Published in final edited form as:

Theochem. 2010 April 15; 945(1-3): 57–63. doi:10.1016/j.theochem.2010.01.011.

Computational Study on the Conformations of Mitragynine and Mitragynaline

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Abstract

A conformational search on mitragynine and mitragynaline, natural products isolated from the leaves of *Mitragyna speciosa*, was performed using the MMFF94s force field and the quantum mechanical B3LYP method. The main difference for the mitragynine conformers is caused by the position of the lone pair of the nitrogen shared by rings 3 and 4. Specifically, the lone pair can be *syn* or *anti* to the exocyclic ethyl group on ring 4. *Syn* was found to be lower in energy than *anti*, because of less steric hindrance between the ethyl and the methylene group adjacent to the N in ring 3. The geometrical parameters for the lowest energy conformer of mitragynine are in excellent agreement with the published X-ray crystal structure's geometry. Because it has one more double bond, mitragynaline has less conformational freedom than mitragynine. The main possible conformational choice in mitragynaline is for orientational flexibility of a C-C single bond in ring 3. The finding of two low energy conformers of mitragynaline differing in ring 3 conformation matches reported X-ray crystal structural data.

Keywords

Conformational search; Mitragynine; Mitragynaline; Molecular mechanics; MMFF94s; B3LYP

1. Introduction

Mitragynine, mitragynaline and corynantheidaline (Fig. 1) are natural products isolated from the leaves of *Mitragyna speciosa* (Kratom) [1], which itself was traditionally used as a coca stimulant or opium substitute [2] and has recently been the subject of much interest as a drug of abuse but also because of its therapeutic potential in treating opioid withdrawal symptoms [3,4]. The isolated molecules have shown strong analgesic activity [5], as opioid agonists or in some cases as opioid antagonists [1,6-10]. Thus, there has been much interest in understanding their chemical properties, in particular their structures.

The first X-ray crystal structure of mitragynine hydroiodide salt, including absolute configuration of the hydroiodide and hydrobromide, was reported in 1965 [11]. Recently, the crystal structure of mitragynine obtained from ethanol solvent [12] as well as of mitragynaline and corynantheidaline [1,13] were also published. In addition, total syntheses

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of (-)-mitragynine were also reported [5,13-15]. These studies have provided great insights into the chemical properties and structures of mitragynine. However, there is a lack of clarity in the literature about the conformational flexibility of the aliphatic regions of the rings in the mitragynine analogs. Understanding the conformation and flexibility of such molecules can assist in predicting reactivity, the most available site for substitution, as well as their bioactive conformation. In this present study, we have performed a detailed conformational analysis, focusing on the accessible low energy structures, of the flexibility of the mitragynine and mitragynaline backbone structures. Our results agree well with the available X-ray structural conformations.

2. Computational methods

All calculations were carried out using the MacroModel [16] and Gaussian 09 [17] programs. Conformational searches were performed for mitragynine and for mitragynaline using the MMFF94s force field as implemented in MacroModel [18-22]. The MMFF94s force field was specifically designed to treat sp^2 nitrogens properly in order to correspond well to crystallographic or liquid-phase experimentally determined structures [23]. Otherwise, it is identical to the MMFF94 force field. It is frequently used [24-26] and has recently again been proven reliable in comparison to other common force fields [25]. The Monte Carlo search method [27,28] as implemented in MacroModel was used for conformational search. Based on the results of the conformational search, selected low energy conformers were further optimized using the B3LYP [29-31] method in conjunction with the 6-31G(d,p) basis set using Gaussian 09. Frequency calculations were performed at the same level of theory in order to confirm that the obtained geometries are minima and to obtain zero-point vibrational energy (ZPVE) corrections. Relative energies were obtained by performing single point calculations at the B3LYP/6-311+G(2df,p) level of theory based on the above optimized geometries with ZPVE corrected, i.e., B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d,p) + ZPVE. All calculations were performed without including solvent effects.

3. Results and discussion

3.1 Conformation of mitragynine

First the conformational analysis of mitragynine was performed. The eight lowest energy minimized conformers (**1-8**) are shown in Fig. 2, as well as an important higher energy conformer (**9**). In total, 33 conformers were found within a relative energy of 20 kJ mol⁻¹ for this flexible molecule.

As can be seen from Fig. 2, a large number of conformers correspond to the free rotation of the exocyclic -OMe, -CH₂CH₃ and -CO₂Me groups. However, there are also some important changes in the conformation of the rings, which are discussed below.

3.1.1 Rings 1 and 2

Because rings 1 and 2 (see Fig. 1) are aromatic, they are expected to be planar and in fact no nonplanar conformations were found in the conformational search.

3.1.2 Ring 3

Ring 3 (see Fig. 1) can be viewed as a piperidine derivative with one unsaturation. Among all the conformations within 20 kJ mol⁻¹ of the minimum, only two different conformations of ring 3 were found (Fig. 3).

As can be seen in Fig. 3, in conformation **A** the nitrogen is above the plane of the aromatic rings (which also includes the ring 3 double bond), while in conformation **B** the nitrogen is below that plane. Interestingly, it has been reported that the nitrogen lone pair in this chemical class plays an essential role in its binding to opioid receptors [1,6]. **A** was found to be more stable than **B**. This may be due in part to the fact that the latter results in steric hindrance between the $-\text{CH}_2-$ group of ring 3 and the exocyclic ethyl group of ring 4 (cf. Figs. 2 and 3). The lowest energy structure containing the **B** conformation was conformer **9** (cf. Fig. 2), which lies 19.7 kJ mol^{-1} higher in energy than the minimum conformer, and hence would not be significantly populated under normal conditions.

In order to further investigate other possible high energy conformations and to avoid the distraction of the exocyclic substituents, a conformational search on the model structure shown in Fig. 4 was performed. In this model, the exocyclic substituents of mitragynine were replaced by methyl groups.

In addition to the above piperidine ring 3 conformations, **A** and **B**, another conformation **C** (Fig. 5) was also found. **C** can be considered as a boat conformation. However, it lies 76.4 kJ mol^{-1} higher in energy than the global minimum. Due to its high relative energy, such a conformation is not expected to be found in biological systems.

3.1.3 Ring 4

Ring 4 (see Fig. 1) can be considered as a piperidine derivative. Two standard chair conformations were found (Fig. 6).

The difference between conformations **D** and **E** is again caused by the presence of the nitrogen atom. Specifically, in **D** the lone pair of the nitrogen is *syn* to the exocyclic ethyl group while in **E** it is *anti*. It should be noted that if considered from the view of ring 3, in **D** the nitrogen is above the aromatic plane formed by rings 1 and 2 while in **E** it is below that plane. Thus, **D** and **E** are in fact the same structure as **A** and **B**, respectively. Hence, **D** is more stable than **E**. The lowest energy conformer containing ring 4 in the **E** conformation is again the conformer **9** (cf. Fig. 1). This is again due in part to the steric hindrance between R_2 ($-\text{CH}_2-$ group as in the discussion of ring 3) and the exocyclic ethyl group of ring 4 (cf. Fig. 2 and Fig. 6).

Other high energy conformations for ring 4 were also investigated using the model shown in Fig. 4. Boat conformations were also found, with the lowest energy structure shown in Fig. 7, which lies 29.7 kJ mol^{-1} higher in energy than the global minimum.

3.2 Comparisons between mitragynine and mitragynaline

Mitragynaline has one more double bond between C15 and C16 (see Fig. 1) than mitragynine and C9-C10-C15-C16-C17-C22 may form a series of conjugated π -bonds to some extent. Thus, mitragynaline has less conformational freedom than mitragynine. The above discussion about ring 4 in mitragynine does not apply to mitragynaline. A conformational search was performed for mitragynaline. The lowest energy conformer is labeled **10** in Fig. 8. Within a relative energy of 20 kJ mol^{-1} only one conformer was found to have a significant difference in backbone conformation: **17**, which differed in the orientation of the C12-C13 bond (see Fig. 8 and the dihedrals involving C12 and C13 in Table 1). Other conformers, similar to what was found for mitragynine, differ from **10** or **17** only in the dihedral angles of the exocyclic $-\text{OMe}$, $-\text{CH}_2\text{CH}_3$ and $-\text{CO}_2\text{Me}$ groups, which are relatively free to rotate.

It should be noted that the key bond lengths, angles and dihedrals of **10** and **17** obtained using the MMFF94s force field are in agreement with the much higher B3LYP level. The

only exception is the orientation of the exocyclic methoxy group. At the MMFF94s level, this group is either above or below the plane of rings 1 and 2 in **10** and **17** (see Fig. 8 and the C8-O7-C1-C2 and C8-O7-C1-C6 dihedrals in Table 1). In contrast, at the B3LYP level, it is in the same plane as ring 1 and 2 with the C8-O7-C1-C2 and C8-O7-C1-C6 dihedrals at 0° and 180° (Table 1), respectively, for both **10** and **17**.

In addition, **17** lies only 3.2 kJ mol⁻¹ higher in energy than **10** at the MMFF94s level. Using a much higher level of theory at B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d,p) + ZPVE, such an energy difference only slightly increases to 5.3 kJ mol⁻¹. Thus, **10** and **17** can be very easily interconverted at room temperature. Indeed, two conformers with a 1:1 ratio were found in X-ray crystallography [1]. Despite the fact that no structural details distinguishing the two conformers other than an illustration were provided in the relevant experimental paper [1], we believe that our theoretical results are consistent with the reported findings.

Since C19 and C18 are connected by a single bond, in principle there could be conformers having different arrangements around the C19-C18 bond. However, in part because of the large size of the exocyclic ethyl group, no such conformer was found within a relative energy of 20 kJ mol⁻¹. Using a model similar to the one for mitragynine shown in Fig. 4, with exocyclic substituents replaced by methyl groups, we searched for all possible low-energy conformations. We found that the lowest conformer which differed in the arrangement around C19-C18 (Fig. 9) lay at least 32.0 kJ mol⁻¹ higher in energy than the global minimum.

3.3 Comparisons with the X-ray structures for mitragynine

Table 2 shows the key bond lengths, angles and dihedrals of our calculated lowest energy mitragynine conformer at both MMFF94s and B3LYP/6-31G(d,p) levels, and those obtained from X-ray crystallography [11,12]. It can be seen that our calculated geometry and all the ring conformation using both MMFF94s and B3LYP methods match very well with experiment, especially with the recent structure of ref 12. In addition, unlike B3LYP, the MMFF94s force field is again found to be unable to correctly produce the geometry of the exocyclic methoxy group. At the MMFF94s level, the methoxy group is above the ring 1 and 2 plane (see **1** in Fig. 2). In contrast, it is in the plane as shown in both B3LYP method and X-ray crystal structure. This thus causes the related angles and dihedrals, such as C8-O7-C1, O7-C1-C2, O7-C1-C6, C8-O7-C1-C2 and C8-O7-C1-C6 (see Table 2), obtained using the MMFF94s force field to deviate from B3LYP.

4. Conclusions

In this study, we have performed a detailed conformational search of mitragynine and mitragynaline using the MMFF94s force field and the quantum mechanical B3LYP method. The main differences in the low-energy mitragynine conformers arise from the presence of the nitrogen atom in ring 3. Specifically, the lone pair of this nitrogen can lie on either side of the aromatic plane formed by rings 1 and 2, so it can be *syn* or *anti* to the exocyclic ethyl group. The lowest energy conformer has the *syn* conformation, because of less steric hindrance between the -CH₂- group adjacent to the nitrogen and the exocyclic ethyl group. As for mitragynaline, due to the additional double bond between C15 and C16, it has less conformational freedom than mitragynine. The only important conformational difference is for the orientation of the C12-C13 bond. It should be noted that this results in two conformers with very close relative energies, and indeed two conformers were reported in the X-ray structure in ref. 1.

Acknowledgments

Partial funding from National Institute of Health's National Center for Research Resources (P20 RR021929). This investigation was conducted in a facility constructed with support from research facilities improvement program C06 RR-14503-01 from the NIH National Center for Research Resources. We also thank the Mississippi Center for Supercomputing Research (MCSR) for providing additional computational resources.

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Fig. 1. The structures of mitragynine, mitragynaline and corynantheidaline. The ring numbering scheme is shown on the mitragynine structure while the carbon numbering scheme is shown on the mitragynaline structure.

Fig. 2. The minimized structures of eight lowest energy conformers and one selected higher energy conformer of mitragynine. Relative energies (MMFF94s) are also shown.

Fig. 3.

A schematic illustration of the two possible conformations of ring 3. The adjacent ring 4 is denoted by dashed lines. The exocyclic ethyl group of ring 4 is also shown.

Fig. 4.
A model structure used to investigate conformational flexibility of the core unit of mitragynine.

Fig. 5.
A schematic illustration of a high energy conformation of ring 3. The adjacent ring 4 is denoted by dashed lines.

Fig. 6.

A schematic illustration of the two possible chair conformations of ring 4. R_1 and R_2 represent the adjacent two carbons in ring 3.

Fig. 7.

A schematic illustration of the lowest energy boat conformation of ring 4. R₁ and R₂ represent the two carbons in ring 3.

Fig. 8.

The minimized structures of the nine lowest energy conformers of mitragynaline. Relative energies (MMFF94s) are also shown.

Fig. 9.
The structures of the lowest energy conformer with a different orientation of the C19-C18 bond, using a mitragynaline model compound with all the exocyclic substituents replaced by methyl groups.

Fig. 10.

The structure of (a) mitragynine from the X-ray crystallography obtained by Carvalho *et al.* [12] and (b) the calculated lowest energy mitragynine conformer at the B3LYP/6-31G(d,p) level of theory.

Table 1

The key bond lengths, bond angles and dihedral angles (the latter are in parentheses) of **10** and **17** at the MMFF94s and B3LYP/6-31G(d,p) levels.

	MMFF94s ^a	B3LYP ^a	MMFF94s ^b	B3LYP ^b
C8-O7	1.43 (1.43)	1.42 (1.42)	107 (107)	107 (107)
O7-C1	1.38 (1.38)	1.37 (1.37)	108 (108)	107 (107)
C1-C2	1.40 (1.40)	1.39 (1.39)	108 (108)	109 (110)
C2-C3	1.39 (1.39)	1.41 (1.41)	110 (110)	109 (109)
C3-C4	1.40 (1.40)	1.39 (1.38)	108 (108)	108 (108)
C4-C5	1.40 (1.40)	1.40 (1.40)	120 (120)	120 (120)
C5-C6	1.40 (1.40)	1.42 (1.42)	111 (111)	109 (109)
C1-C6	1.41 (1.41)	1.42 (1.42)	113 (113)	112 (113)
C6-C9	1.42 (1.42)	1.43 (1.43)	121 (122)	120 (122)
C9-C10	1.38 (1.38)	1.38 (1.38)	116 (116)	115 (115)
C10-N11	1.37 (1.37)	1.39 (1.38)	125 (125)	124 (124)
C5-N11	1.38 (1.38)	1.37 (1.38)	122 (122)	122 (122)
C9-C12	1.49 (1.49)	1.50 (1.50)	120 (121)	115 (117)

	MMFF94s ^a	B3LYP ^a	MMFF94s ^b	B3LYP ^b
C12-C13	1.55 (1.55)	1.53 (1.54)	N14-C19-C18	111 (111)
C13-N14	1.49 (1.48)	1.47 (1.47)	C19-C18-C17	111 (111)
N14-C15	1.40 (1.40)	1.37 (1.36)	C18-C17-C16	112 (112)
C10-C15	1.42 (1.42)	1.44 (1.44)	C17-C16-C15	123 (123)
C15-C16	1.35 (1.35)	1.39 (1.39)	C17-C18-C20	112 (112)
C16-C17	1.47 (1.47)	1.42 (1.41)	C19-C18-C20	111 (111)
C17-C18	1.55 (1.55)	1.53 (1.53)	C18-C20-C21	116 (116)
C18-C19	1.55 (1.55)	1.53 (1.53)	C22-C17-C18	124 (123)
N14-C19	1.46 (1.46)	1.46 (1.47)	C22-C17-C16	122 (122)
C18-C20	1.55 (1.55)	1.55 (1.55)	C23-C22-C17	121 (121)
C20-C21	1.52 (1.52)	1.53 (1.53)	C23-C22-C27	116 (116)
C17-C22	1.36 (1.36)	1.41 (1.41)	O24-C23-C22	128 (128)
C22-C23	1.48 (1.48)	1.48 (1.48)	O25-C23-O24	120 (120)
C23-O24	1.22 (1.22)	1.22 (1.23)	O25-C23-C22	112 (113)
C23-O25	1.36 (1.36)	1.37 (1.37)	C23-O25-C26	115 (115)
O25-C26	1.43 (1.43)	1.43 (1.43)	C17-C22-C27	123 (122)

	MMFF94s ^a	B3LYP ^a	MMFF94s ^b	B3LYP ^b
C22-C27	1.50 (1.49)	1.47 (1.47)	126 (126)	127 (127)
C27-O28	1.23 (1.22)	1.23 (1.23)	93 (-92)	0 (0)
C8-O7-C1	109 (109)	118 (118)	-91 (91)	180 (180)
O7-C1-C2	118 (118)	125 (125)	27 (-26)	26 (-28)
O7-C1-C6	122 (122)	116 (116)	-43 (41)	-48 (46)
C1-C2-C3	120 (120)	120 (120)	37 (-35)	48 (-41)
C2-C3-C4	121 (121)	122 (122)	-160 (147)	-166 (143)
C3-C4-C5	118 (118)	117 (117)	162 (145)	168 (138)
C4-C5-C6	123 (123)	122 (122)	170 (-173)	160 (-171)
C5-C6-C1	118 (118)	119 (119)	53 (52)	56 (55)
C6-C1-C2	120 (120)	119 (119)	0 (3)	5 (12)

^aBond lengths in Å.

^bAngles in °.

Table 2

The key bond lengths, bond angles and dihedrals of the lowest energy mitragynine conformer **1** at the MMFF94s and B3LYP/6-31G(d,p) (in bracket) levels, and those from the X-ray crystal structures reported in refs. 11 and 12.

	This work ^a		Ref. 11 ^a		Ref. 12 ^a		This work ^b		Ref. 11 ^b		Ref. 12 ^b	
C8-O7	1.43 (1.42)	1.50	1.43	1.43			C6-C1-C2	120 (119)	120	119		
O7-C1	1.38 (1.37)	1.35	1.37				C5-C6-C9	107 (107)	108	107		
C1-C2	1.40 (1.39)	1.36	1.38				C6-C9-C10	108 (107)	104	106		
C2-C3	1.39 (1.41)	1.39	1.41				C9-C10-N11	108 (110)	113	111		
C3-C4	1.40 (1.39)	1.41	1.38				C10-N11-C5	110 (109)	107	108		
C4-C5	1.40 (1.40)	1.40	1.40				N11-C5-C6	108 (107)	107	108		
C5-C6	1.40 (1.42)	1.41	1.40				C10-C9-C12	121 (121)	126	121		
C1-C6	1.41 (1.41)	1.41	1.41				C9-C12-C13	111 (109)	110	110		
C6-C9	1.42 (1.44)	1.45	1.44				C12-C13-N14	112 (111)	112	111		
C9-C10	1.38 (1.37)	1.34	1.36				C13-N14-C15	112 (113)	112	111		
C10-N11	1.37 (1.39)	1.37	1.38				N14-C15-C10	109 (109)	106	108		
C5-N11	1.38 (1.38)	1.39	1.39				C15-C10-C9	126 (126)	122	126		
C9-C12	1.49 (1.50)	1.44	1.50				C16-C15-N14	110 (109)	109	109		

	This work ^a	Ref. 11 ^a	Ref. 12 ^a	This work ^b	Ref. 11 ^b	Ref. 12 ^b
C12-C13	1.55 (1.54)	1.54	1.53	C15-N14-C19	111 (111)	108
C13-N14	1.48 (1.47)	1.51	1.48	N14-C19-C18	111 (111)	112
N14-C15	1.49 (1.47)	1.49	1.48	C19-C18-C17	109 (108)	110
C10-C15	1.50 (1.50)	1.56	1.50	C18-C17-C16	110 (111)	110
C15-C16	1.54 (1.54)	1.53	1.53	C17-C16-C15	111 (110)	109
C16-C17	1.55 (1.54)	1.51	1.54	C17-C18-C20	113 (114)	112
C17-C18	1.56 (1.56)	1.64	1.55	C19-C18-C20	113 (112)	113
C18-C19	1.55 (1.54)	1.57	1.53	C18-C20-C21	114 (114)	114
N14-C19	1.46 (1.46)	1.55	1.48	C22-C17-C18	113 (113)	111
C18-C20	1.55 (1.54)	1.57	1.53	C22-C17-C16	117 (116)	117
C20-C21	1.52 (1.53)	1.55	1.52	C23-C22-C17	114 (115)	114
C17-C22	1.53 (1.52)	1.51	1.51	C23-C22-C27	119 (118)	117
C22-C23	1.50 (1.48)	1.41	1.50	O24-C23-C22	123 (124)	124
C23-O24	1.22 (1.22)	1.24	1.20	O25-C23-O24	125 (122)	123
C23-O25	1.40 (1.36)	1.34	1.35	O25-C23-C22	112 (114)	113
O25-C26	1.43 (1.43)	1.44	1.45	C23-O25-C26	114 (115)	115
C22-C27	1.35 (1.35)	1.34	1.33	C17-C22-C27	128 (128)	129

	This work ^a	Ref. 11 ^a	Ref. 12 ^a	This work ^b	Ref. 11 ^b	Ref. 12 ^b
C27-O28	1.37 (1.35)	1.29	1.35	C22-C27-O28	129 (124)	124
O28-C29	1.43 (1.43)	1.45	1.44	C27-O28-C29	118 (116)	113
C8-O7-C1	109 (118)	118	117	C8-O7-C1-C2	91 (0)	3
O7-C1-C2	118 (125)	125	125	C8-O7-C1-C6	-93 (-180)	-177
O7-C1-C6	122 (116)	115	115	C9-C12-C13-N14	-44 (-49)	-46
C1-C2-C3	120 (121)	120	121	C12-C13-N14-C15	65 (67)	68
C2-C3-C4	121 (122)	124	122	C12-C13-N14-C19	-171 (-166)	-174
C3-C4-C5	118 (117)	113	117	C13-N14-C19-C18	172 (169)	176
C4-C5-C6	123 (123)	124	123	C13-N14-C15-C16	-174 (-170)	-174
C5-C6-C1	118 (118)	119	118	N14-C19-C18-C17	59 (58)	56
				N14-C15-C16-C17	-57 (-58)	-63

^aBond lengths in Å.

^bAngles in °.

^cDihedrals are not available in ref. 11.