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Original paper

A quantum-chemical and experimental study of the hallucinogen (±)-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON)

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Summary — The electronic structure of 1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON) was calculated at the CNDO/2 level, and the racemic compound was synthesized and found to be hallucinogenic at doses of 4 mg. DON differs from its similarly active congeners in that a hydrophilic nitro group replaces lipophilic substituents at C-4 of the benzene ring. The implications for the mechanism of serotonin receptor binding of these drugs are discussed.

Résumé — **Une étude de chimie quantique et expérimentale sur le (±)(diméthoxy-2,5 nitro-4 phényl)-1 amino-2 propane (DON) à propriétés hallucinogènes.** *La structure électronique du (diméthoxy-2,5 nitro-4 phényl)-1 amino-2 propane (DON) a été calculée au niveau CNDO/2 et la substance racémique, testée, s'est avérée hallucinogène à la dose de 4 mg. Le DON se distingue de ses congénères à activité semblable par le remplacement des substituants lipophiles du C-4 du noyau benzénique par un groupe nitro hydrophile. On discute la portée de ces faits sur le mécanisme de la liaison entre ces drogues et les récepteurs à sérotonine.*

frontier molecular orbitals / CNDO/2 / electrophilic superdelocalizability / atomic charge / lipophilicity / serotonin receptor affinity / hallucinogenic potency / DON

Introduction

One of us recently proposed a method relating receptor affinity to molecular—electronic structure (*i.e.*, electronic and steric effects) [1]. Its application to QSAR analyses of phenylalkylamines (PAA) [2] has led to significant correlations for this class of psychotropic substances. In this paper, we report a quantum-chemical QSAR study on 1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON), based on an equation developed earlier for PAA [2], which indicates that this compound may be psychoactive at low doses. Pharmacological testing of the target compound showed that it is indeed a potent hallucinogen.

Models, Methods and Calculations

The equation mentioned above relates the variation of relevant molecular—electronic structure factors to the variation of the binding affinity (pA_2) for serotonin receptors in the rat stomach fundus [3]. This sensitive pharmacological preparation appears to be a useful model for the prediction of PAA hallucinogenic activities [3], although exceptions have been noted [4], and several different lines of evidence suggest that non-serotonin receptors are also probably involved in the psychopharmacology of PAA and IAA (indolealkylamines) [5]. These peripheral serotonin receptors are not clearly related to binding sites in the mammalian brain [6—9], but nevertheless, it can be shown that pA_2 values determined using the rat stomach fundus [3] are significantly correlated with affinities for central serotonin binding sites [10].

In the case of the PAA, there has been some controversy regarding the role of the C-4 substituent. It is well known that 2,5-dimethoxy substitution is associated with high hallucinogenic potency, and that introduction of a hydrophobic atom or group at C-4, such as bromine, methyl or ethyl, enhances this activity, while also affecting the qualitative nature of the drug-induced experience in humans [11]. It has been speculated that the receptor possesses a lipophilic site to accommodate this substituent [12]. The affinities of 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropanes for the rat stomach fundus serotonin receptor are generally high ($pA_2 \approx 7.0$), but it has been suggested that the lipophilicity of the C-4 substituent only plays a minor role

in these cases [3]. It seems important therefore to evaluate a broader range of 4-substituted PAA to clarify these points. In particular, a nitro group at this position, though hydrophilic, could be expected to fulfill the electronic and steric requirements of the receptor.

(±)-1-(2,5-Dimethoxy-4-nitrophenyl)-2-aminopropane (racemic DON) was first synthesized more than ten years ago and found to be equipotent with the psychoactive 4-methyl analogue (DOM) in an apparently non-specific rat behavioral assay [13]. The fact that the nitro group is distinctly hydrophilic (π = — 0.28 *vs.* 0.56 for methyl, 0.86 for Br, and 1.02 for ethyl [14]) and that DON itself has an octanol—water partition coefficient which is low in relation to those of its strongly hallucinogenic 4-methyl, -bromo, and -ethyl analogues DOM, DOB, and DOEt (log P = 1.74 *vs.* 2.24, 2.54, and 2.76, respectively) and is not as effective as these on serotonin receptors in the sheep umbilical artery (log RBR = 0.67 *vs.* 1.00, 1.57, and 1.59, respectively) [12], suggested that this compound might not be a very potent hallucinogen in humans. Much more recently, however, it has been shown that DON produces stimulus generalization in rats trained to discriminate DOM from saline, and that its affinity for the rat stomach fundus serotonin receptor lies in the same range as those of the highly potent hallucinogenic PAA [3]. DON had not been included among the compounds used to generate the QSAR for PAA cited above [2]. It thus seemed of interest to determine if this QSAR could predict the experimentally determined pA_2 receptor affinity, and if the correlation between this *in vitro* property and hallucinogenic potency in humans [3] also held for this substance.

The electronic structure of DON was obtained using Molecular Orbital Theory at the CNDO/2 level [15], employing the geometry described in our previous QSAR study [2]. The electron density maps were obtained for the highest occupied molecular orbital (HOMO) and the second highest occupied molecular orbital (SHOMO) from the eigenvectors of DON [16]. For the benefit of comparison, we made the same computations for 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB), 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), and 1-(4-ethyl-2,5-dimethoxyphenyl)-2-aminopropane (DOEt). All the calculations were carried out for the *N*-protonated forms.

Chemistry and Pharmacology

(±)-DON was synthesized as described previously [3]. Since the nitrate was found to be easier to purify than the hydrochloride, the former salt was used in the clinical trials. (±)-DON nitrate was subjected to preliminary screening by eight normal volunteers familiar with the effects of psychotropic substances, following a published procedure [17]. Once the active dose level had been established, the number of subjects was increased to a total of 16 (12 male, 4 female, aged 21—51 years), with a total of 30 trials. The 'double conscious' technique of Alles *et al.* and Shulgin *et al.* [18—20] was used throughout. Some trials were conducted individually and some in group sessions in an informal setting. The subjects were asked to describe their experiences at the end of each session.

Results and Discussion

The relevant molecular—electronic structure indices of DON are presented in Table I with the calculated and experimental receptor affinities and the corresponding data for the 4-bromo, -methyl and -ethyl analogues. It is clear that the 4-nitro compound has superdelocalizability and charge indices which are very close to those of the highly potent DOB. Consequently, the introduction of these values into the appropriate QSAR equation [2]:

$$pA_2 = 14.8645 + 2.4328\ S_2^E + 5.5463\ Q_5 + 8.3527\ Q_8$$

(where S_2^E is the electrophilic superdelocalizability at C-2 and Q_5 and Q_8 are the net charges at C-5 and C-8, respectively) predicts a receptor affinity for DON which is of the same order as that calculated for DOB and very close to the experimental value determined for the more active (*R*)-(—) isomer of DON. It should be stressed that the experimental pA_2 values for DON are affected by particularly large standard deviations [3]. Also, the QSAR was developed using receptor affinities determined for fourteen achiral phenylethylamines, four pairs of enantiomeric phenylisopropylamines and the less active (*S*)-(+) enantiomer of DOB (the pA_2 value for (*R*)-DOB is not available, presumably due to its strong agonist properties [4]).

Table I. Structure indices and calculated and experimental rat stomach fundus serotonin receptor binding affinities of 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropanes.

X	S_2^E	Q_5	Q_8	pA_2 calc.	pA_2 exp. [3]
NO_2	— 3.8702	0.1941	0.1196	7.52	7.49 ± 0.26[a] 7.07 ± 0.47[b]
Br	— 3.9632	0.1909	0.1194	7.11	7.35 ± 0.08[b] 6.93 ± 0.08[c]
CH_3	— 4.0431	0.1457	0.1148	6.79	7.15 ± 0.13[a] 6.41 ± 0.08[c]
C_2H_5	— 3.9916	0.1450	0.1190	6.95	7.18 ± 0.09[b]

[a](*R*)-(—).
[b](±).
[c](*S*)-(+).

The correlation found by Glennon *et al.* [3] between the pA_2 value in the rat stomach fundus and the total hallucinogenic dose in humans (*THD*), predicts a *THD* of 1.94 μmol of DON (0.5 mg of free base or 0.6 mg of the nitrate) from our calculated receptor affinity. Even assuming that the contribution of the (*S*)-(+)-isomer to this activity is negligible, these values suggest that DON may be a potent hallucinogen, if its relatively poor lipid solubility does not prevent it from reaching the CNS efficiently. Acute oral administration of a total dose of 2 mg of the racemic nitrate (6.6 μmol) results, after a period of a little more than 1 h

in an amphetamine-like stimulated state. When 3 mg (10 μmol) are taken, these symptoms are maintained but stomach cramps and anxiety appear, the volunteers declaring that the general feeling is suggestive of the beginning of a hallucinogenic experience. At a total dose of 4.5 mg (15 μmol), the malaise is minimal or absent, and a psychedelic (not psychotomimetic) state ensues, with intense visual hallucinations, enhanced perception of color, slight hyperthermia and often a desire for physical activity. Visual and sometimes auditive distortions persist for about 8 h and amphetamine-like stimulation is usually present at least into the 14th h, although some subjects also reported longer-lasting psychedelic experiences.

Our calculation of a pA_2, similar to the experimental value for (*R*)(—)-DON, using a theoretical correlation equation (*i.e.*, containing no empirical lipophilicity parameters), supports the suggestion that the lipophilicity of the PAA C-4 substituent has little effect on receptor affinity [3]. It must be kept in mind that the hydrophobic constant π increases with group size and is correlated with molecular weight and van der Waals volume [21]. It is therefore of interest that empirical equations, developed using the sum of either the van der Waals volumes or the molar refractions of the ring substituents in PAA (the sum of the substituent π parameters gave no significant correlation [22]), can predict the serotonin receptor affinity of DON extremely well. It seems very likely that this receptor has a region controlling only the size (and presumably the orientation) of the substituent at PAA C-4, but not its lipophilicity, and that the electronic effect of this atom or group is paramount in determining the pA_2 value of the drug.

Regarding *in vivo* properties, it is worth noting that a hydrophilic group at the C-4 of a PAA has no crucial influence on the transport properties of the drug, which reaches its central sites of action in effective concentrations even when log *P* is as low as 1.74 (*cf.* 2.24 for DOM, 2.54 for DOB, and 2.76 for DOEt [12]). More striking in this context is the fact that mescaline should have any central effect at all with its log *P* of 0.78 [12]. It should be remembered that the correlation of pA_2 with *THD* [3], which we have used to predict the activity of DON, is based on a set of data points which includes (±)-DOB and its 4-unsubstituted analogue. It has recently been shown that the hallucinogenic potencies of these two substances are much less than had been generally acknowledged [23, 24]. Furthermore, the literature source [11] of the human pharmacological data indicates that the potencies of (—)-and (±)-DOM and of (±)-DOEt are lower than the figures used to derive the correlation [3]. Therefore, any prediction of *THD* values made in this way probably errs on the low side. The predicted value for DON, from our calculated pA_2 receptor affinity, is 1.9 μmol. This suggests that, if the (*S*)-(+) isomer contributes little to its activity, (±)-DON nitrate should be psychoactive at doses of 1.2 mg or slightly less, while our experimental (acute, oral) *THD* for (±)-DON nitrate is about 4.5 mg. This discrepancy probably reflects the above mentioned source of error in obtaining the correlation between pA_2 and *THD* [3], but it may also be largely explained by the unfavorable partition constant of DON or by more efficient metabolic disposal. The uncertainties involved in these studies, however, do not allow any definitive interpretation. It would therefore be of interest to determine its potencies (and those of related compounds) by different routes of administration circumventing gastrointestinal absorption and the blood—brain barrier.

Figs. 1—4 show the electron density maps for the HOMO and the SHOMO of DON and DOB. Inspection of these figures reveals that the SHOMO of DON (Fig. 2) is very similar to the HOMO of DOB (Fig. 3). Also, the HOMO of DON (Fig. 1) resembles the SHOMO of DOB (Fig. 4). The HOMO and SHOMO of DOB are separated by about 0.9 eV in the CNDO/2 calculation, and the corresponding levels of DON are closer still. The photoelectronic spectra of these substances show that the two lowest ionization potentials differ by 0.98 eV for DOB [25] and 0.73 eV for DON (R. Gleiter, B. K. Cassels and J. S. Gómez-Jeria,

Fig. 1. Electron density map of the HOMO of DON in the plane $Z = 0.5$ Å (10^{-3} e).

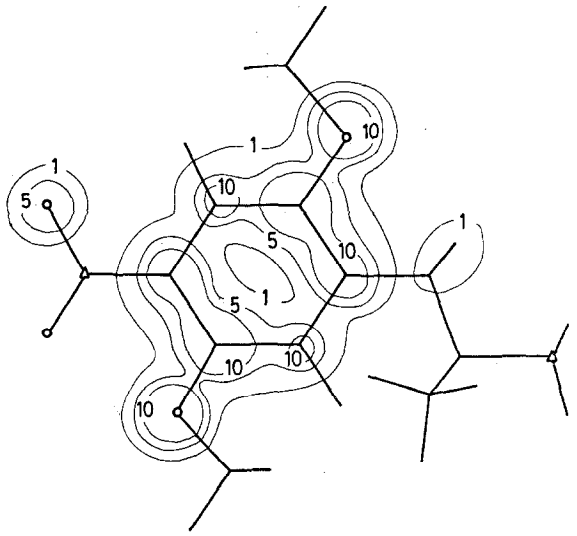

Fig. 2. Electron density map of the SHOMO of DON in the plane $Z = 0.5$ Å (10^{-3} e).

unpublished results). It therefore seems possible that the energy levels are actually reversed.

Figs. 5 and 6 show, respectively, the HOMO and SHOMO of protonated serotonin. Both orbitals appear to be centered in the aromatic system exhibiting π character. If one disregards the C-4 substituent, the SHOMO of DON (Fig. 2) and the HOMO of DOB (Fig. 3) are quite similar to the HOMO of serotonin (Fig. 5). This resemblance could explain, in a first approach, the high serotonin receptor affinities of DON and DOB [3].

The HOMO of DON (Fig. 1) is centered on the oxygen atoms of the nitro group and has π character. The SHOMO of DOB (Fig. 4) flanks the bromine atom, and corresponds to a $3p_y$ lone pair of electrons that might participate in a charge transfer interaction. Thus, the high electron density available at the 4-substituents of DON and DOB and, presumably, of the very potent DOI [11], but not of DOM, DOEt or in serotonin, might also favor receptor binding.

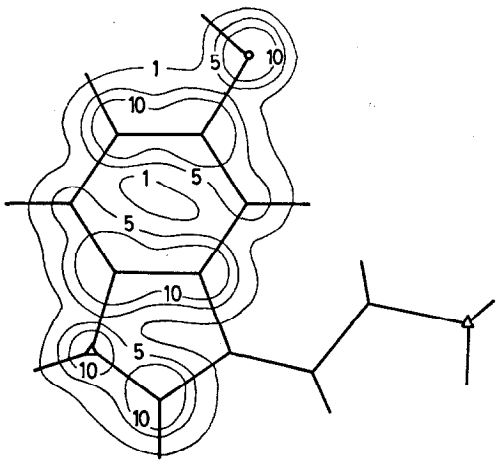

Fig. 5. Electron density map of the HOMO of serotonin in the plane $Z = 0.5$ Å (10^{-3} e).

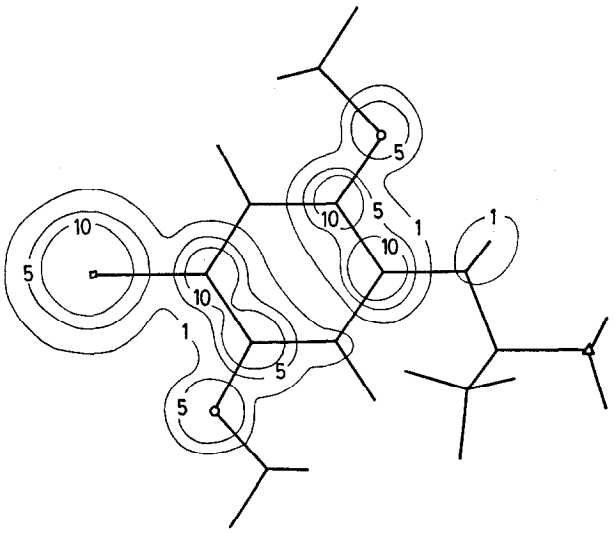

Fig. 3. Electron density map of the HOMO of DOB in the plane $Z = 0.5$ Å (10^{-3} e).

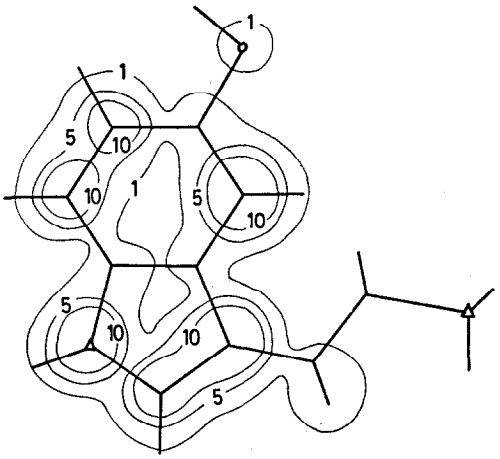

Fig. 6. Electron density map of the SHOMO of serotonin in the plane $Z = 0.5$ Å (10^{-3} e).

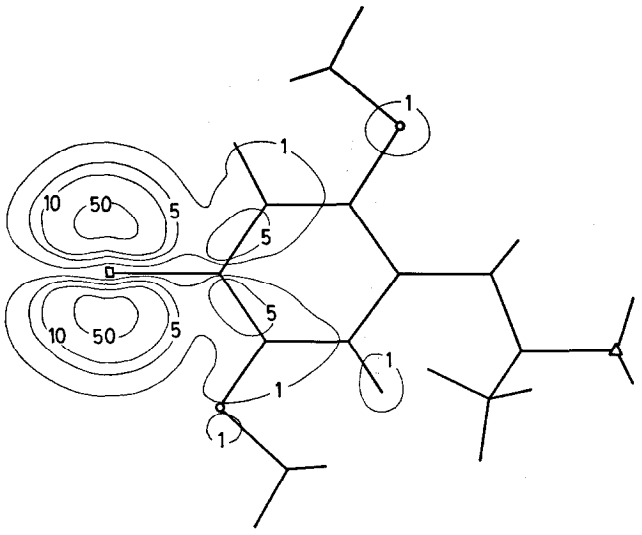

Fig. 4. Electron density map of the SHOMO of DOB in the plane $Z = 0.5$ Å (10^{-3} e).

The main conclusions of this work are: 1) (±)-DON is a very potent hallucinogen when taken orally, and its activity is well correlated with its pA_2 in the rat stomach fundus preparation [3]. 2) The theoretical QSAR developed for PAA [2] is a good predictor of the pA_2 of (*R*)(—)-DON in the same system [3]. 3) Although the hydrophilicity of the nitro group and the consequent low octanol—water partition coefficient of DON do not seem to diminish its affinity for the appropriate receptor(s) in the brain, they may reduce its access to the CNS to an appreciable extent. 4) The similarity of the SHOMO and HOMO of DON and DOB, respectively, to the HOMO of serotonin could be implicated in their high serotonin receptor affinities. The corresponding orbitals of DOM and DOEt (not shown) also resemble those of serotonin in their electron density distribution. 5) The 4-substituents of hallucinogenic PAA appear to enhance receptor binding by modulating the electron distribution in the aromatic ring, primarily at their point of attachment, and also by a direct interaction

with a complementary area of the receptor surface, a situation which cannot occur with the 7-unsubstituted serotonin. 6) The nitro group and the bromine atom of DON and DOB have high electron densities contributing to the occupied frontier molecular orbitals. These electron-rich regions have no counterpart in serotonin, but they may nevertheless add to the pharmacological potency of DON and DOB.

To extend the results of this work in such a way as to clarify the influence of the 4-substituent of PAA on both the receptor affinities and the pharmacologic activities of hallucinogens belonging to this structural class, it will be necessary to test more 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropane analogues with a broader range of X groups, especially those with hydrophilic characteristics.

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