Conformation–Activity Study of Methadone and Related Compounds

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A conformational study of methadone and structurally related analgesics has been performed using Allinger's Molecular Mechanics I (MM1) program. Initial calculations were performed on analogues of normethadone, (5*S*)-isomethadone, (6*R*)-methadone, (3*S*,5*S*)- and (3*S*,5*R*)-isomethadol, (3*S*,6*R*)- and (3*S*,6*S*)-methadol, and (5*S*,6*R*)- and (5*S*,6*S*)-methylmethadone. It was found that two mirror-image arrangements of the phenyl rings are possible with certain conformations of the linear portions of the molecules consistently preferred for each. More detailed calculations were then performed on normethadone, (5*S*)-isomethadone, (6*R*)-methadone, (5*S*,6*S*)- and (5*S*,6*R*)-methylmethadone, and the *N*-demethyl derivative of the last compound with and without an electrostatic (hydrogen bonding) potential function. The results of the calculations are in good agreement with previous experimental work for these compounds in that (1) isomethadone was found to have a more restricted conformation space than methadone due to the proximity of the 5-methyl group to the phenyl rings, (2) methadone was found to have a greater preference for an intramolecular hydrogen bond than isomethadone, and (3) unusual eclipsed conformations were found for (5*S*,6*R*)-methylmethadone. The latter was found to be caused by steric interactions between the *N*-methyl groups and the methyl groups on C5 and C6. It was also found that methadone and isomethadone have significantly different conformational preferences for their *N*-methyl groups and that this may lead to their interacting with the opiate receptor in different conformations. This may then form the basis for Portoghese's hypothesis of different modes of interaction for compounds in this class. It would also account for the inactivity of (5*S*,6*R*)-methylmethadone, which is a composite of two active compounds. Finally, three conformations are picked as being the most likely source of the analgesic activities of these compounds, with the intramolecularly hydrogen bonded one being the best geometric fit to rigid muticyclic opiates.

Methadone (1) and structurally related opiates have the

$$CH_3CH_2COC(C_6H_5)_2CH_2CHCH_3N(CH_3)_2$$
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potential for a great deal of conformational freedom due to possible rotations about various single bonds. This is unlike most opiates, which are multicyclic structures with very limited flexibility. The structural flexibility of the former has led to studies of their conformation in solution using various experimental methods.[1-4] A number of structures in the crystal state have also been determined.[5-8] In addition, there has been a quantum mechanical study of a limited number of methadone conformations using the semiempirical PCILO method.[9]

In general, the experimental studies have suggested that these compounds are not conformationally homogeneous. At least some of them consist of mixtures of conformations whose distribution varies with such factors as the solvent.[1-3] Also, intramolecular hydrogen bonding appears to play a varying role with compounds of this class. Because of this complexity, it has not been possible to determine the conformation or conformations that are responsible for their biological activities.

In addition to conformational heterogeneity, this class of analgesics has a number of unusual pharmacological features. For example, whereas the 6*R* enantiomer of methadone is the only one of the pair that has substantial pharmacological activity, the 3*S*,6*S* isomer becomes the more active enantiomer with the methadols (Table I). This "inversion of stereoselectivity" has led to the concept of differing modes of interaction for methadone-like compounds.[10-12] In isomethadone, on the other hand, in which

Table I. Analgetic Activities of Various Methadone-like Compounds

compd	ED_{50}, mg/kg	compd	ED_{50}, mg/kg
normethadone[a]	2.5	(3*S*)-normethadol[b,c]	10.3
		(3*R*)-normethadol[b]	17.7
(6*R*)-methadone[d]	0.8	(3*S*,6*R*)-methadol[d]	7.6
		(3*R*,6*R*)-methadol[d]	24.7
(6*S*)-methadone[d]	25.7	(3*S*,6*S*)-methadol[d]	3.5
		(3*R*,6*S*)-methadol[d]	63.7
(5*S*)-isomethadone[e]	1.2	(3*S*,5*S*)-isomethadol[e]	6.2
		(3*R*,5*S*)-isomethadol[e]	91.7
(5*R*)-isomethadone[e]	49.8	(3*S*,5*R*)-isomethadol[e]	60.7
		(3*R*,5*R*)-isomethadol[e]	58.7
threo-methylmethadone[f]	>50.0		
erythro-methylmethadone[g]	0.4		

[a] N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. W.H.O.*, 14, 353 (1956). [b] A. F. Casy and M. M. A. Hassan, *J. Med. Chem.*, 11, 601 (1968). [c] Racemate mixture. This compound should be about twice as active as the number indicates, since its enantiomer has very little activity. [d] N. B. Eddy and E. L. May, *J. Org. Chem.*, 17, 321 (1952). [e] E. L. May and N. B. Eddy, *J. Org. Chem.*, 17, 1210 (1952). [f] Racemic mixture of 5*S*,6*R* and 5*R*,6*S*.[4] [g] Racemic mixture of 5*S*,6*S* and 5*R*,6*R*.[4]

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the 5S enantiomer has the activity, there is no such reversal in that (3S,5S)-isomethadol is the only isomer that has substantial activity (Table I). This has been attributed to greater conformational flexibility within the methadone series relative to the isomethadone series.[1-3] In addition, the 3S configuration appears to be crucial for the methadols and isomethadols, since none of the compounds with the opposite configuration has any significant potency (Table I). This has been attributed to a possible hydrogen bond between the hydroxy group and a site in the receptor to which they bind.[10-12]

It has been shown that some of the pharmacological features of the methadone series are indeed related to events at the receptor level. When opiate receptor binding assays were used, it was shown that (6R)-methadone had 10–50 times the affinity for the receptor as its enantiomer.[13-15] The methadols, however, have affinities that are comparable to the *inactive* form of methadone.[14,15] However, N-demethylation of (3S,6S)-methadol results in a 1000-fold increase in its affinity,[15] thus preserving the principle of inversion of stereoselectivity. N-Demethylation also results in a substantial enhancement of receptor affinity in (3S,6S)-acetylmethadol.[15]

A more recent unexpected aspect of these compounds has been the finding that (5S,6R)-methylmethadone, which incorporates the stereochemistry of the active enantiomers of methadone and isomethadone, is totally inactive (Table I). The erythro racemate mixture, however, has very substantial analgesic activity.[4] More recently, it has been shown that (5S,6S)-methylmethadone is the active enantiomer.[16]

We have undertaken a conformation–activity study of methadone and a number of related compounds to see if their analgesic activities (or lack of it) can be related to their conformational patterns. The method that has been used is the MM1 (Molecular Mechanics I) program[17] developed by Allinger and co-workers.[18] Independent observers have confirmed that this program is capable of quantitatively computing thermodynamic values for hydrocarbons for which there is an abundance of thermodynamic data with which to parameterize the method.[19] Indeed, Allinger has occasionally been able to point out incorrect experimental data when it disagreed with his computed results.[20] The parameterization of the MM1 program has now been broadened to include the most common atomic types.

The method of computing conformational energies using empirical potential functions offers distinct computational speed advantages over quantum mechanical methods. This allows one, for example, to perform full minimization of the energy with respect to all internal coordinates for large numbers of conformations and molecules as has been done in this work.[21] It can also be shown that some semiempirical quantum mechanical programs that neglect differential overlap, such as CNDO, INDO, and PCILO, can occasionally give unrealistic energy stabilization for conformations in which nonbonded atoms are allowed to approach too closely.[21-24] In contrast, potential function methods are parameterized to reproduce correctly the steric behavior of molecules.

Table II. Point Partial Charges Placed on the Carbonyl and Amine Groups in Order to Simulate the Electrostatic Interaction between Them[a]

carbonyl group		amine group	
atom	charge	atom	charge
C2	+0.038	C6	+0.453
C3	−0.556	N1	−0.808
O1	+0.479	HN	+0.453
C4	+0.038	C7	+0.453
		C8	+0.453

[a] Dielectric constant of 4.0 was used.

There are a number of environmental factors that will determine the ability of a substrate molecule to bind to its receptor site so as to cause some pharmacological effect.[25,26] In this work, only the intrinsic conformational tendencies of the molecules themselves will be examined to see if they can explain some of the unusual pharmacological features of this class of compounds. Of course, substrate–solvent and substrate–receptor interactions are crucial as well, and it is likely that some facts will only be explainable with a knowledge of those interactions. In particular, the stereospecificity relationships in the methadone series require a knowledge of the receptor, since the conformational behavior of a molecule is always identical with its enantiomer. At the present time, however, very little is known about the actual environment of the opiate receptor.

Methods

Conformational energy calculations were performed with the MM1 (Molecular Mechanics I) program[17] with the supplied parameter set, except for the changes noted. Parameters involving the amine group were kindly sent to us by Professor Allinger. The force constant and bond length for the C–C bonds in the phenyl rings were set to 8.0667 md/Å and 1.3937 Å as prescribed.

The electrostatic interactions that were included in some calculations were modeled by putting point partial charges on various atoms with a dielectric constant of 4.0. These charges were obtained from ab initio quantum mechanical calculations on the model compounds acetone and the protonated form of trimethylamine using an STO 4-31G basis set[27] and are listed in Table II. It should be noted that the MM1 potential function set does not include electrostatic interactions for hydrocarbons in general. For that reason, the point partial charges were only placed on the carbonyl and amine groups and the carbon atoms adjacent to them. While it might have been more realistic to have distributed the charge over the hydrogen atoms of the adjacent carbon atoms as well, this would have resulted in 1–4 charge–charge interactions. Since the MM1 parameter set already accounts for these, most probably with the torsional potentials,[28] they would have been computed twice. By combining the charges that would have been on the hydrogens into the carbon atoms

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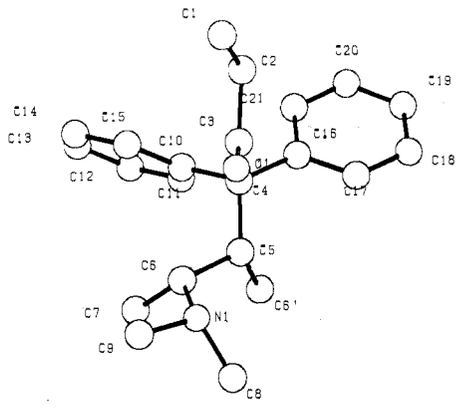

Figure 1. Molecular structure of (5*S*,6*R*)-methylmethadone showing the numbering convention used in this work.

to which they are attached, only electrostatic interactions between the carbonyl and amine regions are computed. It has been shown that an electrostatic potential function alone can model the features of a hydrogen bond.[29,30] One additional change that had to be made for the modeling of the hydrogen bond was to decrease the van der Waals' radius of the amine hydrogen from 1.325 to 1.200 Å, since the original value did not permit the close approach of the amine hydrogen and carbonyl oxygen for a reasonable hydrogen bond. It should be noted that the electrostatic results that are being computed in this work are only qualitative in nature and that very little is known regarding the energetics of a hydrogen bond between a carbonyl oxygen and a tertiary ammonium hydrogen.

Using the numbering convention in Figure 1, there are five dihedral angles that determine the conformation of the linear portion of these molecules. These are τ(C4–C3–C2–C1), τ(C5–C4–C3–C2), τ(C6–C5–C4–C3), τ(N1–C6–C5–C4), and τ(C9–N1–C6–C5). In addition, the τ(C11–C10–C4–C3) and τ(C17–C16–C4–C3) dihedral angles determine the orientations of the two phenyl rings. In the methadols and isomethadols, the hydroxyl group adds yet another dihedral angle that can be varied. Because of the large number of possible conformations that this permits, it was necessary to restrict the molecules to those portions of conformation space that are most likely to be important. Thus, τ(C4–C3–C2–C1) was placed in the trans position for all of the starting conformations, since it is well known that a carbonyl group generally eclipses a methyl group such as in propionaldehyde.[31,32] Also, all of the crystal structures of this class of compounds have this approximate value.[5-8] τ(C5–C4–C3–C2) has generally been restricted to the trans position, though some calculations were also performed with gauche values for methadone and isomethadone. Again, all of the crystal structures of the protonated form of these molecules have this conformation,[6,8] though methadone base does not.[5,7] In order to decrease the number of dihedral angles to be varied by one more, initial calculations were performed on analogues of the compounds in which the $NH(CH_3)_2^+$ group was replaced by a methyl group. A methyl group was used rather than an amine, since it introduced a symmetry into methadone that was useful as an internal check of the reproducibility of the minimizations. The steric behavior of a methyl group would be similar to that of an amine. Thus, in these calculations, only τ(C6–C5–C4–C3) and τ(N1–C6–C5–C4) were varied systematically.

Full energy minimization was performed with respect to all internal coordinates. Initial starting conformations were chosen by placing the atoms in various combinations of trans and gauche conformations with, as it turned out, the two possible orientations of the phenyl rings. It was found that the initial starting point had to be chosen carefully for molecules as sterically crowded as the ones under study here. Otherwise, the final conformation could be quite different from the initial one. While some effort was made to find missing minima (i.e., those that should appear at some combination of trans and gauche dihedral angles), the large number of conformations prevented us from spending too much time searching for any single one. It is impossible to rule out the presence of some missed minima in the areas of conformation space that were examined. However, they almost certainly have relatively high steric energies which often caused the molecule to leave that minimum in the energy surface.

The following convention has been used for dihedral angles: τ(A–B–C–D) is the angle between the planes A–B–C and B–C–D, with the eclipsed form being defined as 0°. Looking along A–B–C–D, a clockwise rotation of the plane B–C–D is considered positive.

All computations were performed on a Perkin-Elmer 3220 superminicomputer. The figures were initially prepared on a TEKTRONIX 4010 graphics terminal using the PLUTO program, with the plotting commands in the TEKTRONIX $PLOT_{10}$ package. Pen and paper plots of the figures were then made on a Nicolet ZETA 1553 plotter which has software that converts $PLOT_{10}$ output to ZETA output.

Results and Discussion

Phenyl Ring Conformations. In the very early stages of this work, it became clear that for every possible conformation of the linear part of the molecule, there were generally two possible equilibrium arrangements of the phenyl rings. These two, which are mirror images of each other, are illustrated with normethadone in Figure 2. Using the atomic numbering convention in Figure 1, ring arrangement I has τ(C11–C10–C4–C3) $\simeq$ 150° and τ(C17–C16–C4–C3) $\simeq$ 90°, while ring arrangement II has τ(C11–C10–C4–C3) $\simeq$ 90° and τ(C17–C16–C4–C3) $\simeq$ 30°.

It should be noted that the two phenyl rings are *not* conformationally equivalent and, therefore, introduce an asymmetry at the C4 carbon atom. For example, it would be expected that the all-trans conformation of normethadone, which doesn't have any chemically asymmetric carbons, would have a superimposable mirror image. However, this is not the case as can be seen from Figure 2 (even after the rearrangement of the *N*-methyl groups). Similarly, for molecules such as methadone and isomethadone which already have a chemical asymmetry, this introduces an energetic asymmetry somewhat analogous to what occurs with diastereomers. Thus, for (6*R*)-methadone, an intramolecularly hydrogen-bonded conformation is only favored with phenyl arrangement I as will be seen below.

There were some additional geometrical regularities that showed up in the calculations. With phenyl ring arrangement I, τ(C4–C3–C2–C1) tended to converge to the range of 160–170° rather than 180°. Similarly, for phenyl arrangement II, τ(C4–C3–C2–C1) tended to the range 190–200°. This feature appeared in all but the most strained conformations. Additionally, for the methadols and isomethadols, τ(H–O1–C3–C2) had a strong preference for ~60° with phenyl arrangement I and for ~−60° with phenyl arrangement II, other positions generally being 1 or more kcal/mol less stable.

Calculations on Analogues. Conformations in which τ_1(C5–C4–C3–C2), τ_2(C6–C5–C4–C3), and τ_3(N1–C6–C5–C4) are described will be referred to as $[\tau_1,\tau_2,\tau_3]$. When τ_4(C9–N1–C6–C5) is discussed as well, the conformation is described as $[\tau_1,\tau_2,\tau_3,\tau_4]$. In addition, a I or II is appended to each of the above to indicate which phenyl folding arrangement is involved.

The results of calculations on analogues of normethadone, (6*R*)-methadone, (5*S*)-isomethadone, (3*S*,6*R*)- and (3*S*,6*S*)-methadol, (3*S*,5*S*)- and (3*S*,5*R*)-isomethadol, and

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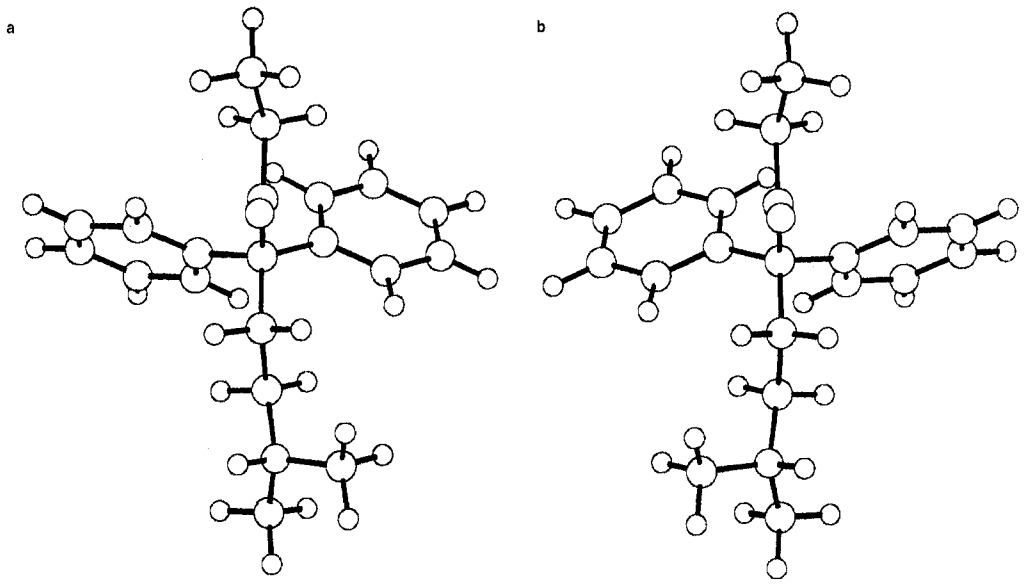

Figure 2. The [178,-175,172,170] I (a) and [-179,175,-171,69] II (b) conformations of normethadone showing the two phenyl ring arrangements that are possible in this series of molecules.

Table III. Steric Energies for Selected Conformations after Energy Minimization of Internal Coordinates[a]

	steric energy, kcal/mol					
conformation	nor-methadone	(6*R*)-methadone	(5*S*)-iso-methadone	(5*S*,6*R*)-methyl-methadone	(5*S*,6*S*)-methyl-methadone	(5*S*,6*R*)-*N*-demethyl-methadone
[180, 60, 60, 60] I				51.2	43.3*	
[180, 60, 60, 180] I				51.9	45.2	
[180, 60, 60, -60] I				54.9	47.0	
[180, 60, 180, 60] I	31.7	38.0	35.2	43.0	44.0	34.6
[180, 60, 180, 180] I	30.6*	35.6*	36.1	41.0*		33.8*
[180, 60, 180, -60] I	31.5	36.2	37.1	41.9	48.7	34.5
[180, 60, -60, 60] I	36.9	41.7	43.4		49.7	
[180, 60, -60, 180] I	33.1	36.2	37.5	43.6	48.2	36.0
[180, 60, -60, -60] I	36.9	40.2	43.3	52.0	51.3	36.5
[180, 180, 180, 60] II	32.1	39.3	35.2	44.6	43.8	35.5
[180, 180, 180, 180] II	31.1	36.2	35.1*	41.0*		33.9
[180, 180, 180, -60] II	31.8	38.1	36.5	43.5	48.0	

[a] Electrostatic interactions have not been included. Lowest energy conformations are indicated by an asterisk. Missing conformations could not be found except for the [180, 60, 60] conformations, in which only the indicated ones were computed. The minimized dihedral angles which describe some of the conformations are listed in Table S3 of the supplementary material.

(5*S*,6*R*)- and (5*S*,6*S*)-methylmethadone are presented in Tables S1 and S2 (see paragraph at the end of paper regarding supplementary material). In these analogues, the $NH(CH_3)_2^+$ group has been replaced by a methyl group. There is an interaction between the phenyl ring arrangement and the conformation of the linear portion of the molecule such that certain regularities occur. In particular, for normethadone and all molecules with a methyl group on the C6 carbon atom, ring arrangement I generally favors conformations in which $\tau_2 \simeq 60°$ and 180° and disfavors those with values of ~-60°. Similarly, ring arrangement II favors conformations in which $\tau_2 \simeq 180°$ and -60° and disfavors values of ~60°. For molecules with the 5*S* configuration, ring arrangement I generally favors conformations with $\tau_2 \simeq 60°$ and disfavors other values, while ring arrangement II favors conformations with $\tau_2 \simeq 180°$ and disfavors other values.

Some calculations have also been performed for (5*S*)-isomethadone and (6*R*)-methadone in which τ_1 was set to 60° and -60° and in which the carbonyl group eclipses one of the phenyl rings rather than the C4–C5 bond. These conformations were found to have only slightly higher energies than those for $\tau_1 \simeq 180°$. It would appear that these conformations might be significantly populated as well. One of these conformations is observed in the crystal structure of methadone base in which there is an N1···C=O intramolecular interaction.[5,7]

Calculations on Full Molecules. Calculations have also been performed on selected conformations of the full structure of (6*R*)-methadone, (5*S*)-isomethadone, and (5*S*,6*R*)- and (5*S*,6*S*)-methylmethadone both with and without an electrostatic potential function. It is expected that the electrostatic potential will qualitatively mimic the features of possible intramolecular hydrogen bonding. The calculations were performed on conformations that are likely to be significant on the basis of the earlier ones with permutation of the three possible orientations of the *N*-methyl groups. The conformational energy results of these calculations are presented in Tables III and IV, with the dihedral angles that describe some of the minimized structures presented in Table S3 of the supplementary material.

The results of the calculations in which an electrostatic (hydrogen bonding) potential has been included are presented in Table IV. As expected, the electrostatic potential stabilized the [180,60,-60,180] I conformations

Table IV. Steric Energies with Electrostatic Function of Selected Conformations after Minimization of all Internal Coordinates

conformation	steric energy,[a] kcal/mol			
	(6*R*)-methadone	(5*S*)-isomethadone	(5*S*,6*R*)-methyl-methadone	(5*S*,6*S*)-methyl-methadone
[180, 60, 180, 60] I	34.9 (−2.5)	32.7 (−1.5)	39.9 (−2.4)	43.0 (−0.9)
[180, 60, 180, 180] I	32.1 (−2.4)	32.3 (−3.0)	37.0 (−2.9)	50.4 (−0.7)
[180, 60, 180, −60] I	32.8 (−2.3)	33.6 (−2.4)	38.4 (−2.5)	47.5 (−1.0)
[180, 60, −60, 60] I	39.3 (−2.5)			46.6 (−3.1)
[180, 60, −60, 180] I	32.4 (−2.7)	33.6 (−2.8)	39.4 (−2.6)	45.0 (−3.3)
[180, 60, −60, −60] I	37.3 (−1.7)	40.2 (−1.9)	48.6 (−1.8)	49.2 (−2.0)
[180, 180, 180, 60] II	38.3 (−0.3)	34.0 (−0.2)	43.5 (−0.3)	43.4 (−0.3)
[180, 180, 180, 180] II	34.6 (−0.4)	34.0 (−0.2)	39.5 (−0.3)	
[180, 180, 180, −60] II	36.5 (−0.4)	35.2 (−0.2)	42.1 (−0.3)	47.5 (−0.3)

[a] Electrostatic component is in parentheses.

in which the amine hydrogen approaches the carbonyl oxygen. For the model used, this stabilization was in the range of −2.6 to −3.3 kcal/mol. More surprising, however, was the finding that there was considerable electrostatic stabilization for the [180,60,180] I conformations as well. This stabilization was −2.3 to −2.5 kcal/mol for the methadone conformations and rose to −3.0 and −2.9 kcal/mol for the [180,60,180,180] I conformations of isomethadone and (5*S*,6*R*)-methylmethadone where there is steric strain and eclipsing as will be discussed below. There was much less stabilization of this conformation with (5*S*,6*S*)-methylmethadone. As expected, there was little stabilization of the [180,180,180] II conformations (−0.2 to −0.4 kcal/mol).

As was noted above, there is experimental evidence that at least some of the compounds under study here consist of mixtures of conformations whose distribution varies with such factors as the polarity of the solvent.[1-3] We would suggest that, to a rough approximation, the calculations in which the electrostatic (hydrogen bonding) potential is *not* included may be more relevant to the conformational behavior of a molecule in a polar solvent, since there may be little advantage for a molecule to form an intramolecular hydrogen bond where there is the possibility of forming competitive intermolecular ones. Under these conditions, conformational preferences may be more dependent on relative steric energies without the electrostatic component. In a nonpolar solvent, however, where there is less possibility of intermolecular hydrogen bonds, an intramolecular hydrogen bond may decisively determine the observed conformation.

Methadone and Isomethadone. The conformational effect on a methyl group on the C5 and C6 atoms appears to be quite different (Tables S1 and S2 of the supplementary material). The (6*R*)-methyl group stabilizes conformations with $\tau_3 \simeq -60°$, since τ(C7–C6–C5–C4) $\simeq$ 180° for them. This is consistent with the well-known fact that a trans conformation is lower in energy than a gauche one in a hydrocarbon. In molecules with the opposite 6*S* configuration, conformations with $\tau_3 \simeq 60°$ are stabilized for the same reason.

The computed results for methadone are in reasonably good agreement with the experimental data for it. Thus, the protonated form of methadone is believed to form an intramolecular hydrogen bond even in polar solvents on the basis of its high pK_a. This agrees with the results of Table III in that the [180,60,−60,180] I conformation is computed to be one of the lowest energy ones even when hydrogen bonding is not included in the calculation. Similarly, analysis of the C5,C6 vicinal coupling constants using proton magnetic resonance indicates that there is a mixture of conformations about τ_3, whose distribution varies with the solvent.[3] The lowest energy conformations found for methadone have $\tau_3 \simeq 180°$ and −60°. However, it appears to be unlikely that the [180,−60,60] II conformation would be significantly populated as has been suggested, since both the N1 and C7 atoms would have gauche dihedral angles.

The (5*S*)-methyl substituent, on the other hand, has more of an effect on τ_2, with preferences for this dihedral angle in the vicinity of 60° with ring arrangement I and 180° with ring arrangement II. Other values for this dihedral angle are generally destabilized. This shows up clearly in both (5*S*)-isomethadone and (3*S*,5*S*)-isomethadol, and this situation is reversed for (3*S*,5*R*)-isomethadol (Tables S1 and S2 of the supplementary material).

Experimental data for the protonated form of isomethadone indicate that intramolecular hydrogen bonding is not likely to be a significant factor for it in polar solvents and that τ_3 exists exclusively at ~180°. The lowest energy conformations, [180,60,180] I and [180,180,180] II, which do not have the possibility of a hydrogen bond, are consistent with this result. There is no experimental evidence regarding the preferred value of τ_2 for this compound.

When one compares the low energy conformations of the analogues of (6*R*)-methadone and (5*S*)-isomethadone, it would appear that the latter has a more restrictive conformation space due to the proximity of the phenyl rings to a methyl group on the C5 carbon. In (5*S*)-isomethadone, only a single value of τ_2 and τ_3 is preferred for each phenyl ring arrangement. These are $\tau_2 \simeq 60°$ and $\tau_3 \simeq 180°$ for I and $\tau_2 \simeq 180°$ and $\tau_3 \simeq 180°$ for II. For (6*R*)-methadone, in contrast, $\tau_2 \simeq 60°$ and 180° are preferred for I and $\tau_2 \simeq 180°$ and −60° for II. In addition, conformations with $\tau_3 \simeq 180°$ and −60° are generally also preferred. This is in agreement with both experiment and the idea that the reversal of stereoselectivity in the methadols is due to their conformational heterogeneity.[3,10-12] However, our results indicate that isomethadone may not be completely homogeneous either, though the possible conformations are more limited.

One interesting and perhaps significant result of the calculations on the molecules with the *N*-methyl groups included is that there appears to be a great deal of repulsion between them and a methyl group on either C5 or C6 for many conformations (Table S3 of the supplementary material). Thus, in (6*R*)-methadone, the equilibrium values of τ_3 fall in the range of −136° to −146° for the [180,60,180] I and [180,180,180] II conformations. This also occurs for (5*S*)-isomethadone in which this dihedral angle falls into the range −129° to −144°, except for the conformation in which the $\tau_4 \simeq 60°$. Such large deviations from the purely staggered form do not appear for normethadone. The worst steric strain for isomethadone

Table V. Conformations That Are Observed in the Crystal State for Molecules for Which Calculations Have Been Performed on the Complete Molecule[a]

	normethadone		(6*R*)-methadone		(5*S*)-isomethadone	
	X-ray[b,c]	calcd	X-ray[d]	calcd	X-ray[d]	calcd
τ(C4-C3-C2-C1)	168, 177	168	157	168	176	164
τ(C5-C4-C3-C2)	175, 172	170	174	171	−167	177
τ(C6-C5-C4-C3)	74, 75	77	76	72	66	70
τ(C6'-C5-C4-C3)					−171	−161
τ(N1-C6-C5-C4)	−165, −167	−170	−146	−145	−153	−175
τ(C7-C6-C5-C4)			98	87		
τ(C8-N1-C6-C5)	71, 73	67	75	69	−155	−176
τ(C9-N1-C6-C5)	−53, −53	−59	−53	−59	81	62
τ(C11-C10-C4-C3)	159, 161	167	152	165	147	159
τ(C17-C16-C4-C3)	98, 96	83	83	85	89	80
rel energy, kcal/mol		0.9		0.6		0.1

[a] Corresponding calculated dihedral angles are listed for the same conformation with the energy of those conformations relative to the lowest energy minimum. [b] Two distinct conformations are found in the crystal state. [c] Reference 8. [d] Reference 6.

appears in the [180,60,180,180] I conformation and results in it being 0.9 kcal/mol less stable than [180,60,180,60] I, which has a more usual staggering of bonds. Significant deviations from the staggered form also appear in the crystal structures of methadone and isomethadone in which the observed dihedral angles are [−174,76,−146,−53] I and [−167,66,−153,81] I.[6]

5-Methylmethadones. After minimization of the energy with respect to all internal coordinates, it was found that the two preferred conformations for the protonated form of (5*S*,6*R*)-methylmethadone had almost total eclipsing of the C6–N1 and C5–H bonds (Table S3 of the supplementary material). These unusual "intermediate" conformations appear to be due to steric repulsion between the *N*-methyl groups and the methyl groups on C5 and C6 and can be thought of as incorporating the steric features of (5*S*)-isomethadone and (6*R*)-methadone. In methadone, the [180,60,180,60] I conformation is relatively unfavorable compared to [180,60,180,180] I, which is 2.4 kcal/mol lower in energy (Table III). In isomethadone, however, the former is preferred by 0.9 kcal/mol. When both of these steric factors are combined in (5*S*,6*R*)-methylmethadone, the [180,60,180,180] I and [180,180,180,180] II conformations are computed to have the lowest energy with τ_3 = −125°, which is the most extreme eclipsing found.

To further explore the steric forces that appear to be crucial in (5*S*,6*R*)-methylmethadone, calculations have been performed on it with one of the *N*-methyl groups omitted. With this change, much of the steric repulsion disappears and one would, therefore, expect more usual conformational behavior for this molecule (Table S3 of the supplementary material). It would be of interest to see if it also recovered the analgesic activity that was lost in the parent compound.

While normally we would be hesitant to report unusual conformations in which a C–H bond almost totally eclipses a C–N bond as being the most favorable for a molecule, the computed results are consistent with the experimental measurement of proton coupling constants for the protonated form of (5*S*,6*R*)-methylmethadone.[4] It was noted that only a conformation with approximately orthogonal C5 and C6 protons could account for the observed data. The calculated value for this angle in both the [180,60,180,180] I and [180,180,180,180] II conformations is 100°, which is in good agreement with experiment. The initial interpretation of the NMR results was that the molecule contained an intramolecular hydrogen bond, since it was also found to have an increased pK_a which indicated preferential stabilization of the protonated form. However, an intramolecular hydrogen-bonded conformation should have an angle of ~180° between the C5 and C6 protons, as can be confirmed using molecular models. Instead, the increased pK_a of the compound appears to be due to the enhanced electrostatic stabilization of the [180,60,180,180] I conformation which appears to be associated with the eclipsing. We do not believe that this conformation should be said to contain an intramolecular hydrogen bond, since the C=O···HN distance is 2.6 Å, which is considerably further than one would expect for such a bond. A similar eclipsed conformation may have been observed as well in the crystal structure of (3*S*,6*S*)-methadol. This compound has substantial analgesic activity but only after N-demethylation.[15] In our calculations on the analogue of this molecule which does not even contain *N*-methyl groups, the [180,−60,180] II conformation was found to converge to τ_3 = 131°, while the exact conformation found in the crystal state is [−171,−78,116] II.[6] As with (5*S*,6*R*)-methylmethadone, this eclipsing was attributed to an intramolecular hydrogen bond. However, our results indicate that there is a tendency for these molecules to assume eclipsed conformations even without hydrogen bonding because of severe steric strain.

Unlike (5*S*,6*R*)-methylmethadone, the protonated 5*S*,6*S* isomer has been shown to have substantial analgesic activity[4,16] and to consist of a mixture of conformations about the τ_3 dihedral angle.[4] As discussed above, the (6*S*)-methyl group stabilizes those conformations with $\tau_3 \simeq 60°$, since τ(C7–C6–C5–C4) $\simeq$ 180° for them. The preferred conformations are then at $\tau_3 \simeq 60°$ and 180° (Table III). It would appear to be extremely unlikely that this protonated isomer would contain an intramolecular hydrogen bond. The [180,60,−60] I conformation is destabilized because it contains a double gauche conformation about the C5–C6 bond. The [180,−60,60] II conformation, which is the other possibility, is unlikely because the (5*S*)-methyl group destabilizes $\tau_2 \simeq -60$.

X-ray Conformations. The results are also in agreement with those of X-ray crystallography in that all of the observed conformations are computed to have relatively low energies (Table V). In X-ray crystallography, of course, only a single conformation is usually observed for a particular molecule, even for those, such as methadone, that are known to have multiple conformations in other phases. The most commonly observed conformation is [180,60,180] I, which appears in the crystal structures of protonated normethadone, methadone, and isomethadone. The [180,180,180] II conformation appears in the crystal structure of (3*R*,6*R*)-acetylmethadol. As was discussed above, the crystal structure of (3*S*,6*S*)-methadol appears to be an unusual eclipsed conformation.

One feature of the crystal structures of normethadone and (6*R*)-methadone is that the *N*-methyl groups are in a double gauche conformation (Table V) which would be expected to be less favorable than one in which one group is trans. The computed relative energies of those conformations would be lower with this change. The likely cause for the crystallographic results are intermolecular packing interactions. The crystal structures of (5*S*)-isomethadone, (3*S*,6*S*)-methadol, and (3*R*,6*R*)-acetylmethadol, however, do have one *N*-methyl group in the trans position.

Intramolecular Geometries. Intramolecular geometrical distances were also computed for the various equilibrium conformations in an attempt to relate their geometries to those observed for rigid multicyclic agonists and antagonists which have more limited conformational freedom. In a recent review of these crystal structures,[33] it was found that the distance between the amine nitrogen and the center of the phenyl ring was in the range of 4.3–4.6 Å, while the distance of the nitrogen to the plane of the ring was 0.7–1.7 Å. None of the equilibrium conformations were found to fall into this range. However, it may be unrealistic to expect a very close correspondence, since both a substrate and the receptor to which it is binding would be expected to have some flexibility. Also, the distance between a point and a plane would be expected to be sensitive to slight tilts of the plane and, indeed, this parameter shows the most variation. The geometrical parameters of a limited number of conformations are reported in Table S3 of the supplementary material. It would appear that the [180,60,–60,180] I conformation, which has an intramolecular hydrogen bond, is the closest fit to the rigid opiates, with a nitrogen–phenyl center distance of 4.0 Å and a nitrogen–phenyl plane distance of 2.9 Å for (6*R*)-methadone and 4.2 and 2.8 Å for (5*S*)-isomethadone. The [180,60,180,60] I and [180,180,180,180] II conformations that have the lowest energies for conformationally more restricted (5*S*)-isomethadone have distances somewhat further than this range.

Analgesically Active Conformation. When this work was initiated, it was hoped that some conformation would be found that would clearly discriminate active compounds, like (6*R*)-methadone, (5*S*)-isomethadone, and (5*S*,6*S*)-methylmethadone, from the inactive (5*S*,6*R*)-methylmethadone. That is, it would have a relatively low energy for the first three but would be relatively inaccessible for the latter. However, if one examines the results of Tables III and IV, it would appear that no such conformation exists. One possible explanation for this is that the eclipsed conformations preferred by (5*S*,6*R*)-methylmethadone are different enough from the equivalent ones in the other compounds to prevent binding to the receptor.

Another interesting possibility that is consistent with our data is that (6*R*)-methadone and (5*S*)-isomethadone bind to the receptor in *different conformations* in line with the different modes of interaction hypothesis. One thing that does emerge clearly from our results is that the two compounds prefer different orientations of their *N*-methyl groups. With this interpretation, the [180,60,180,60] I conformation (or the symmetry-related [180,180,180,60] II) may be responsible for analgesic activity for compounds with the 5*S* configuration, and another one, perhaps [180,60,–60,180] I, may be responsible for the activity of (6*R*)-methadone. The former are very unfavorable for methadone, while the latter is a preferred one for it. This would then also account for the inactivity of (5*S*,6*R*)-methylmethadone, which cannot easily assume any of the above conformations even though it is a composite of active compounds (Table III).

An argument can be made for (6*R*)-methadone and (5*S*)-isomethadone binding to the receptor in different

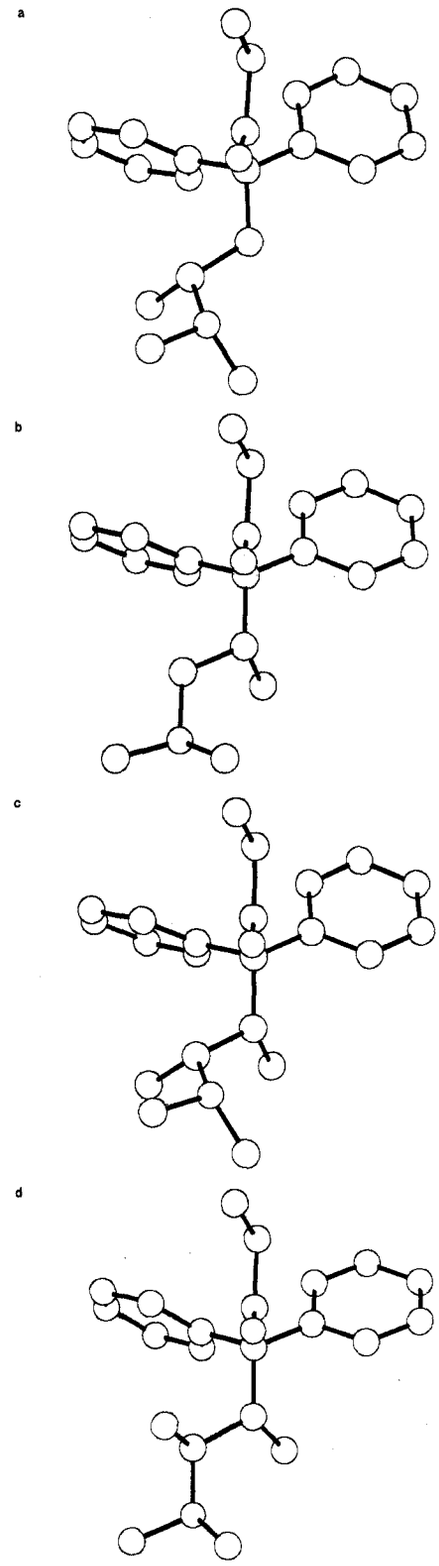

Figure 3. The [180,60,180] I conformations with optimum arrangement of the *N*-methyl groups. Actual dihedral angles are in Table S3 of the supplementary material. Relative energies are as follows: (a) (6*R*)-methadone, 0.0 kcal/mol; (b) (5*S*)-isomethadone, 0.1 kcal/mol; (c) (5*S*,6*R*)-methylmethadone, 0.0 kcal/mol; (d) (5*S*,6*S*)-methylmethadone, 0.7 kcal/mol.

(33) A. Horn and J. R. Rodgers, *J. Pharm. Pharmacol.*, **29**, 257 (1977).

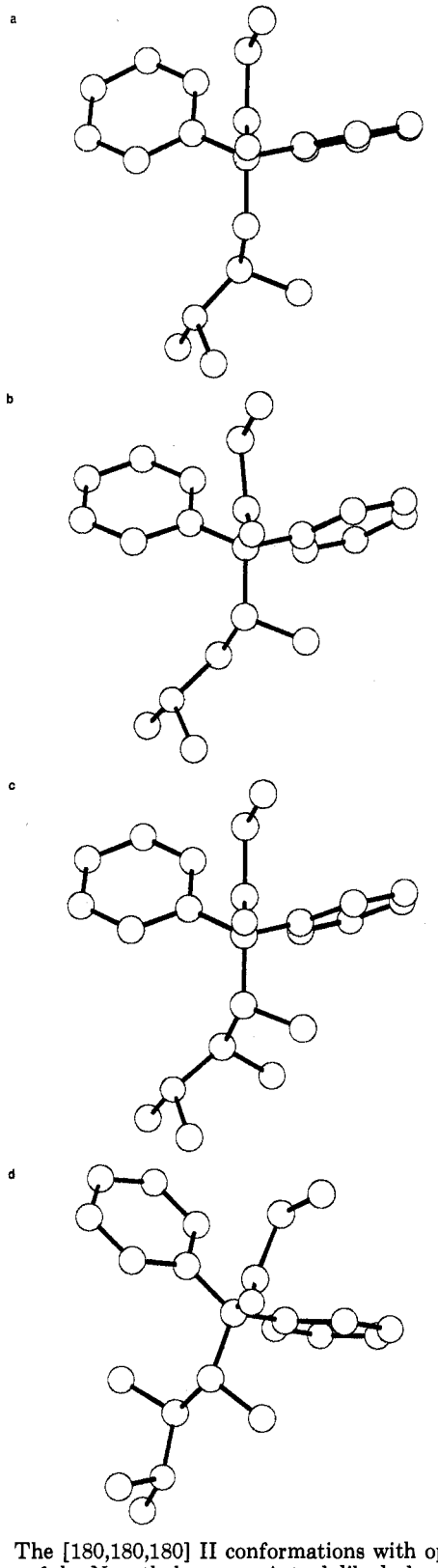

Figure 4. The [180,180,180] II conformations with optimum arrangement of the *N*-methyl groups. Actual dihedral angles are in Table S3 of the supplementary material. Relative energies are as follows: (a) (6*R*)-methadone, 0.6 kcal/mol; (b) (5*S*)-isomethadone, 0.0 kcal/mol; (c) (5*S*,6*R*)-methylmethadone, 0.0 kcal/mol; (d) (5*S*,6*S*)-methylmethadone, 0.5 kcal/mol.

conformations. Since there is an inversion of stereoselectivity in the methadols after N-demethylation as discussed above, this implies that either (6*R*)-methadone and (5*S*)-isomethadone or (3*S*,6*S*)-methadol and (3*S*,5*S*)-isomethadol bind in different conformations. Since the 3*S* configuration appears to be a more stringent factor, the former may be more likely. The hypothesis that the orientations of the *N*-methyl groups is important in these compounds appears to get some support from the substantial enhancement of receptor affinity that occurs in some of the methadols and acetylmethadols with N-demethylation.[15]

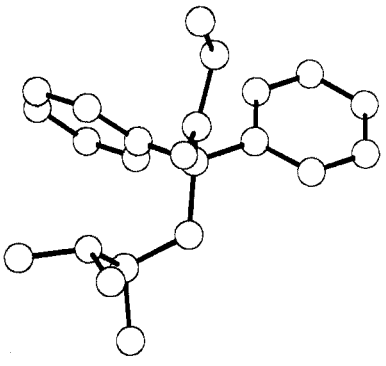

Figure 5. The [180,60,–60,180] I conformation of (6*R*)-methadone with an intramolecular hydrogen bond. Actual dihedral angles are in Table S3 of the supplementary material. Relative energy is 0.6 kcal/mol.

The three conformations that are most likely to be responsible for analgesic activity are [180,60,180] I, [180,180,180] II, and [180,60,–60] I. The first two, illustrated in Figures 3 and 4 with optimum arrangements of their *N*-methyl groups, are the only conformations that appear to be probable for compounds with the 5*S* configuration, due to the proximity of the 5-methyl group to the phenyl rings. Only the first of these appears to have the possibility of electrostatic stabilization. The [180,60,–60,180] I conformation (Figure 5), in which there is an intramolecular hydrogen bond, should also be considered a possibility, since it appears to be the closest geometrical fit to rigid multicyclic opiates. This conformation is favorable for (6*R*)-methadone, but in a very hydrophobic environment, such as a cell membrane, it may become important for other compounds as well. It should be noted, however, that this conformation is very unfavorable for (5*S*,6*S*)-methylmethadone, which has substantial activity. We do not believe that the conformation that is observed by NMR for inactive (5*S*,6*R*)-methylmethadone contains an intramolecular hydrogen bond as has been suggested,[4] since the C=O···HN distance is greater than would be expected for such a bond.

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Note Added in Proof: The crystal conformation for (5*S*,6*S*)-methylmethadone has recently been determined to be [180,64,97,92] I.[16] This is the conformation with the lowest computed energy for that molecule (Table III).

Supplementary Material Available: Two tables are available with conformational energy results for the various examined analogues, and one table is available with detailed dihedral angle and geometrical data for some of the conformations discussed (5 pages). Ordering information is given on any current masthead page. Dihedral angles and/or coordinates of the energy-minimized conformations are also available from the author.