Conformational Energy Differences between Side Chain Alkylated Analogues of the Hallucinogen 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane

Herschel J. R. Weintraub, David E. Nichols,*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

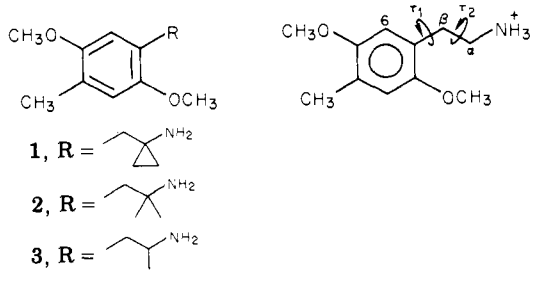
Alexandros Makriyannis, and Stephen W. Fesik

Department of Medicinal Chemistry and The Institute of Materials Science, University of Connecticut, Storrs, Connecticut 06268. *Received November 26, 1979*

Theoretical conformational energy calculations were carried out for the (+) and (−) isomers of the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP). Energies were also calculated for two analogues of DOM, 1-amino-1-(2,5-dimethoxy-4-methylbenzyl)cyclopropane and 1-(2,5-dimethoxy-4-methylphenyl)-2-methyl-2-aminopropane. The method utilized classical, empirical potential-energy functions. A previously proposed active conformational region was studied. Compounds could be ranked in order of potency based on relative conformational energies in this region. Measurement of ^{13}C spin–lattice relaxation times (T_1) for the two α,α-disubstituted DOM analogues confirmed theoretical predictions of very restricted conformational freedom for the dimethyl compound but more flexibility for the cyclopropane analogue.

In continuing studies of the structure–activity relationships of hallucinogen molecules, we have been interested in conformational and steric effects which may define activity. Recent investigations have been directed toward testing a new hypothesis which attempts to identify functional similarities between phenethylamine hallucinogens and tryptamine hallucinogens, including LSD.[1-3] We have suggested that hallucinogens interact with (their) receptor in an essentially planar manner and that the interacting face of the molecule must be free of steric bulk.

To be valid, a structure–activity hypothesis must account for observed biological activity in any compound within the described class. The goal of the present study was to explain why compound 1 is active while 2 apparently is not. Although neither 1 nor 2 have been tested in man, 1 is reported to elicit behavioral effects in cats and possesses in vitro properties similar to those elicited by the known hallucinogen DOM, 3.[4] By contrast, compound 2 is relatively inert.



We earlier suggested[1,2] that stereoselective action for the (*R*)-(−) isomer of psychotomimetic phenylisopropylamine derivatives may be due to the fact that in the proposed active binding conformation the α-methyl is allowed to project away from the binding surface of the receptor. Examination of space-filling (CPK) models seemed to indicate that the conformational properties of molecules 1–3 should be of some interest, especially in the region of the proposed binding conformation.

It was therefore decided to carry out calculations using empirical potential-energy functions to provide information on the probable conformations and the conformational barriers around the two side-chain carbon–carbon bonds. These results would then be compared with experimental information obtained through the measurement of ^{13}C spin–lattice relaxation times (T_1) of the molecules in solution. Such measurements have provided in the past[5,6] a reasonable semiquantitative index of molecular flexibility.

Materials and Methods

Conformational analyses were performed on 1, 2, and both the (*R*)-(−) and (*S*)-(+) isomers of DOM, 3, utilizing the CAMSEQ software system.[7] This program uses classical, empirical potential-energy functions and has proven of value in previous work with biologically active molecules.[8-10] CAMSEQ has been described in detail by Weintraub.[7] In addition, modeling of the molecules in an aqueous environment was accomplished using a recently described cylindrical hydration shell model.[10]

Major rotation angles τ_1 and τ_2 were scanned at 10 or 20° resolution and plotted as isoenergy contour ("Phi–Psi") maps. We previously proposed that the active binding conformation for DOM (3) lay in region $\tau_1 \sim 150°$. By forcing the nitrogen to remain in the aromatic ring plane, τ_2 varies from 270 to 360° (0°) while τ_1 varies from 150 to 180°. Therefore, a more detailed analysis was carried out to determine whether any of the compounds exhibited anomalous behavior in this region. Results of these analyses gave conformational energies which were plotted as a function of rotation angle τ_1. ^{13}C spin–lattice relaxation times (T_1) were measured on a FT Bruker WP-60 spectrometer using 0.52 M solutions at 35 °C. EDTA (10^{-4} M) was added to suppress effects of possible paramagnetic impurities. Solutions were degassed by four freeze–pump–thaw cycles to remove all oxygen. T_1 values for all carbons directly attached to protons were determined simultaneously with complete H_1 decoupling using a

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Table I. Carbon-13 Spin-Lattice Relaxation Times (s) and Effective Correlation Times ($\times 10^{-12}$ s) for 1 and 2 Hydrochlorides[a]

no.	C_3	C_6	C_β	α subst	$PhCH_3$	OCH_3	
1	0.53 (86)	0.53 (85)	0.30 (75)	0.29 (75)	1.63 (9.2)	1.60 (9.4)	1.50 (10)
2	0.48 (94)	0.49 (92)	0.24 (94)	0.41 (37)	1.61 (9.3)	1.60 (9.4)	1.50 (10)

[a] The results given are the average of three determinations.

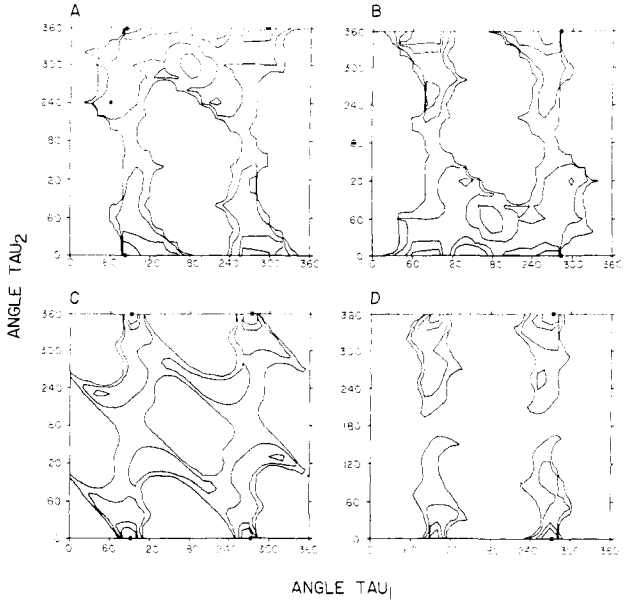

Figure 1. Isoenergy contour maps for the protonated, solvated molecules in aqueous solution. Contour lines are plotted at 1, 2, 5, and 10 kcal/mol above the global energy minimum, which is identified by a solid box at that location: A, (−)-DOM; B, (+)-DOM; C, compound 1; D, compound 2.

$(-180°-\tau-90°-T-)_n$ inversion recovery pulse sequence,[11] where τ is experimentally varied and T is equal to at least five times the longest T_1 to be measured. The T_1 values for individual carbon atoms were then used to calculate the corresponding effective correlation times (τ_{eff}),[12] which measure the period of molecular reorientation of a C–H vector through a given angular displacement. Effective correlation times can thus serve as a measure for the motions of individual ^{13}C atoms and provide a description of the molecule's dynamic behavior in solution. Such measurements allow us to make semiquantitative comparisons on the flexibility of closely related molecules in solution and also give us information about specific molecular interactions which affect their flexibility.

Results and Discussion

Figure 1A–D shows the isoenergy contour maps for (−)- and (+)-DOM (**3**), **1**, and **2**, respectively, as the protonated species in an aqueous environment. The data for (−)- and (+)-DOM were obtained separately but it will be noted that, as expected, the two maps are reflections. The energy surface for 1 displays some similarity to the maps for the DOM isomers, with the extent of the contoured areas indicating the general conformational space allowed to the side chain. In contrast, as seen in Figure 1D, the conformational energy map for compound **2** is markedly different. The large open areas indicate extensive regions in the conformational space where energy exceeds 10 kcal/mol. Conformational mobility therefore appears to be highly restricted and generally confined to the small contoured areas.

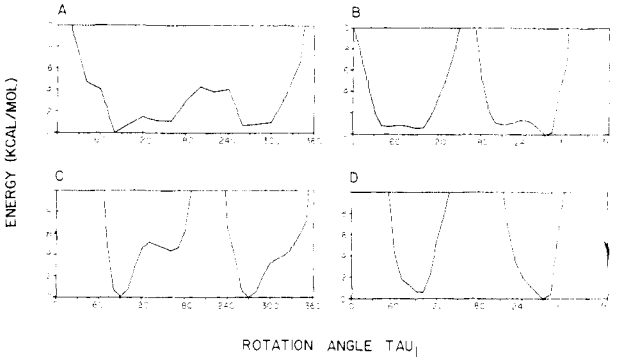

Figure 2. Conformational energy as a function of rotation angle τ_1 for the region $270° \leq \tau_2 \leq 360°(0°)$, with all other interactions minimized. Calculations were performed for the protonated species in an aqueous environment: A, (−)-DOM; B, (+)-DOM; C, compound 1; D, compound 2.

We next focused attention on the energy profile in the proposed[1-3] active binding conformation of these molecules. Figure 2A–D shows conformational energy as a function of rotation angle τ_1, for the region $270° \leq \tau_2 \leq 360°(0°)$, with all other interactions minimized. Energies are expressed relative to the global minima, which is included in the analyzed region, and is defined as zero. It is apparent that (−)-DOM (Figure 2A) has few serious nonbonded interactions in this region. By contrast, (+)-DOM (Figure 2B) shows high energy in the proposed active region, with energy exceeding 10 kcal/mol in the region $\tau_1 = 150–180°$. This is mainly attributable to the interaction between H(6) of the aromatic ring and the α-methyl. If the active binding conformation lies in this region, it is clear that the receptor will expend considerably more energy in "inducing" (+)-DOM to a fit than it will for (−)-DOM. We note in this context that presently available data indicate that the receptor displays a *stereoselectivity*, rather than *stereospecificity*, for the (*R*)-(−) enantiomers of psychotomimetic phenylisopropylamines.[13-15]

Figure 2C shows the energy profile for **1**. The energies appear relatively low, although somewhat higher than for (−)-DOM, in the proposed active region. However, the same assumptions regarding appropriate bond angles in the proposed active conformation do not strictly apply for the cyclopropane analogue. In particular, the nitrogen can remain in the aromatic ring plane with angles for τ_2 extended as low as 240°. If these data are similarly processed, the energy in the entire region $\tau_1 = 150–240°$ drops to less than 6 kcal/mol. The data for **1** have been processed consistent with that for the other compounds for uniformity of comparison. One should be aware, however, that in reality the energies may be somewhat lower than shown. This can be primarily attributed to the bond-angle distortion induced by the cyclopropane ring geometry. A

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major feature of this geometry is that the nitrogen can assume a coplanar relationship with the aromatic ring, while the side-chain conformation is such that there is little nonbonded interaction between H(6) of the aromatic ring and the methylenes of the cyclopropane ring.

Figure 2D illustrates the comparable conformational energy profile for **2**. As one might predict from the results for (+)-DOM, **2** shows a very high conformational energy in the region τ_1 = 150–180°. The large energy is mainly attributable to the peri interaction between the α-methyls and H(6) of the aromatic ring. Whereas in (+)-DOM this interaction can be minimized by rotation of the α methyl, for **2** this is more difficult due to the nonbonded interaction between the two α-methyls. It appears significant, therefore, that all these interactions cannot be minimized simultaneously and the result is very high energy in the proposed binding region. This is consistent with the low observed biological activity of **2**, about one-fortieth that of racemic DOM.[4]

Hence, one can see from inspection of Figure 2 that observed biological activity generally parallels the magnitude of the conformational energy for conformations where the amine nitrogen lies essentially in the aromatic ring plane. That is, (–)-DOM is most active, with low conformational energy, followed by (+)-DOM and compound **1**. The latter possess about one-fifth to one-sixth the biological activity of (–)-DOM and have somewhat higher conformational energies. For compound **2**, with about one-twentieth the activity of (–)-DOM, conformational energy is very high. While this does not imply that there is a direct quantitative correlation, a trend seems apparent.

The relaxation times for individual carbons in **1** and **2** were measured under identical conditions of concentration and temperature. Nevertheless, differences were observed (Table I) between the T_1 and τ_{eff} values of corresponding carbons in the two compounds reflecting the differences in the dynamic behavior of these two molecules in solution.

In the α,α-dimethyl analogue **2** the correlation times for the protonated aromatic carbons are identical with that of the benzylic carbon. This indicates that the ring and the β side-chain carbons are probably rotating in unison and provides evidence for restricted rotation around the Ph–C bond. In the cyclopropyl analogue **1** the protonated aromatic carbons have higher correlation times than the benzylic carbon, indicating that the ring is probably rotating faster and that rotation around the Ph–C bond is less restricted. On the other hand, the similar correlation times of the protonated cyclopropyl and benzylic carbons in **1** are an indication of restricted rotation around the C_α–C_β bond in this molecule.

Hindered rotation can also be observed in the two α-methyl groups of **2**. The τ_{eff} values for these carbons are considerably lower than those of the 4-methyl or the two methoxy carbons on the ring where rotation is considerably less restricted. Finally, the overall shorter correlation times observed in the ring and side-chain carbons of **2** when compared with those of **1** indicate that the α,α-dimethyl analogue in solution is somewhat bulkier than the cyclopropyl analogue.

The general picture emerging from the relaxation data is one in which the α,α-dimethyl analogue shows more restricted rotation around the Ph–C_β bond than the corresponding cyclopropyl analogue. Although this information is only semiquantitative, comparisons between the dynamic behavior of the two molecules in solution can legitimately be made due to the closeness of their structures. The above data indicate that the activation energy around the Ph–C_β bond of **2** is equal to or higher than the energy of activation for the tumbling of the entire molecule in solution. The activation energy for molecular reorientation in molecules of similar size was found to range between 4 and 5 kcal/mol.[16]

Thus, the relaxation times provide experimental verification of the theoretical conformational data obtained using CAMSEQ. While they do not indicate a preference for a particular geometry, they do indicate that the flexibility and allowed conformational states for the α,α-dimethyl compound **2** are greatly restricted when compared with **1**. To effectively utilize this data one must draw some hypothesis regarding the active binding conformation.

If we have correctly identified the active binding conformational region, there are at least two possible explanations for the biological activities, both of which may be operative. First, energy expended by the receptor in inducing the proper conformation in the agonist will proportionately detract from receptor affinity or binding energy. It is often assumed that energy expended in achieving a given binding conformation may be small when compared with binding energy at the receptor. This certainly does not appear to be true in the case of **2**. Second, the simple fact of steric bulk directed toward the receptor at the pro-*S* site on the α carbon may interfere with binding. The fact that **2** is approximately one-sixth the activity of (+)-DOM, whereas (+)-DOM and **1** seem to possess similar potency, indicates, however, that the latter cannot be the sole explanation.

It should be mentioned that the contrasting biological activity of **1** and **2** has previously been attributed to differences in lipid–water partitioning.[4] In particular, it has been suggested that the lipid solubility of **2** is too low for effective penetration to the receptor. We dismiss these arguments based on the fact that the apparent partition coefficient for the highly active DOM (**3**) is essentially the same as for **2**. Furthermore, conventional interpretation of the dose–response curves included in ref 4 clearly indicates a lack of intrinsic activity for **2**. Concentrations of **2** 1000-fold higher than those which were effective for **1** failed to elicit an in vitro response. Yet, the apparent partition coefficients for **1** and **2** differ only by a factor of about 30. We conclude, therefore, that the differences in biological activity between **1** and **2** are most likely attributed to steric and conformational energy differences, rather than to differences in lipid solubility.

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