Preferred Conformers for the Pharmacologically Typical and Atypical Antipodes of Phenylmorphan Opiates

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The conformational preferences of phenylmorphan have been determined by the MM2 (Molecular Mechanics II) program using full energy minimization. Chair-chair conformations of the cyclohexane and piperidine rings were preferred by 2.6 kcal/mol or more. With the preferred chair-chair conformation, three stable orientations of the phenyl ring were found with relative energies of 0.0, 1.0, and 1.2 kcal/mol. The barrier to rotation of the phenyl ring was computed to be 4 kcal/mol. The preferred phenyl orientation for the (+)-antipode was similar to that of morphine using a previously postulated molecular model for opiate substrates. This is consistent with the typical morphine-like pharmacological properties of this antipode. The preferred phenyl orientation of the atypical (-)-antipode appears to be most similar to the phenyl orientation that is invariably preferred by more active prodine antipodes. The preferred conformer was similar to the one observed by X-ray crystallography.

The (-)-antipode of phenylmorphan (Figure 1) has proven to be an opiate with unusual properties. This compound, which is equipotent with morphine as an agonist on in vivo assays, has been shown not to induce physical dependency.[1-3] It also appears to have some antagonistic properties since it precipitates withdrawal in morphine-dependent monkeys.[1,2] More recently, it has been suggested that this compound probably interacts with a different opiate receptor from morphine since it does not substitute for that compound in morphine-dependent rats and has only slight activity on in vitro guineau pig ileum and mouse vas deferens assays.[4] In contrast, the (+)-antipode (Figure 2) is about 3 times as potent as morphine on in vivo assays and has more typical morphine-like properties. It has a high capacity for inducing physical dependency in monkeys, substitutes for morphine in morphine-dependent rats and monkeys, and resembles morphine on the in vitro guineau pig ileum and mouse vas deferens assays.[1,2,4]

This work was undertaken to determine the conformational preferences of the phenylmorphans and to attempt to relate these to their pharmacological properties. In order to compare phenyl-equatorial opiates such as phenylmorphan with phenyl-axial ones such as morphine, a substrate model that accommodates both will be used.[5-7] In this model, the opiate phenyl rings are postulated to be the molecular anchors to the receptor and are the portions of the molecule that must be superimposed. This model is attractive in that it can account for the similarities and divergences in the structure-activity relationships of the two classes. Thus, both generally have their potencies increased by a phenyl meta hydroxyl.[7,8] While the ammonium nitrogen in the two classes are then in very different regions of receptor space, the ammonium hydrogen points to the same location (though from different directions) and could interact with the same negatively charged receptor site. This model is also consistent with an *N*-allyl (or related group) only inducing opiate antagonism in phenyl-axial opiates[2,9-11] since N-substituents in the two classes will be located in very different regions of receptor space.

While it is expected that conformational factors would be important for the pharmacological properties of opiates, other factors are undoubtedly important as well. Perhaps the most significant of these for our work are how an opiate substrate will interact with a particular opiate receptor in terms of its favorable and unfavorable functional groups or stereochemistry. Unfortunately, a detailed topology of opiate receptor sites is lacking at this point in time. For this reason, it is unlikely that conformational analysis of opiate substrates will provide a complete explanation as to their different pharmacological properties. Nevertheless, there is a great deal of information provided in the structures and conformations of opiates and it is our hope that it will be possible to classify opiate substrates on the basis of their conformational preferences and to relate these classes to differences in pharmacological properties.

Methods

The conformational preferences of the phenylmorphans were determined by the MM2 (Molecular Mechanics II) program and parameter set developed by Allinger and Yuh.[12] As in previous calculations for azabicyclane opiates,[7] revised parameters for bond stretching in phenyl carbons[13] and ammonium salts[14] were used with the corrected dipole moment for the amine hydrogen.[15] Full energy minimization with respect to all internal coordinates was performed. In the calculations in which the barrier to rotation of the phenyl ring was determined, the energy was minimized with respect to all internal coordinates aside from the constrained dihedral angle. This program appears to produce quantitatively correct conformational results for a number of opiates and neuroleptics.[7,16-19] The figures were drawn by a modified version

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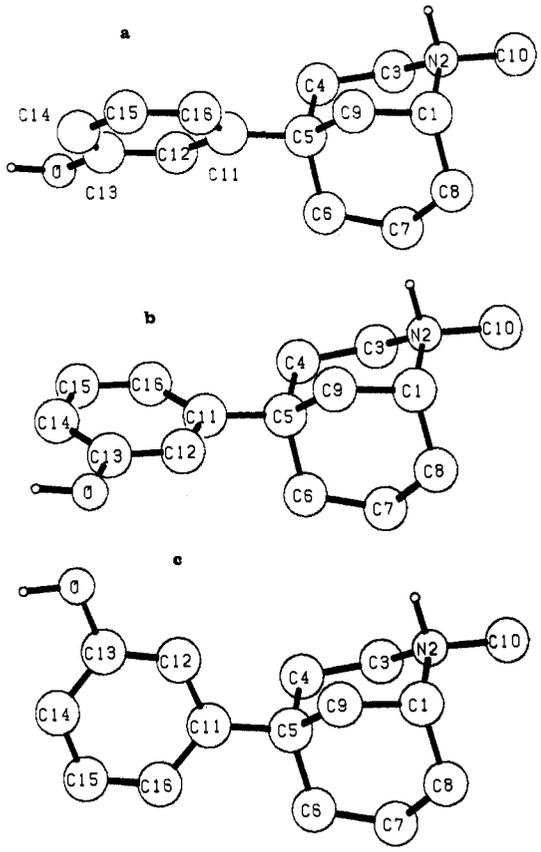

Figure 1. The three energy-minimized chair–chair conformations that are found by the MM2 program for the pharmacologically atypical (–)-phenylmorphan. The relative energies are (a) 0.0 kcal/mol, (b) 1.0 kcal/mol, and (c) 1.2 kcal/mol.

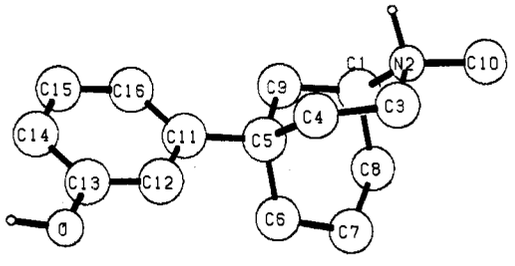

Figure 2. The preferred conformer for (+)-phenylmorphan that has morphine-like pharmacological properties. This is the mirror image of conformer **1a**.

of the PLUTO program on a Nicolet ZETA 1553 plotter. All programs were run on a Perkin-Elmer 3220 computer. The dihedral angle convention is the same as used previously.[16,17]

Results and Discussion

Calculations were performed with the piperidine and cyclohexane rings in chair–chair, chair–boat, and boat–chair conformations. However, the chair–chair conformers were found to be preferred by 2.6 kcal/mol or more and it appears unlikely that the others play a significant role. Three stable chair–chair conformers with different phenyl orientations were found. These are shown in Figure 1 for (–)-phenylmorphan with their dihedral angles listed in Table I. In each conformer, one edge of the phenyl ring eclipses one of the C5 bonds, while the other edge is staggered with respect to the remaining two C5 bonds.

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Table I. Energy Minimized Dihedral Angles and Intramolecular Geometrical Parameters for the Three Stable Chair–Chair Conformers That Were Found for (–)-Phenylmorphan[a]

	conformer 1a	conformer 1b	conformer 1c	X-ray[b]
C8–C7–C6–C5	42	41	41	43
C7–C6–C5–C9	–52	–51	–51	–56
C6–C5–C9–C1	63	62	62	63
C5–C9–C1–C8	–64	–63	–65	–59
C9–C1–C8–C7	53	53	54	45
C1–C8–C7–C6	–42	–42	–42	–36
C5–C4–C3–N2	–45	–44	–44	–46
C4–C3–N2–C1	47	47	48	52
C3–N2–C1–C9	–58	–58	–58	–62
N2–C1–C9–C5	65	66	64	66
C1–C9–C5–C4	–60	–60	–59	–59
C9–C5–C4–C3	50	50	50	50
C10–N2–C3–C4	175	174	175	–178
C10–N2–C1–C9	176	176	176	169
C7–C6–C5–C4	66	66	68	63
C6–C5–C4–C3	–68	–69	–68	–68
C3–N2–C1–C8	67	66	67	61
N2–C1–C8–C7	–72	–71	–71	–75
C16–C11–C5–C6	117	–110	–11	143
C16–C11–C5–C4	–120	13	112	–92
C16–C11–C5–C9	–2	131	–130	26
C12–C11–C5–C6	–63	68	170	–42
C12–C11–C5–C4	61	–168	–66	83
C12–C11–C5–C9	179	–50	51	–159
N2-phenyl center, Å	5.7	5.8	5.7	5.6
N2-phenyl plane, Å	1.3	1.4	0.3	1.3
steric energy, kcal/mol	18.4	19.4	19.6	

[a] The crystallographic structure, which is most similar to conformer **1a** with the phenyl ring rotated about 26°, is included for comparison. [b] Reference 3.

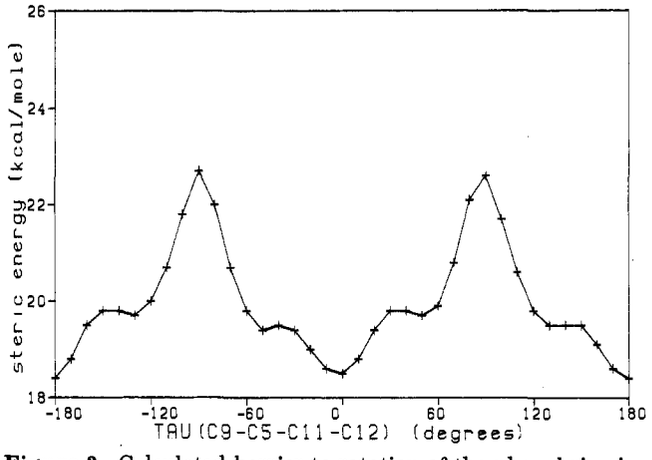

Figure 3. Calculated barrier to rotation of the phenyl ring in (–)-phenylmorphan.

Also, due to the asymmetrical phenyl meta hydroxyl, each of these conformers has a related one in which the phenyl ring is rotated 180° and which has essentially the same intramolecular energy. Since it would be expected that the orientation of the phenyl hydroxyl would be crucial for interaction with a site in the opiate receptor, there are a total of six distinct conformers that should be considered. However, to simplify the remaining discussion, reference will only be made to these three conformers and it should be understood that the 180° rotamers will have identical energies.

Despite the short-range symmetry for phenyl rotation, conformer **1a** is preferred by 1.0 and 1.2 kcal/mol over conformers **1b** and **1c**, respectively. The apparent reason

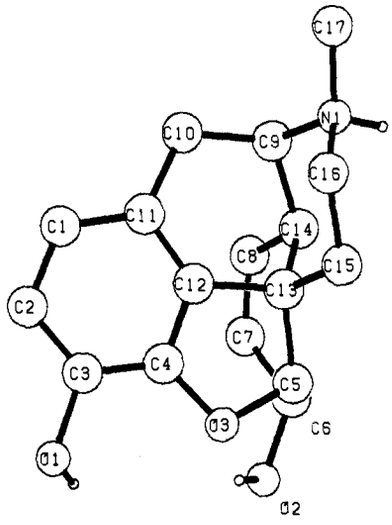

Figure 4. The conformation observed for morphine hydrochloride trihydrate by X-ray crystallography.[20]

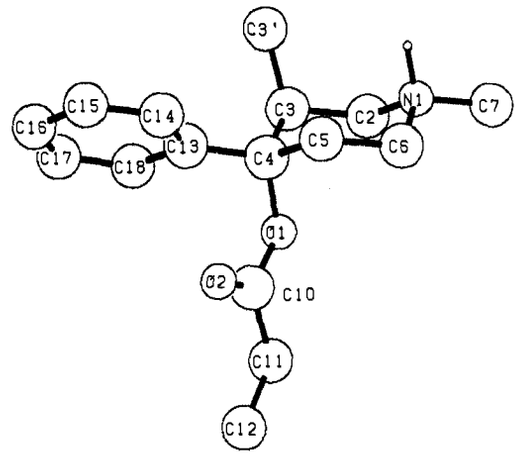

Figure 5. The more active antipode of β-prodine. This conformer is favored by 3.5 kcal/mol or more so that virtually all of the molecules will be found in it.[17,19]

for this is that the phenyl ring fits into the cleft formed by the cyclohexane and piperidine rings. Due to the close contact between C3 and C7,[3] this cleft will be a little wider than the other two. It also appears that the edges of this cleft will be significantly more flexible. This can be seen from the calculated barrier to phenyl rotation in Figure 3 in which the minimum that corresponds to conformer **1a** is considerably broader than the remaining two. These factors tend to relieve unfavorable steric interactions and lower the energy of conformer **1a** relative to the other two. These results are in agreement with crystallography since the conformer found by that method is most similar to conformer **1a** with the phenyl ring being rotated about 26° from that energy-minimized conformer[3] (see Table I). The preferred conformer for (+)-phenylmorphan is shown in Figure 2 and is, of course, simply the mirror image of Figure 1a.

In comparing the preferred conformers of the phenylmorphan antipodes with morphine (Figure 4) using the substrate model discussed above, the common atoms that must be superimposed are C11, C5, C9, and C4 in Figure 2 and C12, C13, C14, and C15 in Figure 4. (While the necessity of superimposing the phenyl rings was stressed above, this was not rigidly done here to emphasize that there are some differences in the orientation of the phenyl ring relative to the piperidine ring even for molecules that are likely to interact with an opiate receptor in similar conformations. Presumably, there is enough flexibility in both opiate substrates and receptors to make this possible.) If one compares the two antipodes of phenylmorphan with morphine in its crystal state,[20] it is clear that the phenyl ring orientation of the preferred conformer of the (+)-antipode corresponds more closely. The dihedral angles that describe the phenyl ring are τ(C12–C11–C5–C4) = −61° and τ(C12–C11–C5–C9) = −179°, while the equivalent angles in morphine are τ(C4–C12–C13–C15) = −104° and τ(C4–C12–C13–C14) = 136°. While the difference between the two compounds is about 40°, the phenyl rings will be in the same quadrant.[5] This is consistent with the compound having a morphine-like mode of action. The agreement between the substrate model and the pharmacological profile of the (+)-antipode also provides some additional evidence as to the correctness of the former. In contrast, the phenyl ring in the preferred conformer for (−)-phenylmorphan will be in the opposite quadrant and may account for its atypical activity.

Interestingly, the preferred conformer for (−)-phenylmorphan also appears to be similar to the conformer that is invariably preferred by the more active antipode in a number of prodine derivatives.[17,19,21] For example, the preferred phenyl orientation in the more active antipode of β-prodine (Figure 5) had dihedral angles of τ(C18-C13-C4-C3) = 65° and τ(C18–C13–C4–C5) = −173°.[17,19] This is virtually identical with the τ(C12–C11–C5–C4) = 61° and τ(C12–C11–C5–C9) = 179° angles preferred in (−)-phenylmorphan (Figure 1a and Table I). It should be noted that, unlike the phenylmorphans, β-prodine is conformationally homogeneous with virtually all of the molecules having the conformation in Figure 5.[17,19] It should also be noted that the prodines have been identified as being atypical analgesics. For example, it has been pointed out that the more active prodine antipodes have the mirror image stereochemical relationship with respect to benzomorphan analgesics.[22] More recently, it was suggested that the more active antipode of α-3-allylprodine binds to the opiate μ-receptor in a non-morphine-like mode since its very potent activity is abolished by the introduction of a phenyl meta hydroxyl unlike the usual situation with opiates.[23] It was also suggested that this compounds binds to the nonphenolic (phenylalanine) portion of the μ-receptor rather than the phenolic (tyrosine) portion. Due to stereochemical and conformational regularities,[21,24] it would appear likely that all of the more active prodine derivatives interact with the same receptor. Finally, when a phenyl meta hydroxyl was introduced into racemic β-prodine, the resultant compound has significant antagonist activity.[25] On the basis of the conformational correspondences between the antipodes of phenylmorphan and β-prodine, the non-morphine-like antipode in Figure 5 would be a likely candidate for the antagonist activity of the phenolic racemate.

As noted above, the phenylmorphans are conformationally heterogeneous with the three conformers in Figure 1 having relative concentrations of 76%, 14%, and 10%, respectively, using the Boltzmann factor. Thus, there is the possibility that conformer **1b**, which is similar to the

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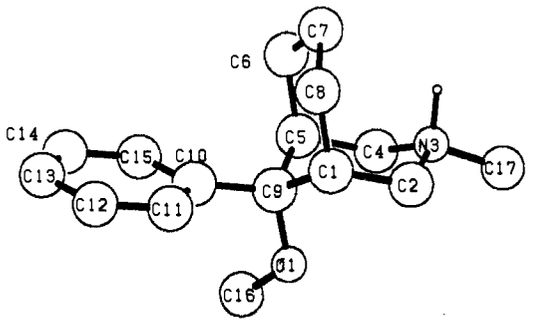

Figure 6. The more morphine-like of the two mirror image conformers that are possible for β-azabicyclane.[7]

morphine-like conformer of (+)-phenylmorphan, may contribute to the agonism of the (−)-antipode. However, by putting methyl groups in the 4- or 9-positions, the resultant compounds become conformationally homogeneous (unpublished results). Especially interesting would be the not yet synthesized β-4-methyl compounds since calculation predicts that they have the same conformational preferences as the parent compounds.

One would also like to compare the phenylmorphans to the structurally related β-azabicyclane[7] (Figure 6), a phenyl-equatorial opiate whose phenolic derivative has 6 times the affinity of morphine for opiate receptors. There appear to be some significant conformational differences between the two. β-Azabicyclane is a very sterically hindered molecule with a very high barrier (16 kcal/mol) to rotation of the phenyl ring. Of the two mirror image orientations of the phenyl ring that are possible, the more morphine-like one has a phenyl ring that differs some 60° from that of morphine though it would still be in the same quadrant. In addition, it would require some 9 kcal/mol for this molecule to achieve a morphine-like phenyl orientation. In contrast, the barrier for phenyl rotation in phenylmorphan is only 4 kcal/mol. Also, while the most morphine-like conformer differs by about 40° from the morphine-like orientation, only about 1 kcal/mol would be required to achieve that conformation (Figure 3).

In summary, there appear to be two distinct phenyl orientations that are associated with different pharmacological profiles for opiates. Compounds in which the preferred phenyl orientation is in the same quadrant as morphine, such as the (+)-antipode of phenylmorphan, appear to be typical morphine-like opiates. In contrast, compounds like β-prodine and (−)-phenylmorphan in which the preferred phenyl orientation is in the opposite quadrant have been identified as being atypical and probably interact with either different receptors as has been suggested for (−)-phenylmorphan or bind to a different portion of the μ-receptor as has been suggested for α-3-allylprodine.

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Registry No. (+)-Phenylmorphan, 91190-14-6; (−)-phenylmorphan, 91190-15-7.

Book Reviews

Serono Symposia Publications from Raven Press. Volume 5. Functional Radionuclide Imaging of the Brain. Edited by Philippe L. Magistretti. Raven Press, New York, 1983. 384 pp. 16 × 24 cm. ISBN 0-89004-962-9 $59.00.

Traditional brain imaging was based on visualization of brain areas associated with breakdown of the blood–brain barrier and presented a static image. The advent of single photon and positron tomography in the last few years, new instrumentation, and new radiolabeled agents introduced valuable techniques for looking at brain function by following the kinetics of radiopharmaceuticals that penetrate the undamaged BBB in relationship to blood flow or agents that are designed to reflect changes in the metabolic feature of brain tissue.

The editors of this book assembled reviews on the new instrumentation and discussions of the old and new techniques used today in brain research in nuclear medicine. As such the editors provide a book that is mostly directed toward an audience of physicians, scientists that require more basic scientific or background information. The book also bridges the information between scientists and physicians who are interested in new methods applied in brain investigations. The book is combined of review reports of authors that contributed to the different areas of investigation. The papers are summaries of the authors' experience in brain imaging.

The book is divided into four sections, starting with an independent and relevant brief preface discussion by Oldendorf on the BBB phenomenom. The first section reviews mainly traditional brain imaging with polar agents, mostly $^{99m}TcO_4^-$, and the discussions summarize brain imaging in cerebrovascular disorders, changes in cerebral blood flow, and changes in the BBB permeability of brain tumors. The second section is combined from reviews on the use of Xe-133 as an indicator of cerebral blood flow. The discussions review the limitations and accuracy of the techniques of the clearance measurements. Selected studies using these methods in patient care are described in ischemia, stroke, and head injury. The use of the technique for the evaluation of CBF in dementia and neuropsychiatry are also reported. Section three is a summary of the state-of-the-art SPECT techniques used for performing noninvasive in vivo measurements of CBF using different radiopharmaceuticals. A special emphasis is being put on the use of iodoamphetamine and HIPDM as lipophilic agents that penetrate the brain in relation to blood flow and have the advantage of being retained in the brain or have a slow washout from brain, therefore allowing collection of high-quality images representing flow. A preliminary study with this agent in epilepsy is reported.

Section four is a contribution from centers that have positron tomography instrumentation. The special strength of the technique in elucidating physiological parameters on a regional basis are demonstrated in the many investigations of CBF and metabolism using simple labels such as O-15-labeled CO, CO_2, H_2O, and O_2 or more complex metabolic substrates such as F-18-labeled fluordeoxyglucose or C-11-labeled methionine. The examples reviewed are cases in stroke, degenerative diseases, epilepsy, ischemia, pathologic aging, dementia, and brain tumors. A preliminary study using ligand–receptor interaction as a concept for investigating brain disorders associated with dopaminergic activity is reported.

The book concludes with a chapter by DeLand reviewing the new progress in cysternography and their clinical significance.

The book appears to fulfill the editors' goal reviewing the current status of functional brain imaging with radionuclides by