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Conformational Analysis of 2-Aminoindans and 2-(Aminomethyl)indans in Relation to Their Central Dopaminergic Effects and a Dynamic Dopamine Receptor Concept

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Conformational analyses on differently substituted 2-aminoindans of significant pharmacological interest were carried out by the molecular mechanics method (MM2). An X-ray structure of (*R*)-4-methoxy-2-aminoindan has shown the ammonium nitrogen ((−)-D-tartaric acid salt) in an axial position. From comparison with other, highly potent, centrally acting dopamine (DA) receptor agonists, it can be predicted that the active enantiomer (*R*)-4-hydroxy-2-(di-*n*-propylamino)indan should have its nitrogen atom in an equatorial position. This places it close to the aromatic ring plane, which is one of several prerequisites for potent DA receptor agonism. MM2 correctly calculates (*R*)-4-methoxy-2-aminoindan and (*R*)-4-hydroxy-2-(dialkylamino)indan to be more stable in the N-axial and N-equatorial conformations, respectively. Conformational analysis of the dimethyl model compound of the moderately potent dopaminergic phenylpropylamine analogue 4-hydroxy-2-[(di-*n*-propylamino)methyl]indan was also carried out, in order to see if any conformations of this compound satisfy the requirements for dopaminergic agonism. Two such stable conformations were found.

4-Hydroxy-2-(di-*n*-propylamino)indan (1) is a highly potent, centrally acting dopamine (DA) receptor agonist in vivo.[1] It is equipotent to the very active DA agonists (6a*R*)-apomorphine (**2**), (*S*)-5- and (*R*)-7-hydroxy-2-(di-*n*-propylamino)tetralin (**3** and **4**, respectively), and *trans*-(4a*S*,10b*S*)-7- and *trans*-(4a*R*,10b*R*)-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline [*trans*-(4a*S*,10b*S*)-7- and *trans*-(4a*R*,10b*R*)-9-OH-4-*n*-PrOHBQ, **5** and **6**, respectively].[2] All of these potent, centrally acting DA receptor agonists (**2–6**) are fairly planar in their respective low-energy conformations. In particular, (6a*R*)-apomorphine (**2**) and the *trans*-OHBQs (**5** and **6**) are conformationally well-defined, and these molecules have their respective nitrogen atoms 0–1.2 Å (see Table I) above the aromatic ring plane when depicted as in Figure 1, which seems to be one of several prerequisites for potent DA receptor agonism.[2,3]

In their first report on phenolic 2-aminoindans, Cannon et al.[4] may have drawn conclusions from the wrong kind of indan atom types for their Dreiding models and erroneously anticipated the indan system to be planar. However, these authors later correctly assigned the envelope conformation of the cyclopentene ring of the indans.[5] This was also correctly done by Hacksell et al. in a paper on monophenolic 2-aminoindans.[1] In their second paper,[5] Cannon et al. predicted the N-equatorial conformation of the dopaminergic indans to be the active one. Seeman et al. presented a new tetrahedral D_2 agonist receptor model where compound 1 is one of the key compounds.[6]

In the further refinement of DA structure–activity relationship (SAR) studies, Cannon et al. presented the resolution, the determination of absolute configuration of the enantiomers, and the pharmacological testing of the enantiomers of compound 1.[7] As could have been predicted, the more active enantiomer has the *R* absolute configuration, thus corroborating stereochemically with the absolute configuration of compounds **2–6** according to contemporary DA receptor concepts.[2-3,8] When displayed as in Figure 1, the ring C to N direction in all compounds is downward.

Cannon et al. used the precursor 4-methoxy-2-aminoindan (**7**) for resolution, via crystallization of its (−)-D-tartaric acid salt, which gave better separation than alternate possibilities.[7] Interestingly, the X-ray analysis showed that, in the crystal, the indan conformation was the one having the ammonium nitrogen in an axial position. The authors remarked that, even though this is the conformation of **7** in the crystal, it does not necessarily mean that it is the conformation of the dialkylated species 1. The latter, due to its potency, really must have its nitrogen in an equatorial conformation so as to be able to reach a position close to the plane of the aromatic ring, at least at the drug–receptor interaction.[2,3]

In order to study these conformational problems, we carried out molecular mechanics calculations with the MM2 program[9] on compound **7** and the model compounds

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Table I. Energy Differences between N-Equatorial and N-Axial Conformations of 4-OMe/OH-2-Amino/Ammonium Indans

	steric energy, kcal/mol[a]		difference, kcal/mol:	distance, Å			
				N–O		N–(aromatic ring plane)[b]	
structure	N-eq	N-ax	N-eq – N-ax	N-eq	N-ax	N-eq	N-ax
7$^+$	8.37	5.48	+2.89	5.40	4.59	−0.29	−2.01
8$^+$	2.28	−0.59	+2.87	5.46	4.59	−0.30	−2.01
7	7.17	6.61	+0.56	5.45	4.84	−0.12	−1.94
8	1.09	0.54	+0.55	5.52	4.89	−0.13	−1.94
9$^+$	11.51	13.45	−1.94	5.46	4.60	−0.13	−2.16
10$^+$	5.45	7.46	−2.01	5.53	4.64	−0.12	−2.16
9	13.3	15.8	−2.52	5.48	4.86	−0.03	−2.05
10	7.21	9.77	−2.56	5.55	4.94	−0.03	−2.04
11				7.32		−0.02	
12				6.59		−0.02	
13				7.41		−0.05	
14				6.55		+0.06	
2				6.53[c]		+1.2[c]	

[a] In each case the lowest energy conformation was selected for calculation. [b] + and − refers to above and below the aromatic ring plane, respectively, when depicted as in Figure 1. [c] There are two different conformations (A and B) of apomorphine in the X-ray structure.[15,16] Both of these converge upon minimization to one single conformation (free amine), from which the data shown were extracted. N–O distance in N–(11-OH).

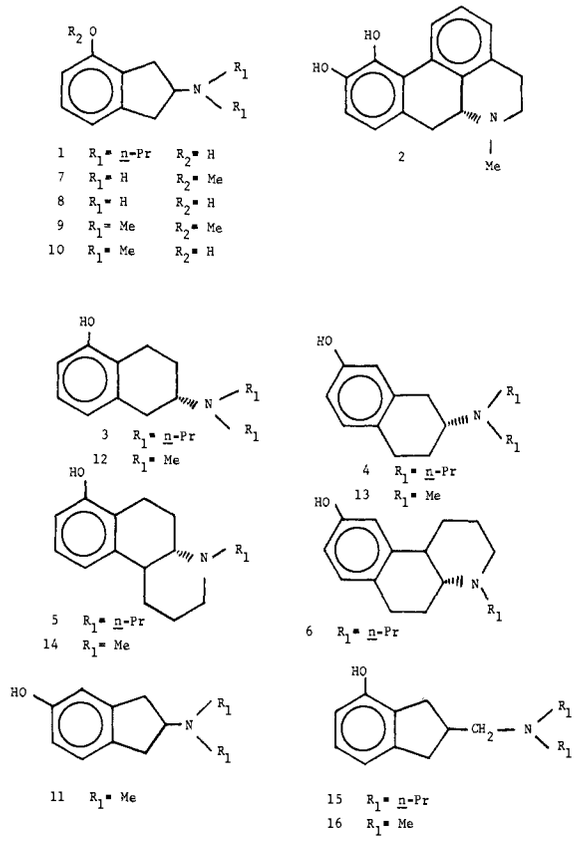


Figure 1. Structures discussed. All structures oriented with their prominent aromatic ring in the plane of the paper and with a relative orientation to one another according to ref 2 and 3.

8–10 in their free amine and ammonium forms, in both the N-equatorial and N-axial conformations (Table I). For comparison, MM2 data were also retrieved for the model compounds (*R*)-5-hydroxy-2-(dimethylamino)indan (**11**), (*S*)-5-hydroxy-2-(dimethylamino)tetralin (**12**), (*R*)-7-hydroxy-2-(dimethylamino)tetralin (**13**), *trans*-(4a*S*,10b*S*)-7-hydroxy-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**14**) and (6a*R*)-apomorphine (**2**) (Figure 1 and Table I).

Another, previously presented,[1] though less potent (by a factor 10–15 as compared to **1**), centrally acting DA receptor agonist is 4-hydroxy-2-[(di-*n*-propylamino)-methyl]indan (**15**), a model compound (**16**) of which was also included in this study. Most DA receptor agonists have the phenethyl or pyrrolylethylamino moiety inherent in their structural framework. In contrast, compound **15** has the phenylpropylamino moiety. In order for this compound to satisfy the structural and stereochemical prerequisites for DA receptor agonism, it should have its (aminomethyl)methylene function in an equatorial position with the *S* absolute configuration of carbon 2. This might, in a particular conformation, bring the nitrogen atom into a position close to the aromatic ring plane, with a C2–N direction downward and with the nitrogen lone pair directed downward, approximately perpendicular to the aromatic ring plane. We studied the energy profile of compound **16** by using the two angle driver option in MM2.[9] The energy surface and a topographical plot are displayed in Figures 2 and 3, respectively, and extracted conformational data are presented in Table II.

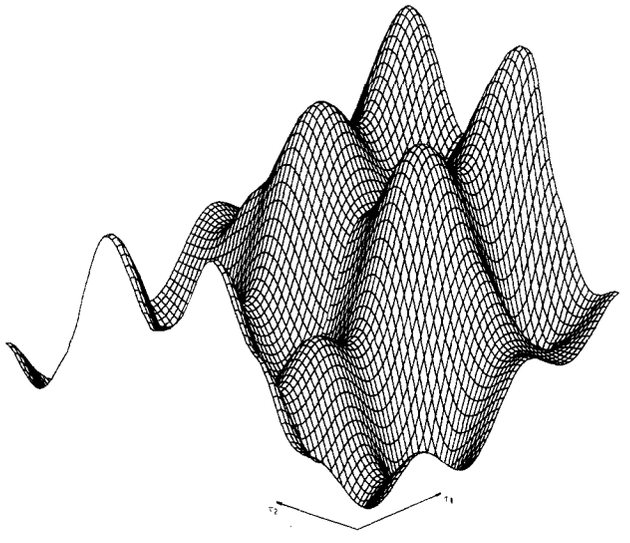
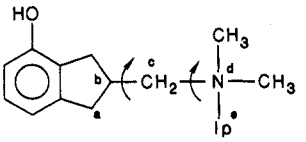


Figure 2. Energy surface for the two angle driver of the side chain of (*S*)-4-hydroxy-2-[(dimethylamino)methyl]indan (**16**). Both τ_1 = a–b–c–d and τ_2 = b–c–d–e were driven 0–360° with 10° increment (cf. Table II).

Computational Methods

All calculations were performed on a Digital Microvax Workstation II, using the MM2 program.[9] Internally developed graphics software was used for molecular display, fit, and data extraction.[10] Starting geometries were cre-

Table II. Conformational Data for Compound 16, Local Minima



conf	τ_1 = a-b-c-d	τ_2 = b-c-d-e	steric energy, kcal/mol	Boltzmann distribution, % (37 °C)	distance, Å	
					N-O	N-(aromatic ring plane)[a]
1	83.5	60.1	10.21	1.56	6.86	−0.65
2	−175.6	56.6	8.13	45.51	5.86	−0.29
3	−41.1	57.5	11.46	0.21	6.27	+1.56
4	69.2	173.2	10.65	0.77	6.92	−0.41
5	170.3	−173.0	10.61	0.82	6.18	−0.41
6	−84.4	165.4	15.42	3.36×10^{-4}	6.17	+0.96
7	54.5	−56.9	8.08	49.35	6.90	−0.31
8	157.1	−60.9	10.19	1.61	6.27	−0.63
9	−87.5	−57.3	11.54	0.18	5.78	1.53

[a] See Table I, footnote *b*.

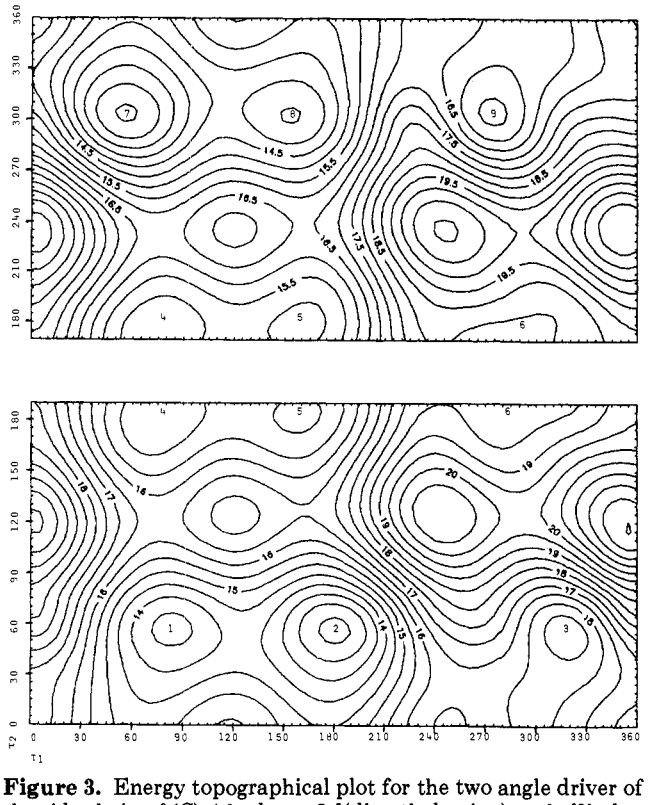


Figure 3. Energy topographical plot for the two angle driver of the side chain of (*S*)-4-hydroxy-2-[(dimethylamino)methyl]indan (**16**). Both τ = a-b-c-d and τ_2 = b-c-d-e were driven 0–360° with 10° increment (cf. Table II).

ated by using the Model graphics input.[11]

Results and Discussion

The results from the MM2 calculations (Table I) are consistent with experiment, i.e., both X-ray analysis[7] and pharmacological data.[7] As seen from Table I, the N-axial conformation of 7^+ (ammonium) is more stable by 2.9 kcal/mol than its N-equatorial counterpart. The same relationship is true also for the hydroxy analogue 8^+ (ammonium). Also, the two free amines **7** and **8** are more stable in their N-axial than in their N-equatorial conformations.

By analyzing the details in the printouts, one can assess the importance of different contributions to the final steric energy. The version of the MM2 program used for these calculations treats hydrogen bonding by modifying the existing van der Waals (VdW) function.[12] The NH···O distances in both the N-axial and especially the N-equatorial conformations are obviously too long for prominent hydrogen bonding between these two functionalities. The strongest contribution in terms of NH···O hydrogen bonding is 0.02 kcal/mol in 7^+-N-equatorial and 0.09 kcal/mol in 7^+-N-axial. The explanation for the stability of 7^+- and 8^+-N-axial is consequently to be found elsewhere. When studying the different components in the final steric energy result, one sees that the differences can be found in lower values of the parts "other" (VdW interactions other than 1,4) and "torsional" in the N-axial conformations. Actually, the outputs show that it is still hydrogen bonding that makes the differences, however, not NH···O but rather NH···C hydrogen bonding to the aromatic carbon atoms. The sum of the two strongest of these contributions are 0.20 kcal/mol in 7^+-N-equatorial and 1.86 kcal/mol in 7^+-N-axial. In the N-alkylated species, the N-equatorial conformations are more stable due to the fact that the bending energies are higher in the N-axial conformations.

The result from the conformational analysis of compound **16** (Figures 2 and 3) shows that there are in toto nine local minima, each of which was subsequently fully minimized (Table II). From an N–(aromatic ring plane) distance point of view, two of these (conformations 3 and 9) can be considered less probable as representing DA receptor agonists. Conformation 6 has a relatively high energy and is thus less abundant (3.4×10^{-4} % in a Boltzmann distribution at 37 °C). There are only two of the remaining conformations that satisfy the requirement of an N-lone pair direction downward and roughly per-

(10) Lii, J.-H.; Yuh, Y., unpublished graphics software from the Department of Chemistry, University of Georgia, Athens, GA 30602.

(11) Still, W. C., Department of Chemistry, Columbia, University, 116th Street Broadway, New York, NY 10027.

(12) The MM2 program (MM2-85, available from the Quantum Chemistry Program Exchange and from Molecular Design, Ltd.) has been modifled (Kok, R., unpublished) to calculate hydrogen bonds. This hydrogen bond term has the same functional form as a van der Waals interaction, and we have adjusted the parameters to reproduce the energies of several ab initio calculations and electron diffraction results on compounds that hydrogen bond either with another molecule or internally. The ammonium hydrogen (type 28) to phenol oxygen (type 6) and aromatic carbon (type 2) have the hydrogen bond parameters: VdW constant ϵ = 2.200 kcal and sum of VdW radii = 2.080 Å, and VdW constant ϵ = 1.000 kcal and sum of VdW radii = 2.180 Å, respectively.

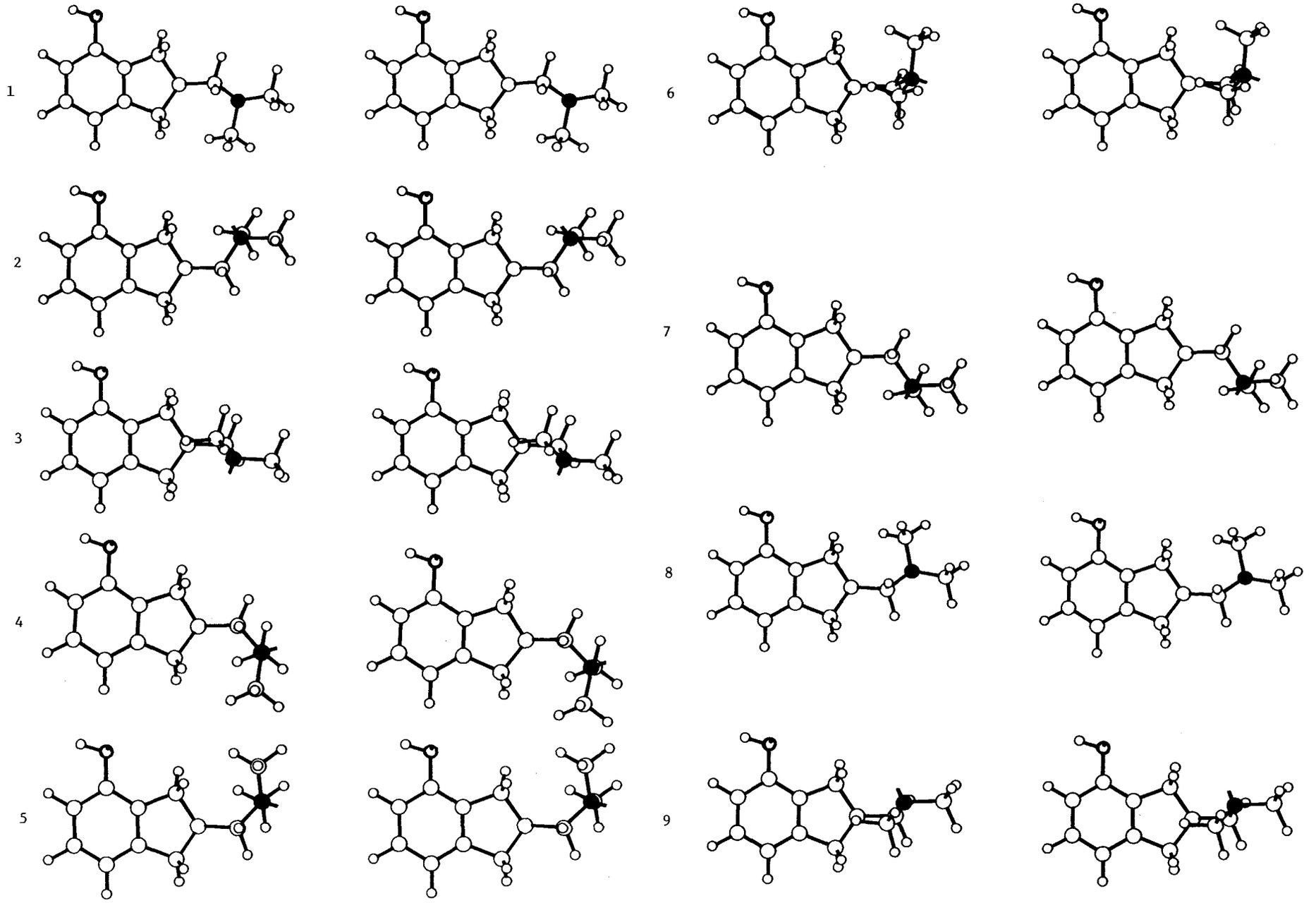


Figure 4. Stereo pictures of conformations 1–9 of the model compound **16**.

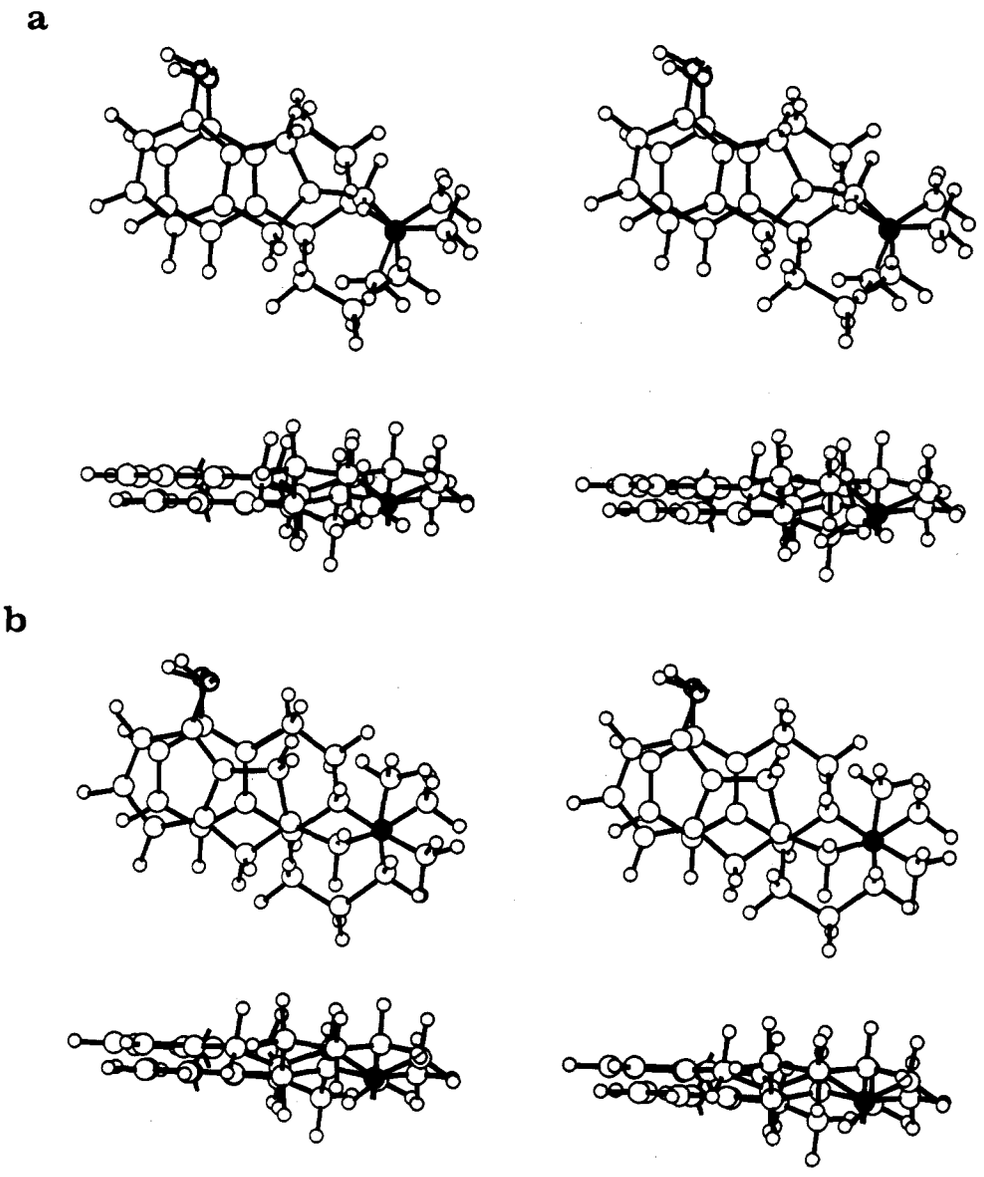


Figure 5. Computer-generated fits between (a) compounds **16** (conformation 1) and **14** and (b) compounds **16** (conformation 8) and **14**. Both *xy* and *xz* plane orientations displayed.

pendicular to the aromatic ring, and these are conformations 1 and 8 (see stereo pictures of all nine local minima in Figure 4).

The fully minimized conformations 1 and 8 were fitted by least-squares methods to compound **14**, used as a DA agonist template in this study.[3] Both conformations 1 and 8 have similar energies (10.2 kcal/mol), which are 2.1 kcal/mol above the global minimum represented by conformation 7 (8.1 kcal/mol), and both give reasonably good fits to the template as seen from Figure 5. This figure was created by fixing the nitrogens at the same points, fitting only the oxygens, and keeping the aromatic rings parallel in the *xy* plane, in which the aromatic rings of all compounds to be fitted were oriented before fitting. The distance between the two aromatic rings is 0.64 Å in this fit, which is well within the 0–1.2 Å for DA agonists (Table I). The fact that both conformations 1 and 8 have higher energies than the global minimum might provide an explanation for the lower potency of **15** as compared to i.a. **1**.

The N···O distances in conformations 1 and 8 are 6.86 and 6.27 Å, respectively, also well within the 5.5–7.4 Å for extremes of highly potent DA receptor agonists[6] (Table

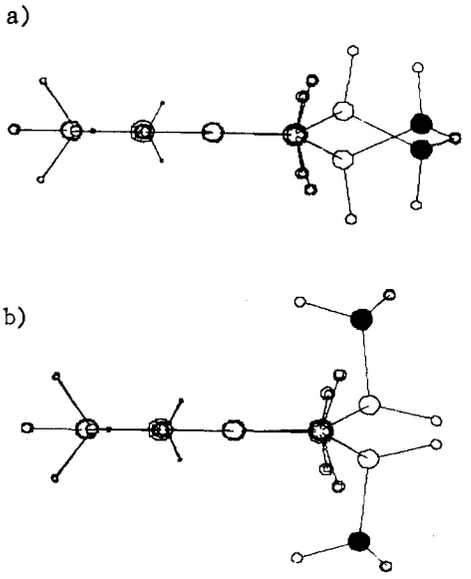


Figure 6. Fictive fits of (a) N-equatorial (*R*)- and (*S*)- and (b) N-axial (*R*)- and (*S*)-4-methoxy-2-aminoindan (**7**) (no lone pair included).

I) (see below). The extremely short intramolecular distance N···O in compound 1 (5.5 Å) is somewhat puzzling compared with the corresponding distances in the other potent DA agonists 2–6 (6.6–7.4 Å).[6] Recent DA receptor speculations by Carlsson and Löfberg[13] might offer a tentative explanation for this situation. These authors suggested that DA agonists and antagonists possibly may interact with the same receptor site. Antagonists generally have high affinity, perhaps filling out most of the receptor. In contrast, agonists generally have lower affinity, but instead show intrinsic efficacy. Agonists really should not fit to the receptor by filling it out but maybe stick to one side of the receptor (presumably the side binding the nitrogen) and attract the other side, thus activating the receptor via a conformational change. If so, agonists could have different sizes and still induce similar conformational changes in the receptor. The question thus would not be how small, but rather how large an agonist can be and still activate the receptor. At a certain size it might be that an agonist turns into an antagonist because it has affinity but it might be too large to perform the conformational change necessary for receptor activation. This new concept does not violate previously presented DA receptor models, but rather provides a complement to them.[2-3,8] The idea of a flexible DA receptor has also been presented by Nichols, who stated that this receptor undoubtedly possesses the flexibility to allow accommodation to a variety of agonist conformations with N···O distances ranging from 6.5 to 7.5 Å.[14]

Cannon et al.[7] tried other indan derivatives in their attempts to resolve compound 1. However, the D-(−)-tartaric acid salt of compound **7** was the best choice. In hindsight it is understandable that it turned out this way since the two axial enantiomers are geometrically more different than the two equatorial enantiomers (see Figure 6a,b). Maybe one could develop this into a predictive concept by using conformational analysis with MM2 calculations before attempting the resolution. However, the complicating factor of crystal packing might seriously distort conformations so that the predictions based on isolated molecules might turn out to be wrong.

In summary, this study provides an explanation for the unexpected N-axial conformation of the X-ray structure of compound (*R*)-**7**.[7] In addition, it supports the suggestion of Cannon et al. that, at the DA receptor, the N-equatorial conformation of compound 1 is the more stable one.

This study also provides an explanation for the dopaminergic effects of the atypical phenylpropylamine, compound **15**, thus emphasizing that one is not limited to phenethylamines in the design of new DA agonists. If the prerequisites of an aromatic ring with a hydrogen bond donor function, proper chirality, and a basic nitrogen with a defined lone-pair direction, possibly substituted with alkyl groups of a certain size, are satisfied, one may be able to come up with completely new structures that will exhibit DA receptor agonist properties. In particular, the *N*-(hydrogen bond donor function) distance is not a very critical parameter and can obviously vary, at least between 5.5 and 7.4 Å without loss of potent agonist effects. In addition, the N–(aromatic ring plane) distance is not very critical either, since in the very potent D_1/D_2 receptor agonist 6a*R*-apomorphine that distance is as long as 1.2 Å (Table I). These findings support the dynamic DA receptor concept, which is also fully compatible with previously presented DA receptor concepts.[2-3,8]

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Registry No. 1, 94843-89-7; 7, 94903-37-4; 7 ((−)-D-tartrate), 106626-16-8; 8, 106626-18-0; 9, 106626-19-1; 10, 106626-20-4; 11, 106626-21-5; 12, 106626-22-6; 13, 106626-23-7; 14, 106709-18-6; 15, 106626-17-9; 16, 106626-24-8.

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