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Molecular Mechanics and ^{1}H NMR Conformational Study of 3,8-Diazabicyclo[3,2,1]octanes and Related cis-2,6-Dimethylpiperazines Active on Opioid Receptors

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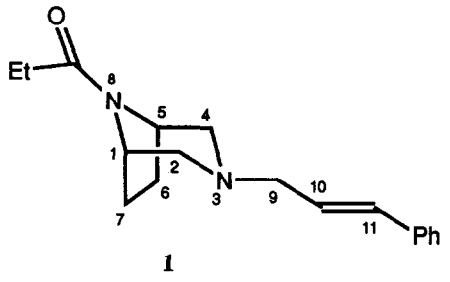
Abstract: 3-Trans-*cinnamyl-8-propionyl-3,8-diazabicyclo[3,2,1]octane* ***1****, its monocyclic analog 4*-trans-*cinnamyl-1-propionyl*-cis-*2,6-dimethylpiperazine* ***2*** *and their isomers having the nitrogen sustituents exchanged,* ***3*** *and* ***4****, have been submitted to conformational analysis by molecular mechanics and ^{1}H NMR spectroscopy. The results of molecular modeling indicate that, while the monocyclic compound* ***2*** *has a preferred conformation very similar to the corresponding bicyclic compound* ***1****, compound* ***4*** *is quite different with respect to* ***3****; it is the only compound with equatorially oriented substituents on the carbon atoms of the hexacyclic ring. This feature could explain the low affinity of* ***4*** *towards μ receptors, as compared with the high affinity of* ***1-3****.*

The synthesis and the analgesic properties of 3,8-diazabicyclo[3,2,1]octanes were reported by Cignarella et al.[1] The structural requirements for optimum activity seemed to reside in the presence of a propionyl group at N8 and an aralkyl group with a three carbon chain at N3. Among the most active compounds the 3-*trans*-cinnamyl-8-propionyl derivative (**1**) was approximately ten times more potent than morphine in the Randall and Selitto test (rat). The isomer of **1** in which the N3 and N8 substituents were exchanged, **3**, was found 1/5 as active as **1**. The related 4-cinnamyl-1-propionyl-*cis*-2,6-dimethylpiperazine (**2**) and its isomer 1-cinnamyl-4-propionyl substituted (**4**), formally derived from **1** and **3** by breaking of the endoethylenic bridge, were 1/5 as active as **1**, and inactive, respectively.[2]

The increasing evidence of the existence of different opioid receptors, recently renewed the interest for analgesics **1-4** which were submitted to binding experiments towards μ and δ receptors, as well as to a re-evaluation of the analgesic potency *in vivo* by the hot plate test in the mouse. Using ^{3}H-DHM as radioligand for μ receptors, **1** (k_i= 37 nM) and **3** (k_i= 68 nM) exhibited an affinity of the same order of magnitude than morphine (k_i= 15 nM).[3] In the *cis*-2,6-dimethylpiperazine series, **2** retained high μ-affinity (k_i= 22 nM) while the isomer **4** (k_i= 4400 nM) was poorly active.[4] All the compounds exhibited a noticeably



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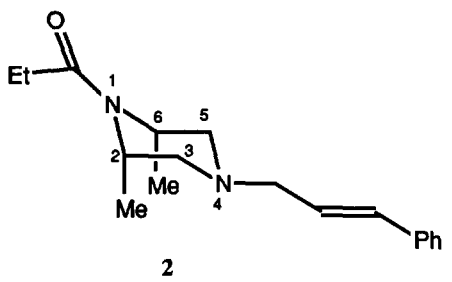

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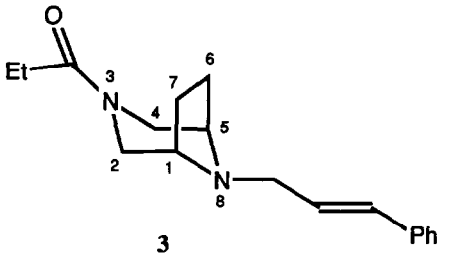

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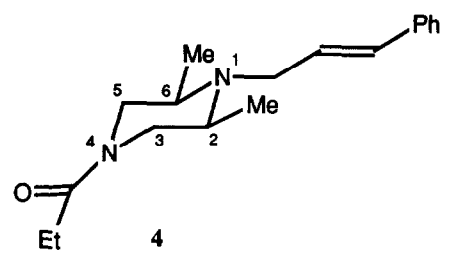

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lower affinity towards δ receptors using ^{3}H-DADLE as radioligand. These results were consistent with *in vivo* experiments. Compound **1** exhibited an analgesic potency about 5 times higher than that of morphine, while the isomer **3**, though 10 times less active than **1**, displayed agonist-antagonist properties.[3] Conversely, **2** was found equiactive to **1**, while the previously reported inactivity of **4** was confirmed.[4]

The high decrease of activity on going from compounds **1-3** to compound **4** indicates that the structural and/or conformational properties of these compounds play a significant role in the modulation of their activity. So, we undertook a conformational analysis study of compounds **1-4**, with the aid of molecular mechanics calculations and verified the obtained results through ^{1}H NMR spectroscopy.

RESULTS AND DISCUSSION

The overall conformation of compounds **1-4** is mainly due to the conformational behavior of the piperazine ring which is, in turn, influenced by the substituents on the two nitrogen atoms. It is well known that the nitrogen linked to a carbonyl group and the nitrogen of a tertiary amine have quite different geometries. In the former case the N-$C_{carbonyl}$ bond has considerable double bond character and the nitrogen atom has sp^2 hybridization thus allowing a planar arrangement of the N and $C_{carbonyl}$ atoms and of the atoms bonded to them. On the contrary, a tertiary amine nitrogen atom has sp^3 hybridization with the lone pair occupying a tetrahedral position. It can be therefore predicted that an acylpiperazine is quite similar, in the conformational behavior, to the corresponding acylpiperidine having a CH_2 instead of the NH group. A molecular mechanics study of N-formyl and N-acetyl piperidine has been published by Schnur et al.[5] who found the chair conformation of the piperidine ring to be preferred by 2-3 kcal/mol over the twist-boat conformations. Though unsubstituted N-acylpiperazines do not greatly differ from N-acylpiperidine, substituents at the ring carbon and nitrogen atoms of **1-4** could, in principle, modify the energetic ranking of conformations. Moreover, nitrogen inversion at the tertiary amine center and rotation around the two bonds N3-C9 and C9-C10 in the aralkyl chain represent other degrees of freedom which could influence the conformational behavior of **1-4**.[6]

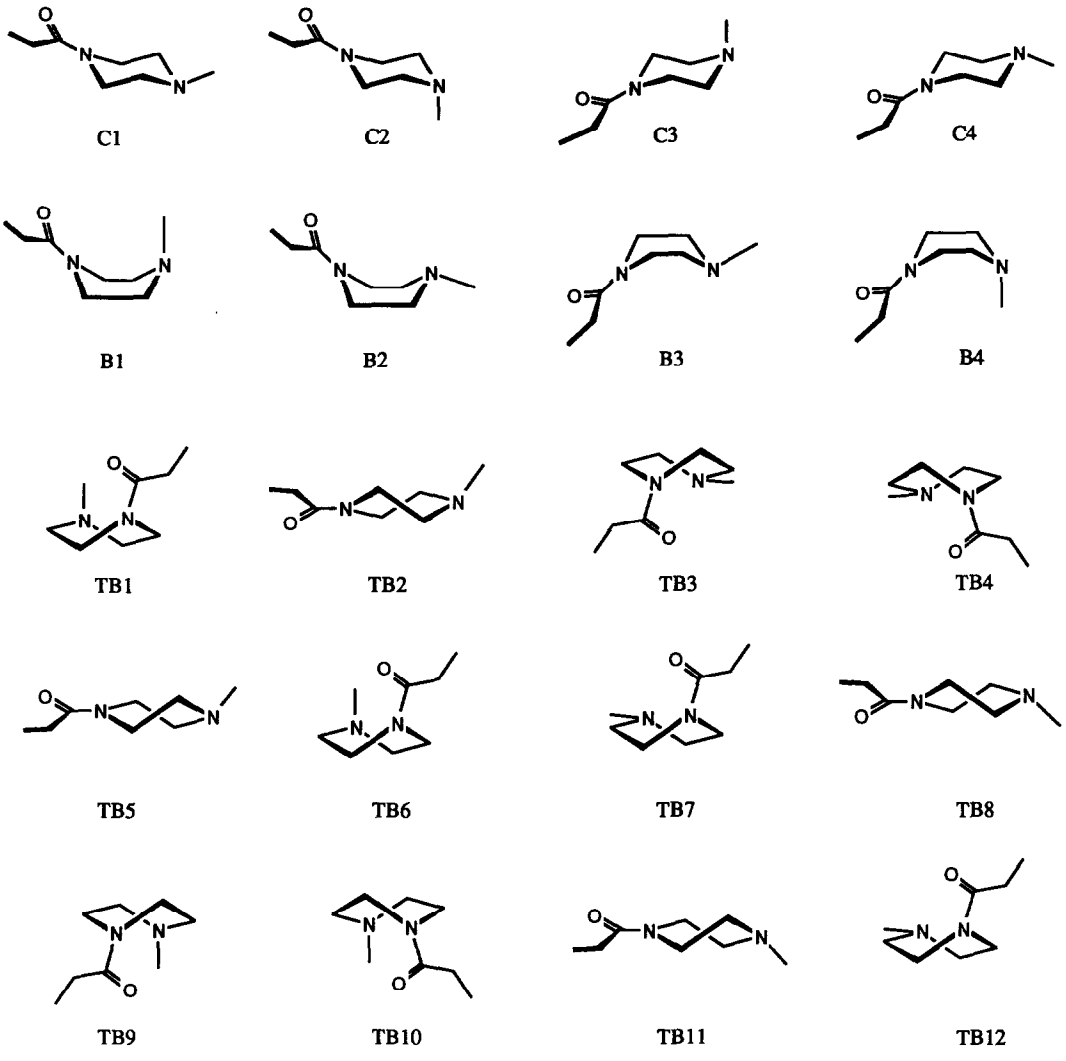


Fig. 1. All possible chair, boat, and twist-boat conformers of the piperazine ring of compounds **1-4** and **5-8**.

Using the MM2(85) program,[7] the conformational space of **1** was fully explored. This molecule can, a priori, adopt the two chair C1 and C2 and the two boat B1 and B2 conformations (figure 1); rotation around the N3-C9 and C9-C10 bonds has been simulated in each of the four cases so that 20 different local minima have been located and are reported in Table 1, whereas in figure 2 the geometry of the two lowest minima **1**-C1a and **1**-C1b is plotted. Four cluster of conformations are obtained; in each cluster the same conformation of the rings and the same configuration at the tertiary nitrogen is observed whereas the aralkyl chain is folded differently. When the chain is equatorially oriented (conformers **1**-C1 and **1**-B2) it has a higher degree of mobility then when it is axially oriented (conformers **1**-C2 and **1**-B1) due to the severe crowding which occurs in the latter case when the rotation around the N3-C9 bond brings the chain below (**1**-C2) or above (**1**-B1) the six-membered ring. As energies in each cluster are grouped in very small ranges (1-1.5 kcal/mol) it

Table 1. Relative Energies (kcal/mol) and Selected Torsional Angles for Conformations of Compound **1**.

Conformation	E_{rel}	τ(C4-N3-C9-C10)	τ(N3-C9-C10-C11)
1-C1a	0.0	-170	-120
1-C1b	0.0	-65	119
1-C1c	0.7	62	-108
1-C1d	0.7	67	107
1-C1e	0.8	-169	92
1-C1f	0.8	-64	-91
1-C2a	8.4	-165	122
1-C2b	8.4	64	-121
1-C2c	9.5	67	91
1-C2d	9.5	162	-88
1-B2a	10.1	169	118
1-B2b	10.2	66	-120
1-B2c	10.8	170	-95
1-B2d	10.9	-59	108
1-B2e	10.9	-66	-107
1-B2f	11.0	62	95
1-B1a	13.9	-170	-121
1-B1b	14.3	-64	120
1-B1c	15.3	-163	88
1-B1d	15.4	-64	-92

Table 2. Relative Energies (kcal/mol) for Conformations of Compounds **5-8**.

Conformation	E_{rel}	Conformation	E_{rel}	Conformation	E_{rel}	Conformation	E_{rel}
5-C1	0.0	**6**-C1	0.0	**7**-C1	0.0	**8**-C1	3.9
5-C2	8.4	**6**-C2	7.5	**7**-C2	0.4	**8**-C2	4.6
5-B1	14.3	**6**-C3	11.1			**8**-C3	1.1
5-B2	10.1	**6**-C4	7.8			**8**-C4	0.0
		6-TB1	8.6			**8**-TB1	7.1
		6-TB2	9.7			**8**-TB2	6.1
		6-TB5	7.6			**8**-TB3	8.0
		6-TB6	7.9			**8**-TB4	7.7
		6-TB7	6.5			**8**-TB5	6.4
		6-TB8	9.7			**8**-TB6	7.4
		6-TB9	17.7			**8**-TB7	3.4
		6-TB11	7.7			**8**-TB9	8.7
		6-TB12	5.7			**8**-TB10	8.3
						8-TB12	3.7

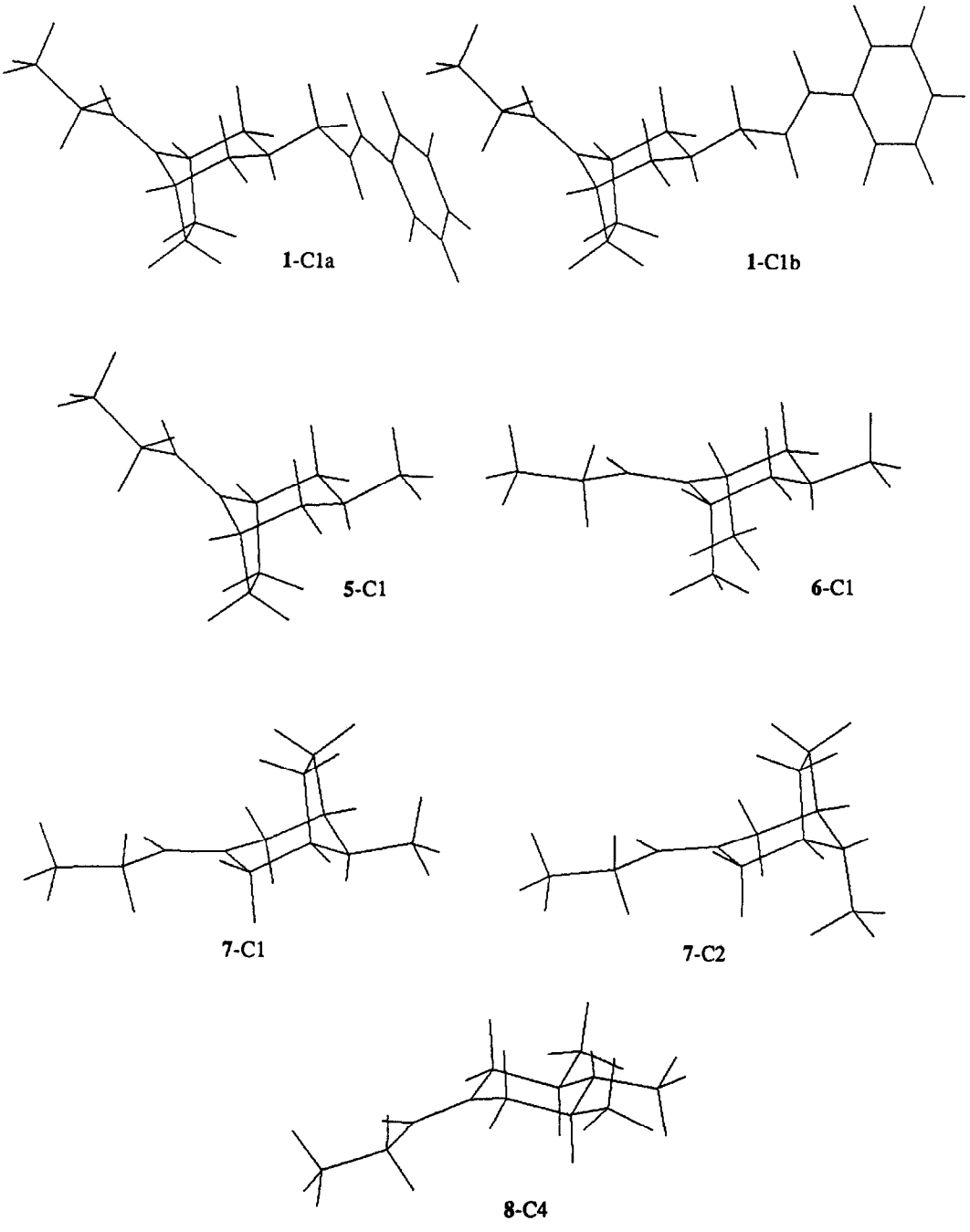
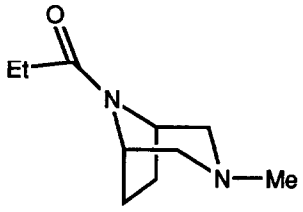


Fig. 2. Representation of the MM2 calculated low energy conformers for compounds **1** and **5-8**.



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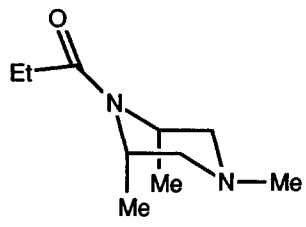

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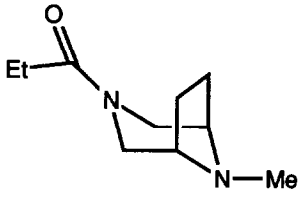

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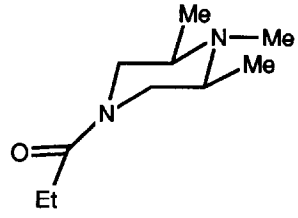

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can be supposed that the aralkyl chain has only a very small influence on the conformational behavior of the bicyclic part of the molecule. Thus, we used compound **5**, having a methyl group instead of the entire chain, as simplified model for **1**. Table 2 reports the results obtained after exploration of the conformational space of **5**. Only four conformations are found as local minima, each representing one of the four clusters found for **1**. More interestingly, the energy ranking of the four conformations of **5** closely parallels the energy ranking of the four clusters of conformations, clearly indicating that the rather flexible aralkyl chain does not exert a significant role in determining the conformational behavior of the system. For this reason we decided to replace in all the further calculations the cinnamyl with a methyl group as its inclusion in the calculations makes them more time consuming without giving any useful information. Since the cinnamyl moiety has a significant role in the interaction with the receptor, this only means that we cannot predict through calculations its "active" orientation. However, this orientation is probably inside the cluster of allowed orientations, all extending far from the bicyclic system.

Due to the strict similarity of compounds **2-4** to **1**, we can safely suppose that the cinnamyl moiety has some conformational mobility also in these cases and that the conformational behavior reported in Table 1 for the aralkyl chain also holds for **2-4**; as a consequence, also in these cases for each conformation of the cyclic portion of the molecules there is a cluster of almost isoenergetic allowed orientations of the cinnamyl group.

With the attention focussed on the cyclic moiety we then undertook the conformational analysis of compounds **6-8** (as models for **2-4**). Contrary to **5** (and **1**) where pseudo-rotation in the six and the five-membered rings is completely forbidden and the only degree of freedom corresponds to the chair-boat conversion of the six-membered ring, a certain degree of flexibility is obviously expected for compound **6** and, a priori, it cannot be excluded that some twist-boat conformation has an energy level comparable or lower than that of the chair ones. The molecule could adopt four different chair (C1 to C4, figure 1) and twelve twist-boat (TB1 to TB12, figure 1) conformations. By proper use of the double driver option of MM2 with successive runs and different couples of torsional angles we generated the starting geometries corresponding to these sixteen conformations which, when allowed to relax, yielded the local minima described in Table 2. It is worthy of note that, while the four C starting geometries yielded four different local minima, we found less than twelve TB minima as some TB forms do not exist as defined energy minimum.

Table 3. Selected ^1H NMR Data of Compounds **1-4** (500 MHz, $CDCl_3$, Chemical Shifts in ppm from TMS, Coupling Constants in Hertz); in Brackets Calculated[8] Values of the Coupling Constants of Compounds **5-8**.

1	H-2eq	H-4eq	H-2ax	H-4ax	H-1	H-5	$J_{1,2eq}$	$J_{5,4eq}$	$J_{1,2ax}$	$J_{5,4ax}$
	2.78, dd	2.72, dd	2.19, dd	2.29, dd	4.06, bd	4.63, bd	2.7	2.7	1.8	~2
							(2.8)	(2.8)	(2.6)	(2.6)
2	H-3eq	H-5eq	H-3ax	H-5ax	H-2	H-6	$J_{2,3eq}$	$J_{6,5eq}$	$J_{2,3ax}$	$J_{6,5ax}$
	2.74, bd		2.10, dd		4.0, m	4.5, m	≤1		4.5	
							(1.5)	(1.5)	(4.8)	(4.8)
3	H-2eq	H-4eq	H-2ax	H-4ax	H-1	H-5	$J_{1,2eq}$	$J_{5,4eq}$	$J_{1,2ax}$	$J_{5,4ax}$
	3.42, bd	4.17, bd	3.30, bd	2.88, bd	3.26, m		2.5	2.5	2.0	2.0
							(1.9)	(1.9)	(3.6)	(3.6)
4	H-3eq	H-5eq	H-3ax	H-5ax	H-2	H-6	$J_{2,3eq}$	$J_{6,5eq}$	$J_{2,3ax}$	$J_{6,5ax}$
	3.6, m	4.41, bd	2.93, dd	2.47, dd	2.63, m		--	2.5	11.0	11.0
							(3.7)	(3.7)	(11.4)	(11.4)

The results described in table 2 show that, though **6** is more flexible than **5**, this flexibility appears only in highly energetic local minima and that the chair conformation **6**-C1, which accounts for about 99.7% of the overall population at room temperature is quite similar to the conformation **5**-C1 of **5** (see figure 2); in fact it shows a diaxial orientation of the methyl groups in positions 2 and 6. This orientation is largely favored over the diequatorial as conformations **6**-C3 and **6**-C4, showing this arrangement, are less stable than **6**-C1 by 11.1 and 7.8 kcal/mol, respectively, in consequence of the severe strain produced by the interaction of the equatorial methyl groups with the oxygen atom and the ethyl group of the propionyl moiety.

Also compound **7**, as **5**, showed a rigid situation but with only two local minima (Table 2 and figure 2). Differently from **5**, the boat conformations B3 and B4 do not exist as defined local minima. The two chair conformation have about the same energy as, in this case, in the usually preferred equatorial orientation the N-methyl group suffers a steric interaction with the ethylidene bridge.

The conformational search procedure above described for **6** was then applied to compound **8**. Once more, the chair conformations of the piperazine ring was found preferred over the twist-boat ones but, contrary to **6**, the diequatorial orientation of the C-2 and C-6 methyl groups (**8**-C3 and **8**-C4 conformers) was largely preferred over the diaxial one (Table 2 and figure 2); conformations **8**-C1 and **8**-C2 are less stable than **8**-C4 by 3.9 and 4.6 kcal/mol, respectively.

At last, in order to confirm the calculated conformations of the model N-methyl compounds **5-8**, the corresponding N-cinnamyl compounds **1-4** were submitted to high field ^1H NMR analysis to determine the coupling constants of vicinal protons in the six membered rings. The considerable double bond character of the amide C-N bond makes compounds **1-4** unsymmetrical and complicates their ^1H NMR spectra. The barriers normally found for rotation around the C-N linkage (12-22 kcal/mol) have the proper magnitude to allow the well known coalescence phenomenon. Actually, when the 500 MHz ^1H NMR spectra of **1-4** were recorded, we observed several exchanges of protons of the piperazine ring; however, for all the four compounds the coupling constants between the vicinal hydrogen atoms in the piperazine rings could be determined (Table 3). Application of the Altona equation[8] to the allowed conformations of **5-8** yielded the coupling constants also reported in brackets in Table 3. The agreement between calculated and experimental values ensures that the calculated conformations of **5-8** exactly represent the solution conformations of **1-4**.

The conformational results above illustrated indicate that while the monocyclic compound **2** has a geometry very similar to that of the bicyclic analog **1**, compound **4** is quite different with respect to **3**. Dimethylpiperazine **4**, in fact, is the only compound with equatorially oriented substituents on the carbon atoms of the hexacyclic ring. Interesting to note, this feature could explain the very low affinity of **4** towards μ receptors, as compared to the high affinity of **1-3**. If one assame the existence of a small lipophylic pocket on the receptor surface, only the two-carbon bridge of **1**, **3** and the axially oriented methyl groups of **2** could efficiently accommodate in it giving rise to efficient interaction.

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