Conformational Analysis and a Crystal Structure of Bupropion, an Antidepressant with Dopamine Reuptake Blocking Activity

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A conformational analysis has been performed on the antidepressant bupropion using the MM3-92 program. In addition, the structure of the compound in the crystal state was obtained. There is good agreement between the computed global minimum and the structure observed by crystallography. The three-dimensional structure of the preferred conformer of bupropion is consistent with the three-dimensional structures of other dopamine reuptake blockers such as cocaine, CFT, and methylphenidate.

INTRODUCTION

Bupropion is a clinically used antidepressant whose mechanism of action is not entirely clear. Neurons contain presynaptic transporters that remove released neurotransmitters from the synapse in order to terminate neuronal firing. Compounds that increase synaptic serotonin by selectively blocking this reuptake process at serotonergic neurons, such as fluoxetine and sertraline, constitute one major class of antidepressants. Other antidepressants increase the levels of norepinephrine by blocking its reuptake (imipramine) or by inhibiting enzymes that are responsible for its metabolism (phenelzine). However, bupropion is unique among antidepressants in its selectivity for dopamine transporters relative to serotonin and norepinephrine transporters, and it has been suggested that this in vivo dopaminergic stimulant effect[1,2] may be responsible for its antidepressant activity. This property of the compound, however, is relatively weak, and its effects on assays of antidepressant activity occur at lower doses than the stimulant effects of blocking dopamine transporters.[2,3] More recently, the antidepressant activity of bupropion has been attributed to a noradrenergic mechanism.[4,5]

In addition to antidepressant effects, bupropion is also effective in treating attention deficit hyperactivity disorder (ADHD) in both children and adults.[6−8] ADHD is generally treated with stimulants such as methylphenidate which increase synaptic dopamine by blocking its reuptake at dopamine transporters. The efficacy of bupropion in ADHD is consistent with its activity as a dopamine reuptake blocker though, as indicated above, its affinity for the dopamine transporter is rather weak with a measured IC_{50} of 1530 ± 381 nM for displacing [^{3}H]cocaine as compared with 33.9 ± 11.8 nM for methylphenidate.[9]

A pharmacophore for dopamine reuptake blockers that includes compounds such as cocaine, CFT, and a variety of other compounds has been proposed.[10] More recently, methylphenidate was incorporated into the pharmacophore.[11] There was a close correspondence between the three-dimensional structures of methylphenidate and a representative compound such as CFT, particularly the sequence from the ammonium group through the ester group. The pharmacophore model also suggested that adding an *N*-methyl group to methylphenidate analogues should *decrease* their affinities for the dopamine transporter since the added *N*-methyl group would preferentially be placed in the position required for an ammonium hydrogen. Based on five pairs of analogues with varying substituents on the phenyl ring, this prediction was found to be correct since the addition of an *N*-methyl group decreased affinity for the dopamine transporter from 4 to 30-fold relative to the corresponding secondary amine.[12] Superficially, bupropion also shares a number of molecular features with cocaine, CFT, and methylphenidate such as an amine group, an aromatic ring, and a carbonyl group (Chart 1). While the affinity of bupropion for the dopamine transporter is relatively weak, it is still of interest to understand the molecular basis for this activity by determining its preferred three-dimensional structure and comparing it with the three-dimensional structures of other dopamine reuptake blockers.

Buproprion is used clinically as a racemate, and we were unable to find any evidence that the compound has ever been resolved into enantiomers. One of the goals of the present work is to see if either of the enantiomers is a better fit to the dopamine reuptake pharmacophore than the other.

EXPERIMENTAL SECTION

Molecular Mechanics Studies. Energy minimizations of possible conformations of bupropion were performed with the MM3-92 program and parameter set[13] and all internal degrees of freedom were allowed to vary. Calculations were for the protonated form of the molecule. There were missing torsional parameters for the atomic sequences $C_{carbonyl}-C_{sp3}-N_{ammonium}-C_{sp3}$ and $C_{sp2}-C_{carbonyl}-C_{sp3}-N_{ammonium}$ which were approximated by the substitution of a similar atom into the atomic sequence. Specifically, $C_{carbonyl}-C_{sp3}-N_{amine}-C_{sp3}$ was available for the first missing parameter, and $C_{sp3}-C_{carbonyl}-C_{sp3}-N_{amine}$ was available for the second. These parameters are "trial" parameters in MM3-92 and provided

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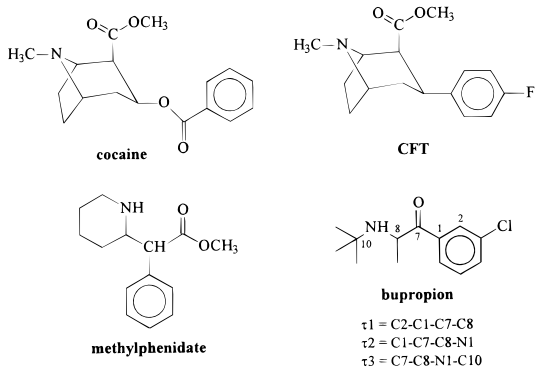
Chart 1



a zero torsional contribution. Initial Cartesian coordinates for the calculations were generated by the PCMODEL program[14] or the DRIVER option of the MM3-92 program. The convergence criterion was set to 1/8 of the default value to ensure complete convergence with the diagonal Newton−Raphson optimization method. Using the atomic numbering in the figures, the three single bonds about which significant rotation can occur are τ1(C2−C1−C7−C8), τ2(C1−C7−C8−N1), and τ3(C7−C8−N1−C10) and these are listed as [τ1,τ2,τ3]. Least squares superpositions were performed with the PCMODEL program.[14] The superpositions of bupropion with CFT were with respect to the ammonium nitrogen, the carbonyl oxygen, and the first atom of the phenyl ring.

Single-Crystal X-ray Diffraction Analysis of Bupropion. $C_{13}H_{19}ClN^{+}O\ Cl^{-}\cdot{}^{1}/_{2}(C_2H_5OH)$, FW = 299.23, triclinic space group $P\bar{1}$, a = 7.571(1), b = 9.310(1), c = 11.687(1) Å, α = 94.58(1)°, β = 101.49(1)°, γ = 90.15(1)°, V = 804.5(2) Å^3, Z = 2, ρ_{calc} = 1.235 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 3.575 mm^{-1}, F(000) = 318, T = 293 K.

Bupropion was purchased from Research Biochemicals (Natick, MA) and recrystallized by slow evaporation from MeOH/CH_3NO_2. A clear colorless 0.03 × 0.36 × 0.46 mm crystal in the shape of a plate was used for data collection on an automated Siemens P4 diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 35 centered reflections within 7.4 ≤ 2θ ≤ 25.0°. The data collection range of hkl was $-1 \le h \le 8$, $-10 \le k \le 10$, $-12 \le l \le 12$, with [sin θ/λ]$_{max}$ = 0.54. Three standards, monitored after every 97 reflections, exhibited linear decay of 2.0% during the data collection. A set of 2764 reflections was collected in the θ/2θ scan mode, with scan width [2θ(K$_{\alpha1}$) − 0.4] to [2θ(K$_{\alpha2}$) + 0.4]° and ω scan rate (a function of count rate) from 5.0°/min to 30.0°/min. There were 2111 unique reflections, and 1681 were observed with $F_o > 4\sigma(F_o)$. The structure was solved and refined with the aid of the SHELXTL system of programs.[15] The full-matrix least-squares refinement on F_o^2 varied 187 parameters including atom coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms bonded to nitrogen or oxygen were refined, while other hydrogens were included using a riding model [coordinate shifts of carbon atoms applied to attached hydrogen atoms with bond lengths of 0.96 Å, idealized bond angles, and U_{iso} (H) set to 1.2 U_{eq} (C) or 1.5 U_{eq} (C) for methyl groups]. Final residuals were $R1 = 0.056$ ($R1 = \sum||F_o| - |F_c||/\sum|F_o|$) and $wR2 = 0.147$ ($wR2 = [\sum(w\Delta^2)/\sum[w(F_o^2)^2]]^{1/2}$ where $\Delta = (F_o^2 - F_c^2)$) with final difference Fourier excursions of 0.24 and −0.46 eÅ^{-3}.

RESULTS AND DISCUSSION

Molecular Mechanics. The conformational results for bupropion with a high and low value of the dielectric constant are summarized in Table 1. For τ2 and τ3, minima in the energy surface were searched for with expected gauche and trans torsion angles. However, many of these were not stable conformations, and these are indicated by blank entries in Table 1.

With respect to the relative orientation of the phenyl ring and the ketone group, there are four distinct conformations possible. The phenyl ring can be rotated 180° which, due to the asymmetrical placement of the chlorine substituent, results in nonequivalent conformers. These have essentially the same energy under these calculation conditions, and only one conformer is listed in Table 1. In addition, while one would normally expect the phenyl ring and ketone group to be coplanar to maximize resonance interactions within the molecule, the energy minimized conformers were always nonplanar. This appears to be primarily due to a short contact between an ortho proton on the phenyl ring and the proton attached to the chiral carbon atom. For the global minimum, where the ketone group makes an angle of 31° from the phenyl ring, this distance is 2.16 Å. If one rotates the phenyl ring to be coplanar with the ketone group, this distance shortens to 1.75 Å. As a consequence, the ketone group can be on one or the other side of the phenyl plane. Generally, these have similar energies though only one of these conformers is sometimes stable. Entries in Table 1 only include one of these possible conformers, and only one is shown in Figure 1 as the global minimum.

With respect to τ2, this controls the relative positions of the ketone and ammonium groups. The global minimum is one in which the ketone oxygen approaches the ammonium group. Conformers in which the ketone group eclipses the methyl group or the adjacent hydrogen atom are less favorable by about 2 and 4 kcal/mol, respectively.

With respect to τ3, this controls the orientation of the *tert*-butyl group. The global minimum conformation is one in which this bulky group is trans to the methyl group on the asymmetric carbon atom and this is favored by 1.4−2.9 kcal/mol. This conformer is not stable when $\tau1 \approx 60°$ since this places the *tert*-butyl group in close proximity to the phenyl ring.

The global minimum of bupropion is characterized as having a close approach of one of the ammonium hydrogens to the carbonyl oxygen with a distance of 2.7 Å. These minima are favored even when a high value of the dielectric constant is used in the calculations to damp out strong electrostatic interactions. This parallels the situation in cocaine, CFT, and methylphenidate where the global minimum places the carbonyl oxygen in the vicinity of the ammonium nitrogen even in the absence of strong electrostatic forces.[10,11] However, in the latter three compounds, the ammonium hydrogen is separated from the carbonyl oxygen by four atoms which allows for a good, approximately linear hydrogen bond. There is experimental evidence for the presence of this hydrogen bond in cocaine.[10] In bupropion, however, there are only three atoms between

Table 1. Computed Conformational Energies of the *S*-Enantiomer of Bupropion with Low and High Values of the Dielectric Constant[a]

$\tau 2$, $\tau 3$	conformer $D = 1.5$	steric energy (kcal/mol)	conformer $D = 80$	steric energy (kcal/mol)
gauche (+), gauche (+)	[−142,62,71]	17.4	[150,61,69]	19.5
gauche (+), trans			[−135,78,−139]	18.2
gauche (+), gauche (−)				
trans, gauche (+)				
trans, trans	[−149,131,−144]	14.1	[−143,122,−169]	19.0
trans, gauche (−)	[−150,132,−75]	12.0	[−149,128,−72]	16.1
gauche (−), gauche (+)				
gauche (−), trans	[−114,−113,−172]	17.3	[−128,−101,−169]	20.3
gauche (−), gauche (−)	[−105,−91,−62]	16.9	[−124,−89,−58]	18.9

[a] Gauche and trans values of $\tau 2$ and $\tau 3$ were systematically searched for and blank entries indicate that these were not stable conformers.

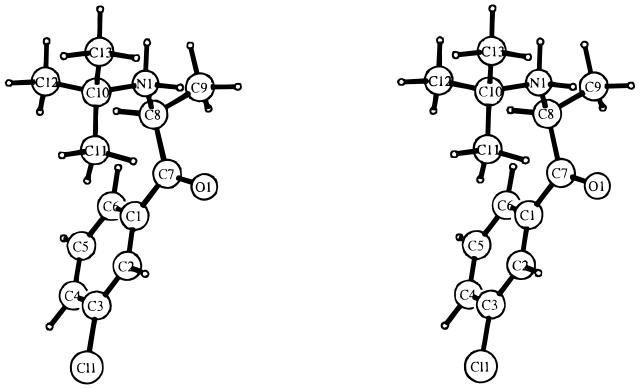


Figure 1. Stereoscopic view of one of the global minima found for bupropion by calculation with a dielectric constant of 80.

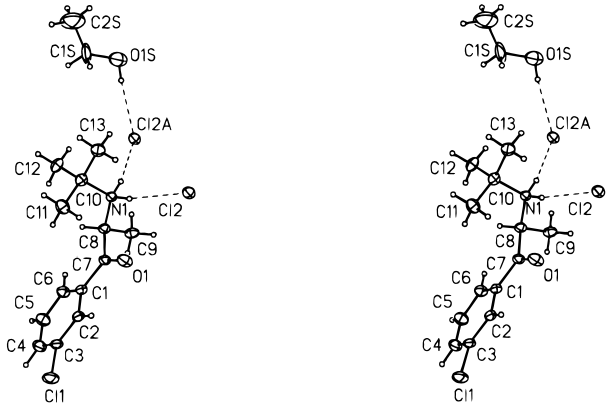


Figure 2. Stereoscopic view of bupropion in the crystal state.

the carbonyl oxygen and the ammonium hydrogen, and the two bonds are approximately parallel to each other.

Crystal Structure. The structure of bupropion in the crystal state is shown in Figure 2, and this is similar to the global minimum found by computation. Fractional coordinates of the non-hydrogen atoms for the structure are listed in Table 2. Using the same notation as for the computations, the conformer is [−170,146,−81]. The ketone group is 10° out of the plane from the phenyl ring as opposed to 31° for the computed global minimum. The distance between one of the ortho protons and the proton attached to the chiral carbon is 2.16 Å which matches the distance found in the global minimum. The second dihedral angle has a value of 146° as compared with 128° in the computed structure, while the third dihedral angle is −81° as compared with −72° in the computed structure. When one superimposes the 16 heavy atoms in the crystal structure of bupropion with those in the computed global minimum in a least squares sense

Table 2. Atomic Coordinates [$\times 10^4$] and Equivalent Isotropic Displacement Parameters [Å^2 $\times$ 10^3]for Non-Hydrogen Atoms in Bupropion[a]

atom	x	y	z	U_{eq}
Cl(1)	10099(2)	13137(1)	9695(1)	85(1)
Cl(2)	3070(1)	6275(1)	5861(1)	55(1)
N(1)	7010(4)	6914(3)	5354(2)	40(1)
O(1)	6583(4)	8698(3)	7243(3)	73(1)
C(1)	9667(5)	9288(4)	7904(3)	45(1)
C(2)	9251(6)	10598(4)	8447(3)	50(1)
C(3)	10617(6)	11464(4)	9083(3)	54(1)
C(4)	12388(7)	11066(5)	9231(4)	67(1)
C(5)	12803(6)	9764(5)	8691(4)	66(1)
C(6)	11446(5)	8882(5)	8019(3)	55(1)
C(7)	8126(5)	8401(4)	7201(3)	48(1)
C(8)	8493(5)	7078(4)	6418(3)	44(1)
C(9)	8518(6)	5754(4)	7103(3)	58(1)
C(10)	7090(5)	7833(4)	4347(3)	49(1)
C(11)	7375(6)	9416(4)	4790(4)	66(1)
C(12)	8652(6)	7307(5)	3774(4)	64(1)
C(13)	5289(6)	7579(5)	3496(4)	64(1)
O(1S)	5093(11)	3554(10)	1236(7)	106(3)
C(1S)	5376(60)	4842(44)	583(37)	191(23)
C(2S)	4858(58)	4943(45)	−643(35)	184(17)

[a] U_{Eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

(Figure 3), the average atomic deviation is 0.35 Å. Very good agreement between the computed global minimum and experimental data also occurs for methylphenidate and a variety of analogues[10,16,17] providing additional evidence that molecular mechanics calculations can be a reliable method for determining molecular conformation.

The asymmetric unit consists of a molecule of bupropion, a chloride ion, and half of an ethanol molecule. The ethanol is located on an inversion center midway between the carbon atoms of the ethanol and is disordered. The arrangement of the ions and solvate within the cell is largely determined by the intermolecular hydrogen bonding. Each of the ammonium hydrogens participates in a hydrogen bond (Table 3) with the chloride anion linking the bupropion cations into pairs centered on an inversion center. There is also a weak hydrogen bond between the ethanol and the chlorine ion (Table 3) which, due to the disorder, is present only half the time so that each chlorine anion participates on average in two and a half hydrogen bonds.

Pharmacophore. One of the goals of the present work was to examine the preferred conformations of bupropion to see if the compound fits the previously determined pharmacophore for dopamine reuptake blockers. To that end, the *S*-enantiomer of bupropion was superimposed in a least squares sense onto the preferred conformer of the highly

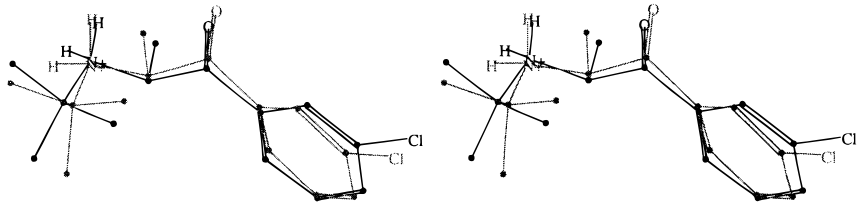


Figure 3. Stereoscopic view of the least squares superimposition of the heavy atoms in the crystal structure (dark line) of bupropion (light line) with those in the computed global minimum.

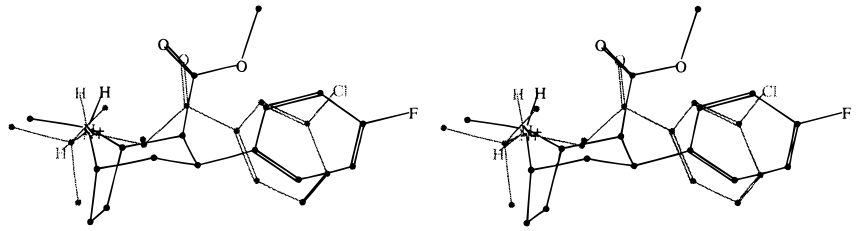


Figure 4. Stereoscopic view of the least squares superposition of the global minimum of the *S*-enantiomer of bupropion (light line) with global minimum of CFT (dark line).

Table 3. Parameters for Hydrogen Bonding in the Crystal State

H	H−Cl2 (Å)	∠X−H−Cl	X−Cl (Å)	X
H1A	2.36	155.1	3.218	N
H1B[a]	2.30	169.2	3.183	N
H1SA[a]	2.56	167.3	3.391	O

[a] Symmetry operator: $1 - x, 1 - y, 1 - z$.

potent CFT using the ammonium nitrogen, the carbonyl oxygen, and the phenyl carbon that is attached to the rest of the molecule. The least-squares fit for the three points is 0.56 Å. As can be seen in Figure 4, one obtains a reasonable superposition of the two compounds using these three points with one of the ammonium hydrogens pointing in the correct direction and the carbonyl oxygen and the phenyl ring having similar three-dimensional orientations. This suggests that bupropion also fits the pharmacophore for dopamine reuptake blockers. Since it is unclear which enantiomer of bupropion has the greater activity, the superposition was also performed with the *R*-enantiomer. However, both enantiomers were found to fit the pharmacophore equally well using the same three key atoms. While the two enantiomers place their steric bulk differently, it was not possible to distinguish which of these would better fit the dopamine transporter in the absence of detailed knowledge of the structure of the dopamine transporter.

The structural factors that are responsible for the relatively weak activity of bupropion as a dopamine reuptake blocker are unclear. Bupropion contains a carbonyl group that is present in many dopamine reuptake blockers such as cocaine, CFT, and methylphenidate though the carbonyl is part of an ester group in the latter three (Chart 1). However, ketone analogues of cocaine are highly potent.[18] It should be noted that the presence of a carbonyl or ester group which can hydrogen bond to the transporter is not an absolute requirement for activity as a dopamine reuptake blocker.[19] A meta-halogen substituent on the phenyl ring also generally results in potent activity in dopamine reuptake blockers such as analogues of CFT,[20] methylphenidate,[21] and mazindol[22] as well as 3-phenyl-1-indanamines[23] and pyrrolo[2,1-*a*]isoquinolines.[24] The phenyl ring is clearly attached differently in bupropion and CFT despite similar three-dimensional orientations, and there may be subtle differences in this that may adversely impact activity. However, the phenyl ring attachment is also different in potent compounds such as CFT, cocaine, and methylphenidate, and it was concluded that the dopamine transporter can accommodate different positions of the phenyl ring.[10,11] The remaining factor that could be the basis of the weak potency of bupropion is the steric placement of the *tert*-butyl and/or the asymmetric methyl group. However, given the lack of knowledge of the structure of the transporter, we were unable to determine which of these is making an unfavorable interaction.

CONCLUSIONS

The conformational preferences of bupropion were determined by MM3-92 calculations, and its structure in the solid state was determined by X-ray crystallography. There was good agreement between the computed global minimum and the crystal structure. The three-dimensional structures of the preferred conformers of both enantiomers of bupropion were found to be a good fit to a previously determined pharmacophore for dopamine reuptake blockers.

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Supporting Information Available: Tables of bond lengths and angles, anisotropic thermal parameters, and atomic coordinates for the hydrogen atoms (3 pages). See any current masthead page for ordering and Web access instructions.

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