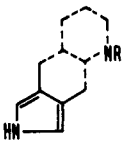

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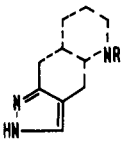

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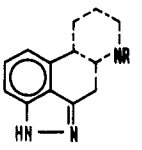

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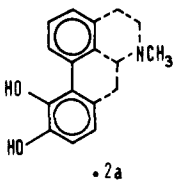

• 2a

The MEP patterns of the model ergoline analogues could be compared straightforwardly with those of the hydroxyaminotetralin derivatives calculated previously.[28] However, we selected **2** as a representative of DA analogues in order to make an additional comparison with the MEP

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pattern generated in the surroundings of the dihydroxybiphenyl fragment. 2,3-Dihydroxybiphenyl (**2a**) was assumed to be an adequate model of **2**.

Ab initio wave functions were calculated by using the Gaussian 80 program[29] at the HF level with the minimal STO-3G basis set.[30] The MEP calculations were carried out with a modified version of the Polyatom program package.[31] The MEP was calculated in the plane of the aromatic ring and in a parallel plane, at a distance of 1.6 Å.

Geometrical parameters of the model compounds could have been derived from structure determinations of the parent compounds. Since these were not available in all cases (**4**, higher energy tautomeric form of **5** and **6**), we had to use the geometries of simpler derivatives of the model compounds.[32,33] The geometries of **7** and **8** were derived from experimental data on serotonin and pyrrole, respectively. The geometry of the biphenyl fragment of **2** determined by X-ray diffraction[34] was used for the construction of **2a**. Standard values of bond lengths and angles were used for the hydrogen atoms as well as for the CH_3 and OH substituents.[33] We considered only two planar hydrogen-bonded arrangements of the OH groups in **2a**. Having performed ab initio geometry optimizations on both tautomeric forms of **9** and **10**, it was convenient to use these results as a consistent set of geometrical parameters for the MEP calculations. The bond lengths and angles of all non-hydrogen atoms were fully optimized at the HF/STO-3G level, using an analytical gradient method. The details of the calculations will be published elsewhere. For comparison, we also calculated the MEP maps of **7** and **10** with the geometries derived from the crystallographic data on dihydroergotamine[35] and 2-azadihydroergotamine.[36] The results indicated that slightly different geometry does not significantly affect the MEP patterns.

Experimental evidence on the structures of **2**, dihydroergotamine; 2-azadihydroergotamine, and **5**[15] indicate conformational congruence of the catechol- and pyrr(az)oleethylamine fragments including N lone pair directions. The spatial correspondence of the MEP patterns with respect to the aliphatic N atoms was estimated by using Cartesian coordinates adapted from the experimental data. The superimpositions of the ergoline analogues on **2** are represented two dimensionally, as projections onto the plane of the aromatic ring, implying congruent chiralities at the asymmetric centers. They were produced by keeping the positions of the aliphatic N atoms coincident and matching visually the most negative MEP regions (bounded by an isopotential contour of −0.025 hartree).

Results

The calculated energy difference between the in-plane OH rotamers of **2a** is 25 kcal/mol. This indicates that the rotamer with the OH hydrogen atoms away from the phenyl ring is strongly favored due to the severe repulsion of the OH and the phenyl ring hydrogen atoms. The result obtained in the rigid geometry approximation is of qualitative value only; it should merely help in the choice of the lower energy rotamer for the MEP calculation. The energy difference between the tautomeric forms 1*H*- and 2*H*-**10** was calculated to be 12 kcal/mol in favor of the 1*H* tautomer. X-ray[37] and NMR structure determinations[38] of indazole are consistent with the 1*H* tautomer. The same is true of **10** incorporated in the 2-azaergoline framework.[36] The tautomeric equilibrium constant for indazole in water solution is 40.[39] On the contrary, it is close to unity for *C*-methyl substituted pyrazoles.[39] The calculated energy difference between the pyrazole tautomers, 3,4- and 4,5-dimethylpyrazole, is only 1.7 kcal/mol, the latter being more stable. Our calculations of tautomeric energy differences of **9** and **10** compare favorably with the ab initio calculations for **9** and indazole based on INDO geometry optimizations.[40,41] It is interesting to note that the tautomer of **5** found in the crystal structure[15] corresponds to the lower energy tautomer of **9** according to the calculations.

In order to avoid presenting an excessive number of figures resulting from the calculations of the MEP for different rotamers and tautomers in the two parallel planes, only those are presented that have been actually used in the superimpositions of the molecular frameworks.[42] MEP maps calculated in the molecular plane show that the molecules are surrounded by positive isopotential contours. However, **9**, **10**, and **2a** have deep negative minima in the vicinity of the heteroatom lone pairs. The positive (in-plane) contours merely depict an area occupied by an aromatic ring and did not lead us to strictly defined correlations. The MEP calculated in a parallel plane at 1.6 Å from the molecular one is mostly negative with deep minima for all the molecules within the series. The MEP of **2a** was calculated in the parallel planes above and below the catechol ring because the phenyl substituent removes the symmetry. The comparison of the MEP maps indicated that they retained the characteristic features of the alkyl-substituted catechols, i.e., two negative minima in the vicinity of the O atoms.[17] Figure 1a shows the MEP pattern calculated below the catechol ring (with reference to **2** as drawn above). The MEP pattern of **7** (Figure 1b) is characterized by a deep negative minimum located over the benzene ring. It is very similar to that calculated for tryptamine.[22] The MEP map of **8** (Figure 1c) indicates the relative unimportance of the dimethyl substitution. The broad minimum spreads over the C3 and C4 atoms in agreement with the map of pyrrole.[26] The characteristic of the MEP maps of azaindoles[41] and pyrazole[26] is a deep minimum in the vicinity of the pyridinic N atom. Tautomeric rearrangement results in a change of the location of the minimum. Parts d and e of Figure 1 show the MEP maps of the tautomers **9** and **10**, respectively.

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(42) The pertinent data are available from the authors on request.

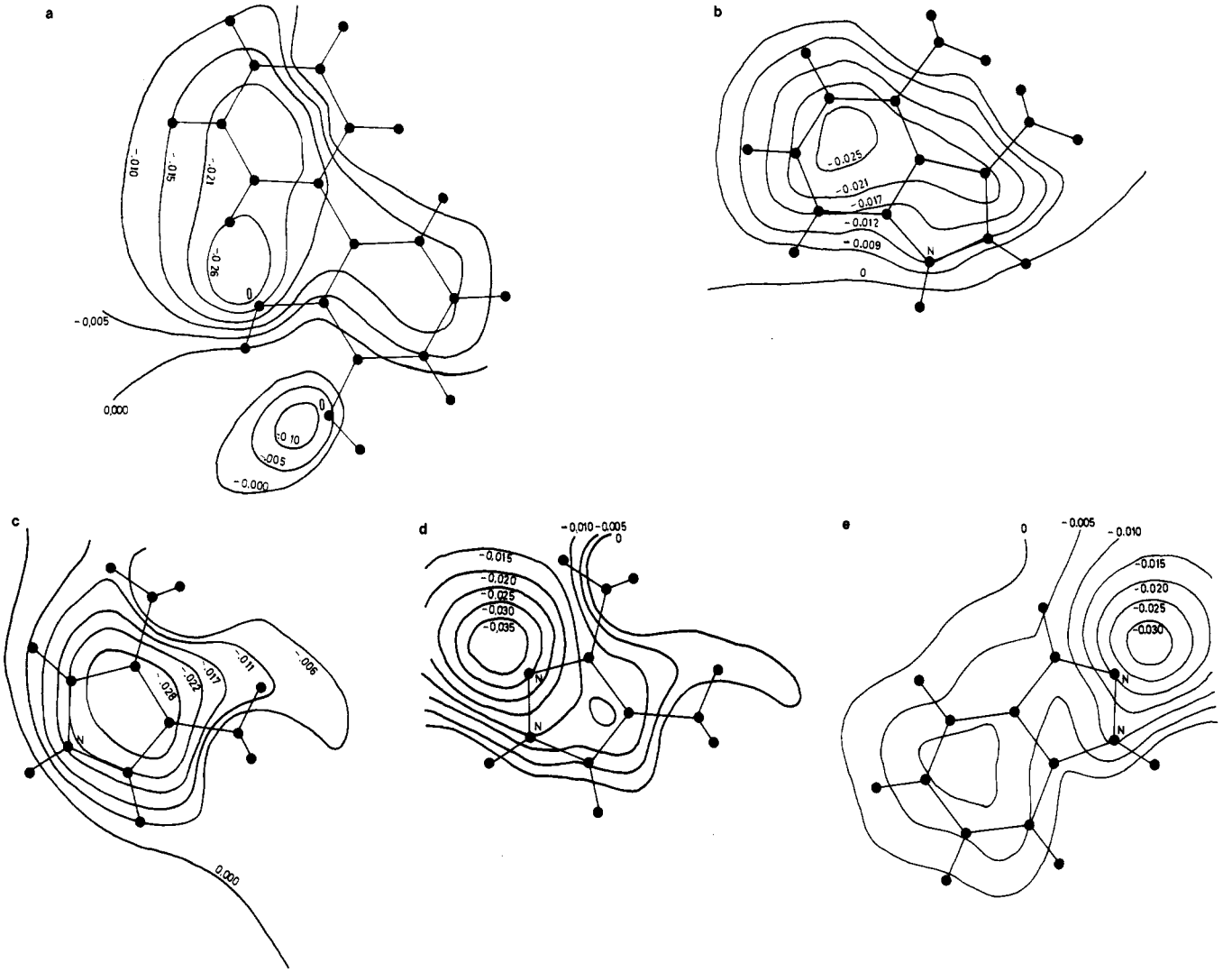

Figure 1. Molecular electrostatic potential map of (a) 2,3-dihydroxybiphenyl calculated in a plane parallel to the catechol ring, at a distance of 1.6 Å, (b) 3,4-dimethylindole, (c) 3,4-dimethylpyrrole, (d) 3,4-dimethylpyrazole, and (e) 3,4-dimethylindazole. Values are in hartrees.

Discussion

Figure 2a–d shows that the matching of the most negative MEP region of **2** with that of **1**, **4**, **5**, and **6** is optimal. It is important that the most negative region in the plane above the catechol ring is close to the "*m*-OH" group (if **2** is viewed as a constrained analogue of DA), which has been shown to be essential for DA activity.[2] Since the tautomeric energy difference of pyrazole derivatives is relatively small, the matching of the higher energy tautomer of **5** is considered to be acceptable (Figure 2c). The matching of the lower energy tautomer was not as good as with the higher energy one. The distance between the positions of the tautomer minima is more than 2.5 Å. The MEP correlation of the pyrazole with the catechol ring resembles that of the thiazole and the catechol ring that was invoked to demonstrate the spatial correspondence between the β-adrenergic drugs tazolol and isoproterenol.[18,19]

While superimpositions based on a simple steric viewpoint obtained by fitting the "acidic" functions show poor congruence of molecular volumes,[10] MEP-based superimpositions shown in Figure 2a–c indicate optimal matching of molecular volumes, too. However, the orientation of the superimposed **6** with respect to **2** (Figure 2d) is notably different from that of **1** (Figure 2a). The molecular frameworks of **6** and **2** occupy different spatial areas. In view of the high steric requirements of DA receptors, one may expect that the shape of molecular bulk might be as important in fitting the receptor site as is the correct three-dimensional dispositions of pharmacophoric groups.[43] The DA inactivity of 2-azaergoline derivatives[14,36] may well be explained by the uncongruent superimposition of molecular volumes since the model of the DA pharmacophore based on fitting the "acidic" functions does not discriminate between the structures of **1** and **6**. In contrast to the superimpositions shown in Figure 2b,c, where the indole NH and the catechol OH group are closely located, the superimposition of **1** and **2** (Figure 2a) does not support the correspondence of the "acidic" functions. On the basis of the optimal matching of the MEP minima, we are proposing this specifically positioned minimum to be an element of the DA pharmacophore. Such a pharmacophoric element implies some sort of stacking interaction of the aromatic ring with a polar group (or a heterocyclic aromatic ring) located at the receptor site. Equivalent hypotheses supported by the theoretical calculations of model drug–receptor interactions have been advanced for

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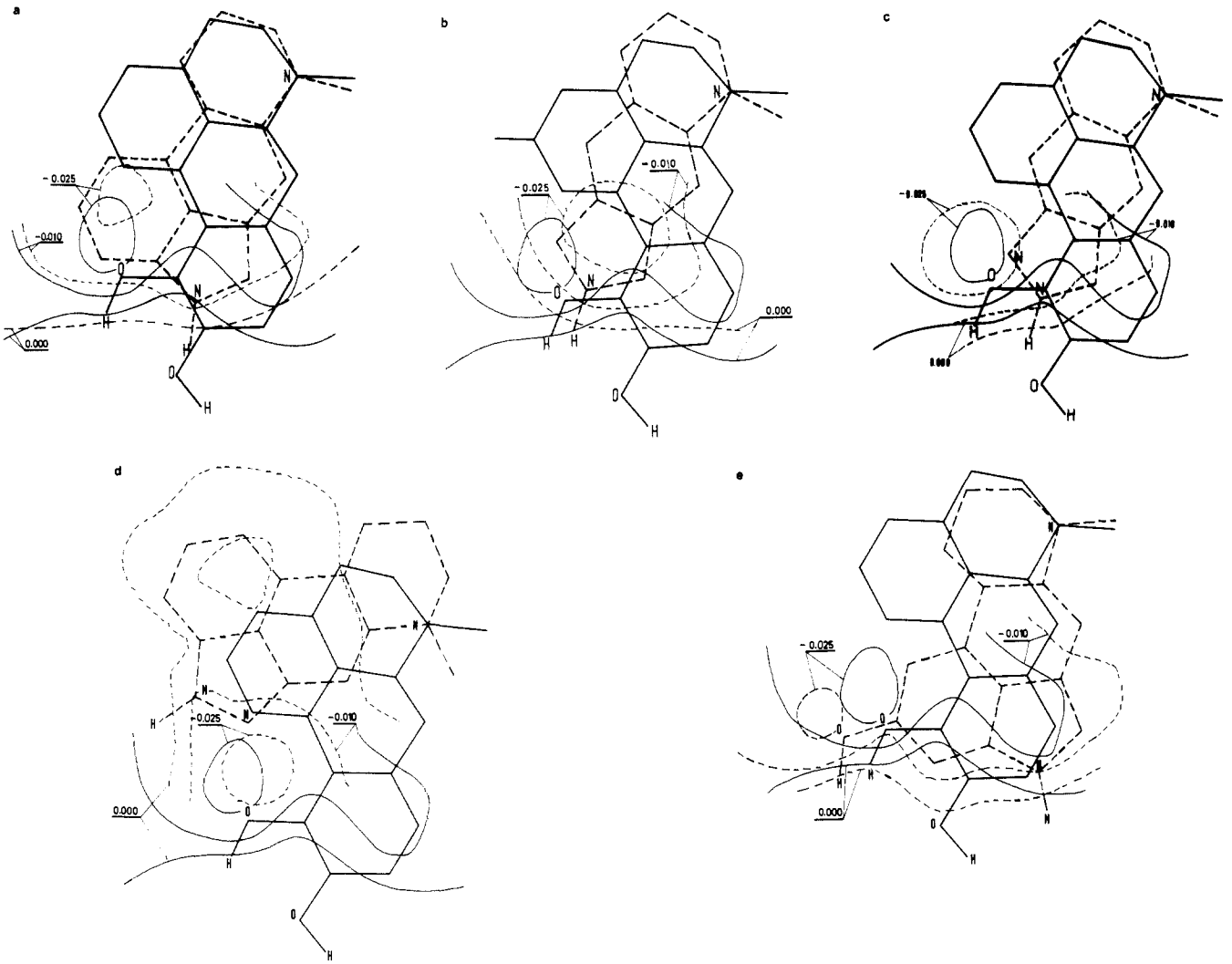
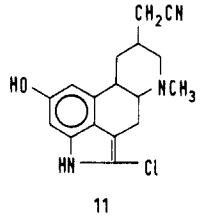


Figure 2. Superimposition of (a) ergoline and apomorphine showing the correspondence of the electrostatic isopotential curves −0.025, −0.010, and 0.000 hartree, respectively, (b) octahydropyrrolo[3,4-*g*]quinoline, (c) octahydropyrazolo[3,4-*g*]quinoline, (d) 2-azaergoline, and (e) 13-hydroxyergoline.

β-adrenergic[18,19] and serotonergic agonists.[22,27]

It is interesting to consider the present correlations by taking into account recent reports on high DA activity of 13-hydroxylergotrile[44] (**11**) and 6-hydroxy-4-[2-(di-*n*-propylamino)ethyl]indole[45] (**12**).



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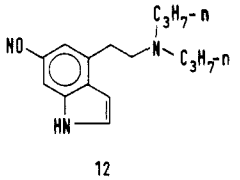

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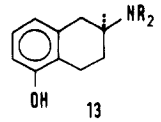
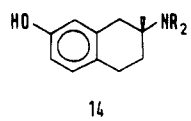
The molecular superimposition of 13-hydroxyergoline and **2** was obtained by using the MEP map of 6-hydroxy-3,4-dimethylindole calculated according to the lines described above. The MEP pattern contains two distinct minima—one above the center of the benzene ring and a deeper one close to the O atom. The map fully corresponds to one of 6-hydroxytryptamine, calculated by Weinstein et al.,[20] differing only in the in-plane orientation of the OH group. The resulting superimposition (Figure 2e) reveals that the mutual orientation of the hydroxyaminotetralin fragments is equal to that of 5-hydroxyaminotetralin (**13**) and 7-hydroxyaminotetralin (**14**) put forward previously[5,6] in order to account for the different chirality of the more active enantiomers. The opposite configurations of **13** and **14** are necessary for an optimal steric matching of the OH groups and the chiral centers with the amino groups, respectively, obtained by rotating one molecule against the other (**15**).[28]



13



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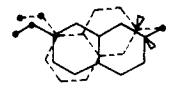

15

The MEP-based model can easily accommodate the nonhydroxylated aminotetralin (**16**) and naphth[1,2-*b*]-1,4-oxazine (**17**) derivatives, which are supposed to possess some DA activity in vivo or exhibit binding affinity for the receptor sites marked with [^{3}H]DA ligands. Both effects

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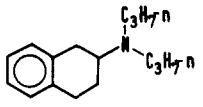
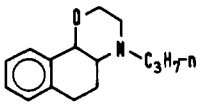
are much weaker when compared with their hydroxylated counterparts.[46,47]



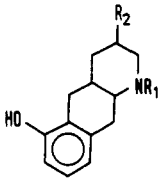
16



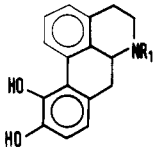
17

The MEP of phenylethylamine calculated 1.6 Å above the benzene ring has negative values with the minimum of −10 kcal/mol above the center of the ring.[48] The benzenic analogues are therefore superimposable on the molecular frameworks of potent DA agonists. However, it is doubtful whether their low activity could be interpreted in terms of the lower absolute MEP values only.

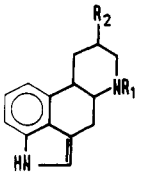
Very recently, Nordmann and Petcher reported the synthesis of DA active compounds—C3-substituted octahydrobenzo[*g*]quinolines (**18**) that combine the essential moiety of **2** (**19**) with the C8 substituents of **1** (**20**).[49]



18



19



20

The superimposition shown in Figure 2a demonstrates that C8 of **1** and C3 of **2** (or of the benzo[*g*]quinoline fragment) are closely located. Therefore, the respective substituents will also occupy the same spatial area. The MEP-based superimposition of **1** onto **2** reinforces Nichols' proposition of the geometrical congruence of the pyrroleethylamine and phenylethylamine fragments. With regard to the MEP pattern generated above the indole ring, we feel that discussing which part of **1** represents the DA pharmacophore makes no real sense since the indole system gives a unique MEP pattern. Dissection of the indole ring of **1** may result in either pyrrolo[3,4-*g*]- or benzo[*f*]-quinoline, which on the basis of MEP patterns are both compatible with **1**; the compatibility of benzo[*f*]quinoline is improved by "*m*-OH" substitution of the phenylethylamine fragment.

Conclusion

The stereochemical similarity between the DA analogues and the ergoline-like structures assessed with the MEP patterns calculated in the surroundings of the aromatic moieties corroborates the assumption that these structures might share the same receptor sites when binding to and activating certain subtypes of the DA receptors. Our results suggest that the analysis of the three-dimensional relations between rigid DA agonists based on the MEP might be useful for SAR considerations in addition to the other structural characteristics that influence significantly DA activity, such as arylethylamine fragment conformation and *N*-alkyl substituents and C8 substituents of ergoline-like compounds. The quantitative SAR must await for consistent pharmacological data from a larger series of structurally different drugs.

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Registry No. Ergoline, 478-88-6; apomorphine, 58-00-4; 3,4-dimethylindole, 81784-47-6; 3,4-dimethylpyrrole, 822-51-5; 3,4-dimethylpyrazole, 2820-37-3; 3,4-dimethylindazole, 16640-81-6; octahydropyrrolo[3,4-*g*]quinoline, 84064-22-2; octahydropyrazolo[3,4-*g*]quinoline, 102628-64-8; 2-azaergoline, 73621-49-5; 1,3-hydroxyergoline, 102537-65-5; 2,3-dihydroxybiphenyl, 1133-63-7.

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