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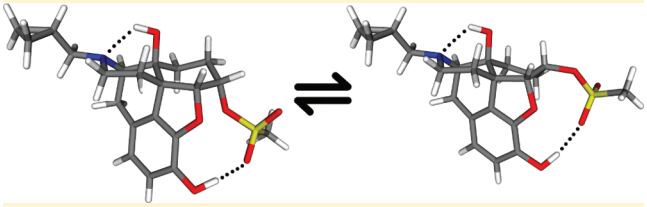
Conformational Analysis of 6α- and 6β-Naltrexol and Derivatives and Relationship to Opioid Receptor Affinity

Jennifer A. Bayron, Amy M. Deveau, and John M. Stubbs*

Department of Chemistry and Physics, The University of New England, 11 Hills Beach Road, Biddeford, Maine 04005, United States



ABSTRACT: Naltrexol and its C_6 α and β desoxy, iodo, mesyl, tosyl, trifyl, dimethylcarbamyl, and diphenylcarbamyl derivatives were studied in their energy-minimized C ring chair-like and boat-like conformations using B3LYP/6-31G** and SM5.4/A to estimate aqueous solvation free energy. The results were compared to experimental opioid receptor binding affinities. The total energy difference between β conformers correlated well with MOR binding affinity, while the aqueous solvation free energy correlated well with the KOR binding affinity.

INTRODUCTION

Computational methodologies are a powerful tool to correlate conformational preferences and chemical properties with the biological activity of stereoisomers. In cases where a ligand binds to a membrane-bound receptor to initiate a downstream biological signaling cascade, like in G-protein coupled opioid receptors,[1] such computational perspectives are invaluable; relationships between structure, biological activity, and solvation can be studied in silico without the complexity, time, and expense of formal lab experiments.[2−7]

Although there are three primary subtypes of opioid receptors—mu (MOR), kappa (KOR), and delta (DOR)[8]—the mu opioid receptor has been widely investigated because of its importance in pain and addiction pathways.[9] To reverse overdose of MOR agonists used in pain treatment or to minimize side effects of MOR agonists during long-term therapy, MOR antagonists are often administered.[10−12] There exist two primary types of opiate antagonists: neutral antagonists and inverse agonists.[13,14] Sadée et al.[15] have proposed that neutral antagonists of the MOR, rather than inverse agonists, are therapeutically relevant in treating opiate abuse and addiction because they minimize the withdrawal syndrome.

Portoghese and others have previously investigated structure−activity relationships[16−22] and conformational preferences[23−25] of C_6 naltrexol and naltrexone derivatives. With this in mind, we wanted to apply these ideas to a recently synthesized series of sulfonate ester and carbamate derivatives of 6β-naltrexol (Figure 1) by the Deveau group that exhibited

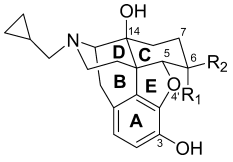


Figure 1. General 6-naltrexol derivative structure with ring labels in bold and select atom numbers, where α corresponds to R_1 = substituent, R_2 = H, and β corresponds to R_1 = H, R_2 = substituent.

nanomolar or subnanomolar affinity at the MOR.[26] Although these high affinity agents differ by small structural perturbations [(tosyl versus mesyl) and (diphenyl versus dimethyl)], structure−activity trends were reported for both receptor binding affinity and subtype selectivity. As the rigid fused core (rings A, B, D and E), rotatable cyclopropylmethyl substituent, and C_{14} hydroxyl are present in all derivatives, we hypothesize that the activity of these compounds is determined by three key differences in the compounds: (a) the chemical identity of the C_6 substituent, (b) the chirality of the C_6 stereocenter (alpha vs beta), and (c) the accessible, stable, low-energy conformations of ring C. In this report, in silico approaches are used to investigate conformational preferences of (chair versus boat) and solvation effects on low-energy conformations for 6α- and 6β-naltrexol and their tosylate, mesylate, triflate, iodide, and carbamate derivatives. Therefore, this investigation of the C ring and its conformation has been undertaken to determine the lowest energy conformers and evaluate how structure and conformation inform chemical reactivity and opioid receptor binding. Although gas-phase minimum energy structures are not necessarily the important conformations in a biological setting, we believe in this case that the limited flexibility of the rigid fused core implies that the biologically relevant conformations will not differ greatly from those studied here, as has been done previously.[27]

METHODS

Each isomer was energy minimized at the B3LYP/6-31G** level with the LAV3P** pseudopotential used for iodine, as needed. Two C ring conformers, boat-like and chair-like (referred to subsequently as simply boat and chair), were separately minimized with any remaining degrees of freedom (such as rotation of the cyclopropyl group) considered at the lowest energy only. The aqueous solvation free energy was determined with the SM 5.4/A model of Cramer and Truhlar[28] at the gas-phase minimum energy geometry. All calculations described in the Results and Discussion section were carried out with Spartan '04 for Windows.[29] To confirm the

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Table 1. Relative Energies of Boat to Chair Conformers Both in Gas Phase (ΔE_{gas}) and Including Aqueous Solvation ($\Delta G_{total} = \Delta E_{gas} + \Delta G_{solv}$)

			α		β	
C_6 substituent	abbrev.	structure	ΔE_{gas} (kJ mol^{-1})	ΔG_{total} (kJ mol^{-1})	ΔE_{gas} (kJ mol^{-1})	ΔG_{total} (kJ mol^{-1})
hydroxy	OH	$-OH$	0.9	−4.5	−6.2	0.3
dimethylcarbamyl	ODMC	$-OC(O)N(CH_3)_2$	3.9	−5.8	15.5	19.5
diphenylcarbamyl	ODPC	$-OC(O)N(C_6H_5)_2$	2.1	−5.5	18.4	21.4
tosyl	OTs	$-OS(O)_2pC_6H_4CH_3$	21.3	20.4	21.7	19.5
mesyl	OMs	$-OS(O)_2CH_3$	17.1	16.8	23.3	19.8
trifyl	OTf	$-OS(O)_2CF_3$	20.0	21.2	24.0	22.5
iodo	I	$-I$	−13.6	−13.6	23.4	25.4
desoxy	H	$-H$	8.4	8.8	–	–

appropriateness of this methodology, select additional calculations were carried out with Gaussian 03[30] that showed that the addition of diffuse functions via the basis set 6-31++G** had a small (≤5 kJ mol^{-1}) effect on the relative (chair versus boat) gas-phase energy minima, based on calculations on 6β-OH, 6β-ODMC, and 6β-OMs. Additionally, the energy difference between solvation at the gas-phase minimum energy structure and the minimum energy structure including solvation effects, i.e., the relaxation energy in the presence of solvent, was minimal (≤1 kJ mol^{-1}) for 6β-OH using the PCM solvation model.

RESULTS AND DISCUSSION

Preferred C Ring Conformation. The energy differences of the boat relative to the chair conformations of ring C are listed in Table 1 for each compound both in the gas phase, ΔE_{gas}, and with aqueous solvation considered, $\Delta G_{total} = \Delta E_{gas} + \Delta G_{solv}$. The lowest energy conformation of each compound's C ring was in most cases the chair as expected on the basis of the preferences of cyclohexane. However, the boat was the preferred conformation in the cases of 6β-OH (without solvation), 6α-I (with and without solvation), as well as 6α-ODMC and 6α-ODPC (with solvation). This is consistent with earlier studies of some 6α-substituted opioids.[23−25] Detailed investigation of the energy-minimized structures revealed two different causes. In the case of 6β-OH, the boat conformation is the lowest energy conformation because it can form an additional hydrogen bond between the C_6 and C_{14} hydroxyl groups (Figure 2). The explanation in the cases of the 6α-I and to a lesser extent 6α-ODMC and 6α-ODPC derivatives is not a favoring of the boat but rather a disfavoring of the chair. In the chair conformation, each group is pointed down and thus interacting unfavorably with $O_{4'}$ in the E ring due to steric strain. In the case of the 6α-I chair, for example, the size of an iodine atom causes an interaction with $O_{4'}$ that distorts the substituent's geometry with respect to the C ring and thus disfavors this conformer. This is evident in the C_5-C_6-I as compared to C_7-C_6-I angles of 114.6° and 109.5°, respectively, distorted from the roughly equal values of 110.8° and 111.3° in the boat conformation.

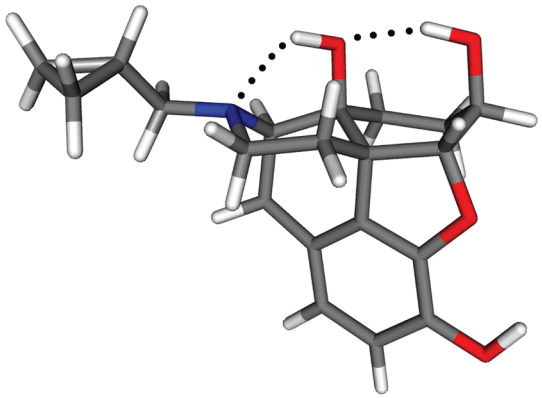

Figure 2. 6β-naltrexol boat conformer with intramolecular hydrogen bonds shown.

Intramolecular hydrogen bonds between the A ring hydroxyl group and an oxygen on the C_6 substituent were determined to exist when the H···O distance was within 2.7 Å (Table 2). Whereas both chair and boat conformers for the α sulfonate esters hydrogen bond to the A ring hydroxyl group (Figure 3), this is lacking in the α carbamates. In the chair conformation of the α carbamates this absence is due to the substituent's structure that would result in close proximity of amide to the C ring. The boat conformation disfavors hydrogen bonding likely due to proximity of the carbonyl oxygen to $O_{4'}$.

Table 2. A Ring Hydroxyl Hydrogen Closest C_6 Substituent Oxygen Distance for Conformations with a Hydrogen Bond Present

C_6 substituent	α chair (Å)	α boat (Å)	β chair (Å)	β boat (Å)
ODMC	–	–	2.231	–
ODPC	–	–	2.307	–
OTs	1.996	2.093	2.247	–
OMs	1.953	2.093	2.181	–
OTf	2.036	2.282	2.639	–

The aqueous solvation free energies are listed in Table 3. For a given compound, the relative values for the conformers studied here are interpreted according to the idea that the more the polar portions of the molecule (such as hydroxyl groups and oxygen atoms) are accessible to solvent, the more favorable the solvation free energy will be. In the case of the 6α carbamates, there are large differences between the chair and boat solvation free energies, 9.6 and 7.5 kJ mol^{-1} for ODMC and ODPC, respectively. The chair form for both of these compounds has the C_6 substituent aligned close to the A and E rings, whereas the boat form extends the substituent away from the rest of the molecule. In this more open shape, the boat conformer likely allows more interaction between the polar portions of the molecule and the solvent. For 6α sulfonate ester substituents, there is little difference between solvation energy

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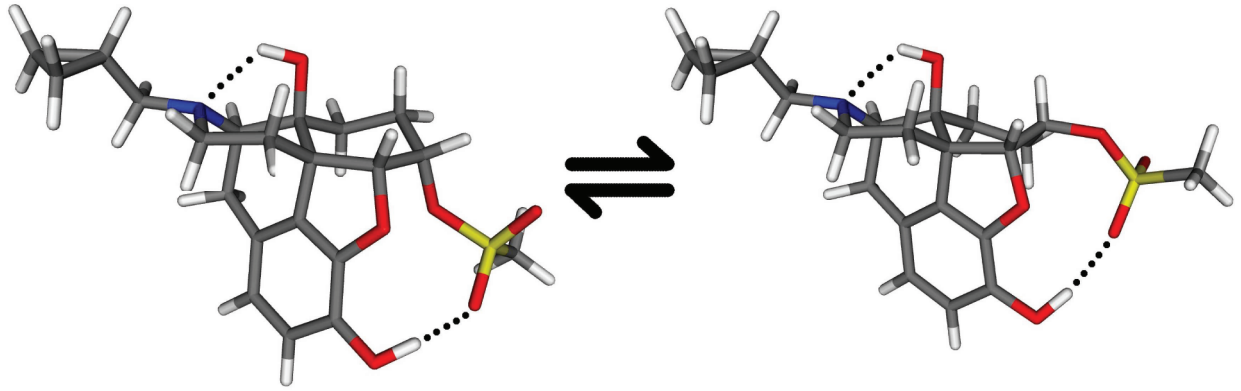

Figure 3. 6α-OMs in chair (left) and boat (right) conformations, both hydrogen bonding to A ring hydroxyl group.

Table 3. SM 5.4/A Aqueous Solvation Free Energies

C_6 substituent	α chair (kJ mol^{-1})	α boat (kJ mol^{-1})	β chair (kJ mol^{-1})	β boat (kJ mol^{-1})
OH	−31.6	−36.9	−40.2	−33.7
ODMC	−25.4	−35.0	−30.9	−26.9
ODPC	−29.0	−36.5	−31.1	−28.1
OTs	−50.1	−51.0	−51.7	−53.9
OMs	−51.3	−51.6	−55.6	−59.0
OTf	−34.7	−33.6	−39.2	−40.6
I	−26.7	−26.7	−27.9	−25.9
H	−24.7	−24.4	–	–

values for either conformer. This is likely due to both conformers being able to make a hydrogen bond (Table 2 and Figure 3) to the A ring's hydroxyl group, exposing approximately the same amount of polar sulfonate and A ring hydroxyl group to the solvent in either conformation. For 6α-OH, the boat form extends the OH group further away from the molecule, allowing more interactions with solvent and more favorable solvation energy. Finally, as is expected, the 6-H and 6α-I substituents show little difference between solvation free energies due to the absence of a group interacting with the solvent. For the 6β-OH compound, as the boat form already makes a strong hydrogen bond, it interacts less with the solvent than the chair form does, leading to the substantially lower (6.5 kJ mol^{-1}) aqueous solvation free energy for the chair form. For the remaining 6β molecules considered, there is little difference between solvation free energy values for either conformer. However, in the cases of the ODMC, ODPC, and I groups, there is a slightly higher solvation free energy for the boat conformation relative to the chair, whereas for OMs, OTs, and OTf, the boat conformation has a more favorable aqueous solvation relative to the chair conformer. As all the β carbamates and sulfonate esters in a chair conformation have an intramolecular hydrogen bond to the A ring's hydroxyl group (Table 2), the difference is likely due to the boat conformer where the sulfonate esters partially block the C_{14} hydroxyl group from the solvent but balance this by exposing both the sulfonate ester group itself and the A ring hydroxyl group. On the other hand, the carbamates being branched block more of the C_{14} hydroxyl group from solvent exposure while not offsetting this as much with the comparatively less polar amide group, which is also partially obscured by the amide nitrogen's substituents. Finally, the 6β-I conformers have a higher solvation free energy for the boat form that can be understood in terms of the iodine atom in the boat conformer partially blocking the C_{14} hydroxyl group.

Comparison to Binding Data. The work of Pelotte et al.[26] studied binding affinity for the 6β derivatives OH, ODPC, ODMC, OTs, and OMs for mu, kappa, and delta opioid receptors in terms of K_i, the inhibition constant (Table 4). As

Table 4. Experimental Binding Affinities, K_i,[26] Compared to ΔG_{total} and G_{solv} from This Work

C_6 substituent	MOR K_i (nM)	ΔG_{total} (kJ mol^{-1})	C_6 substituent	KOR K_i (nM)	chair G_{solv} (kJ mol^{-1})
6β-ODPC	0.56	21.4	6β-OTs	1.66	−51.7
6β-OTs	0.79	19.5	6β-OMs	6.75	−55.6
6β-OMs	1.11	19.8	6β−OH	7.42	−40.2
6β-ODMC	1.85	19.5	6β-ODPC	14.7	−31.1
6β−OH	2.12	0.3	6β-ODMC	28.2	−30.9

K_i is a measure of the dissociation equilibrium, a low value corresponds to high affinity (i.e., small amount dissociated). From the experimental data, the trends in affinity are for mu, ODPC > OTs > OMs > ODMC > OH with a range of a factor of 3.8 (i.e., the highest affinity divided by the lowest is equal to 3.8); for kappa, OTs > OMs > OH > ODPC > ODMC with a range of a factor of 17; for delta, OTs > ODPC > OMs > OH > ODMC with a range of a factor of 65. In considering our data in Tables 1 and 3, with respect to mu affinity, the compound with the lowest affinity, OH, either favors the boat conformation (gas phase) or has the boat as populated as the chair (with solvation). Second, although the range is not large, the ΔG_{total} for the four remaining compounds tested shows a trend of highest affinity with highest ΔG_{total}, lowest affinity with lowest ΔG_{total}, and intermediate values in the middle, i.e., a ranking based in Table 1 from highest to lowest ΔG_{total} values is ODPC > OMs ≥ OTs ≈ ODMc > OH, essentially identical with mu affinity(Table 4). On the basis of this trend, OTf and I should have even higher affinities at the MOR, and prevalence of the chair conformation appears to be a factor in binding affinity, although we note that OTf is highly reactive and unlikely to be stable in solution.

The $|G_{solv}|$ for a given conformer has a ranking of OMs > OTs > OH > ODPC ≥ ODMC, very similar to the affinity ranking for the KOR. Thus, the molecule most stabilized in water has the highest affinity and that with the weakest interaction with water has the least affinity. This may indicate that the environment of the KOR nearest to the C_6 substituent is highly hydrophilic. On the basis of this trend, the binding of

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OTf should be the same as OH (and weaker than OMs or OTs), and I and H should be weaker than the five studied compounds. There appears to be no trend in this data consistent with the DOR binding affinity. A linear regression analysis was carried out on each of these trends in the form of the relationship between ln K_i and either ΔG_{total} (for the MOR) or $G_{solv,chair}$ (for the KOR). The resulting fit for MOR was ln K_i = a ΔG_{total} + b with a = −0.042 ± 0.027 mol kJ^{-1} and b = 0.81 ± 0.49 and a correlation coefficient of −0.67. For KOR, the fit was ln K_i = c $\Delta G_{solv,chair}$ + d with c = 0.073 ± 0.033 mol kJ^{-1} and d = 5.1 ± 1.4 and a correlation coefficient of 0.79. It should be emphasized that the trends discussed above are unlikely to be applicable to ligands with molecular structures that differ from naltrexol or its C_6 derivatives. Because of a lack of experimental knowledge of the receptor, it is difficult to conclusively rationalize either of these trends. However, a possible explanation of the MOR trend, where an increased preference for the chair form leads to higher binding affinity, is that the chair form binds more strongly to the receptor than the boat form, and because of this, the more favorable the chair form is the higher the binding affinity will be. The trend for the KOR, where a more favorable aqueous solvation energy is related to a higher binding affinity, could potentially be explained in terms of the receptor environment around the C_6 substituent. If the receptor's interaction is similar to water's interaction with the C_6 substituent, then the enthalpic part of the receptor−substituent interaction would be similar to that of the water−substituent interaction, while the entropic part would be different and likely unfavorable for water−substituent interactions, yet likely negligible for receptor−substituent interactions. In this manner, it could be possible for binding affinity to be related to aqueous solvation free energy.

If the binding affinities of the 6α-substituted compounds are also described by the above trends, then the expected MOR affinity ranking would be OTf > OTs > OMs > OH > ODPC ≥ ODMC > I. As the preferred conformer for the 6α compounds depends on the substituent, the choice of which conformer's $|G_{solv}|$ to choose to predict the expected KOR affinity ranking is unclear. On the basis of a choice of all chair values, the order of affinity would be OMs > OTs > OTf > OH > ODPC > I > ODMC. Alternatively, ranking the $|G_{solv}|$ values on the basis of preferred conformation (as determined by ΔG_{total} in Table 1) the order of affinity would be OMs > OTs > OH ≥ ODPC > ODMC ≥ OTf > I, the only differences being where OTf and I fall in the ranking.

CONCLUSIONS

6α- and β-naltrexol and derivatives exist primarily in either chair-like or boat-like conformations of their C ring, the relative energies of which depend on the C_6 substituent and its interaction with the rest of the molecule. The chair-like conformation is preferred in all cases except for 6β-OH, 6α-I, 6α-ODMC, and 6α-ODPC. Two trends in this work were found to be consistent with experimentally determined opioid−receptor affinities. For 6β compounds at the MOR, binding affinity increases as the total energy difference (including aqueous solvation free energy) between chair and boat increases. At the KOR, binding affinity increases as the aqueous solvation free energy of a given conformer increases. These two trends indicate the importance of the chair conformation and the environment's polarity, respectively, and are limited in applicability to the ligands studied here or closely related molecules.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jstubbs@une.edu.

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