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Quantum Chemical Studies of Methadone

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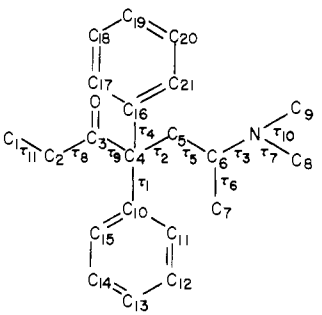
Quantum chemical calculations were performed on the flexible methadone molecule to test the hypothesis that it structurally mimics the fused ring structure of morphine. In these calculations using the semiempirical, PCILO method, protonated and nonprotonated conformations were considered representative of different types of intramolecular interaction at the morphine receptor. Calculated energies for these conformations were compared to those calculated for protonated and nonprotonated extended chain and crystal structure conformers. Lowest energy conformations showed intramolecular bonding but the resultant molecular geometries were not very morphine-like. A comparison of the structure of methadone to that of meperidine seemed equally as valid.

Methadone (1) and morphine are two classic opiate narcotics exhibiting comparable analgesic potency in human[1] and animal[2,3] studies yet differing radically in chemical structure. Evidence that both act at the same



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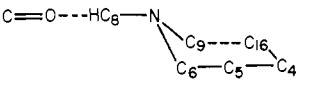
receptor site has been available for some time. Both precipitate the narcotic abstinence syndrome, exhibit cross tolerance,[4] and are antagonized in a similar way by nalorphine[4] and naloxone.[2] Methadone, in common with rigid opiates, exhibits stereoselectivity in its biological activity [the potency ratio of D(−) to L(+) isomers is approximately 18:1[5]] and in binding to receptors in isolated rat brain homogenate [the binding ratio of D(−) to L(+) is 10:1[6]]. The active form of methadone binds only one-fourth as strongly as morphine to the rat brain homogenate receptor.[6]

While both compounds have similar ED_{50}'s in rats and humans, methadone has been found to be 30 times less effective than morphine using intraventricular data available from the rabbit tooth pulp test.[7] These results are consistent with the enhanced lipophilicity of methadone[7] but a less efficacious mode of action at the receptor site.

To explain how both molecules could act at the same receptor site various investigators[8-13] have proposed structures in which the flexible methadone molecule forms specific intramolecular bonds involving its two functional groups to produce an overall structure more closely resembling that of the rigid morphine. These investigators have used space-filling models as well as chemical intuition and structural inferences from spectroscopic data to develop conformational models necessary to justify the forms of internal bonding their hypotheses require. Recently developed methods in molecular orbital theory now allow us to examine, more quantitatively, the plausibility of the previously proposed structures. We also examine other candidate conformers designed to more closely mimic morphine. The focus of our study is to identify and characterize low-energy conformations of methadone and to explore how methadone can be accommodated at the morphine receptor site.

In 1954, Gero[8] proposed a protonated conformer of methadone with a hydrogen bond between one of the *N*-methyl groups and the oxygen presumably confining the molecule in a rigid position and causing formation of a pseudopiperidine ring (2).



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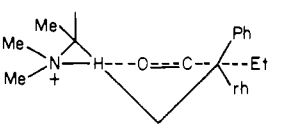
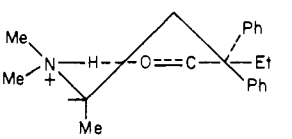
Another structure for the protonated form has been proposed[9-11] based on intramolecular bonding between the nitrogen proton and the carbonyl oxygen leading to a seven-membered "piperidine" ring with the methyl group on the asymmetric carbon equatorial (**3a**) or axial (**3b**) to the pseudopiperidine ring.



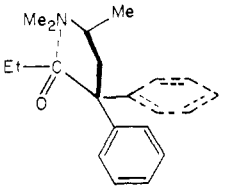
3a



3b

It has also been suggested[5,9,13] that a nonprotonated conformer of methadone (**4**) involving direct interaction

between the basic nitrogen and carbonyl carbon atoms (forming a five-membered "pyrrolidine" ring) is the pharmacologically active form. The basis of this hypothesis[9] was the observed pK_a lowering in methadone over a compound with an H atom in place of the COC_2H_5 group which was attributed to an enhanced stabilization of the methadone base over the acid form. However, as



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noted by Portoghese in 1969,[11] the pK_a of the more closely related deoxymethadone is 7.9, increasing to 9.0 in methadone. In contrast to the original conclusion,[9] this increase is indicative of intramolecular interactions between the carbonyl and amine groups in methadone which favor the protonated form over the base. Most,[5,13] but not all,[28] current thought is that methadone with a pK_a of 9.0, in common with other opiates with similar pK_a's, acts in its protonated form at the receptor site while the nonprotonated form is needed for transport across the blood–brain barrier. Both forms were considered in this study.

No conclusive experimental evidence supporting or refuting the biological presence of any of the postulated conformers has been obtained.[14] A recent proton magnetic resonance and circular dichroism study[14] is not inconsistent with a conformer like **3a,b** for protonated methadone and indicates also that the nitrogen–carbonyl carbon interaction in the nonprotonated form (**4**) is weaker than previously proposed. An x-ray crystallographic study of the methadone base[15] does, however, indicate formation of a five-membered ring by nitrogen–carbonyl carbon interaction. Superposition of this ring on the piperidine ring of morphine, however, places neither phenyl ring of methadone in a suitably overlapping position. An earlier x-ray crystallographic study of (+)-methadone hydrobromide showed no intramolecular hydrogen bonding between the nitrogen proton and carbonyl oxygen.[16] Thus, in spite of long-standing consideration of the problem, the question of the most likely conformation of methadone at the receptor site remains open.

Experimental Section

A procedure was developed to explore the plausibility of previously proposed structures involving intramolecular interaction (**2**, **3a,b**, **4**) and additional structures of our own design. Parallel methods were applied to x-ray crystal structures[15,16] and extended chain structures with no specific intramolecular interaction.

It was assumed that the spatial arrangement of methadone in its low-energy states (our major concern in this study) is primarily a function of conformation and unaffected to a first approximation by the practical necessity in this study of using standard bond lengths and angles. To use bond lengths and angles as additional variational parameters in a systematic or exhaustive manner would require a calculational effort far greater than is currently feasible by quantum mechanical methods for so large a molecule. Alternately, using modified values of bond lengths and angles to reflect specific types of strain or interaction as in the crystal structures would tend to bias the results in favor of the anticipated structures.

The first step in evaluating the plausibility of each structure considered was to construct a three-dimensional scale model estimating initial values of 11 torsion angles needed to define the entire rotational structure. The convention used to define these angles $\tau_{AB\text{-}CD}$ shown in 1 was the clockwise rotation of atom A into atom D while looking along the B-C axis from atom B to C. Structural similarity to rigid opiates was judged by how well methadone's atoms, particularly the phenyl rings, the amine nitrogen, and polar oxygen group, considered essential to analgesic activity could be superimposed on those of morphine.

To further refine these angles, an interactive computer program was developed to monitor nonbonding interatomic distances as a function of changes in geometry. Input to the program follows that of the PCILO program written primarily for conformational analysis.[17] The program was initialized by reading a full description of the molecular geometry in terms of bond lengths, angles, torsion angles, and rotation axes. The user was then allowed to interact with the program varying parameters such as angles of rotation about each axis. Each change of geometry generated a table of interatomic distances less than a specified minimum distance and excluding distances between atoms less than three times removed from each other in the bonded network. With this procedure it was possible to select those conformers with minimal interference between atoms forced together by the requirements of the particular model.

In a third step, the plausibility of each such conformer was checked by an initial energy calculation using a semiempirical molecular orbital program called perturbation configuration interaction using localized orbitals (PCILO). The details of this method are well documented in the literature[17] and it has been used to study a variety of biological molecules such as cholinergics,[18] hallucinogenics,[19] dipeptides,[20] and opiates.[21] If the energy resulting from this initial calculation was unusually high, the torsion angles of the conformation were adjusted with the interactive program. This procedure was continued iteratively until an energetically reasonable conformation was obtained.

In a final step, each structure resulting from this iterative procedure was subjected to further energy calculations for a series of refined torsion angle variations to identify its nearest local minimum energy conformation. For this search an automatic procedure developed by us for use with PCILO was employed. Each rotation axis angle was minimized in an interval of ±3° using a parabolic fit of energy to the angle value. If the interval was too small the search continued along the energy surface until successive parabolic fits produced axis angles varying by no more than 1°. The procedure was applied serially to each rotation axis in each set of calculations. If the initial and final conformation as a function of all 11 rotation axes differed in energy by more than 1 kcal/mol the procedure was repeated starting from the previous final result until energy convergence (to 1 kcal/mol) was obtained and a local minimum identified for each structure selected.

Eight protonated conformers (1–8) and four nonprotonated conformers (I–IV) listed in Table I were selected for study. These were intended to simulate previously proposed structures as well as to investigate our independent attempts to enhance similarity to morphine. In Table I, conformers 1 and I correspond to the protonated and nonprotonated crystal structures, respectively, while **2** and II are based on extended chain-like structures with no specific intramolecular interaction. Conformer **3** in Table I is based on H-bonded structure **2**, while **4** and **5** are based on structures **3a** and **3b**, respectively. Conformer **6** was designed to simulate the morphine–piperidine ring and parts of the furan and cyclohexyl (B) rings of morphine. Conformer **8** was designed for maximum similarity to rigid opiates by reproducing angle for angle the rotation angles found in the methadone segments shared with morphine. Conformer **7** is the nearest accessible local energy minimum to this conformer. Nonprotonated conformer III was based on structure **4** with N···C=O interaction, while IV was an attempt to match the morphine structure in a fashion similar to conformer **6**.

Input geometry for the nonprotonated[15] and protonated[16] methadone crystal structures was taken directly from the experimental results of the x-ray crystallographic studies. This involved placing the hydrogen atoms for the protonated methadone but not for the nonprotonated form. Since the study of protonated methadone was on the inactive (+) isomer, the torsion angles were converted to correspond with the active (−) isomer. Energy calculations were made using the exact experimental input geometry and also for variations with regularized bond angles, bond lengths,[22] and other normalizing features, such

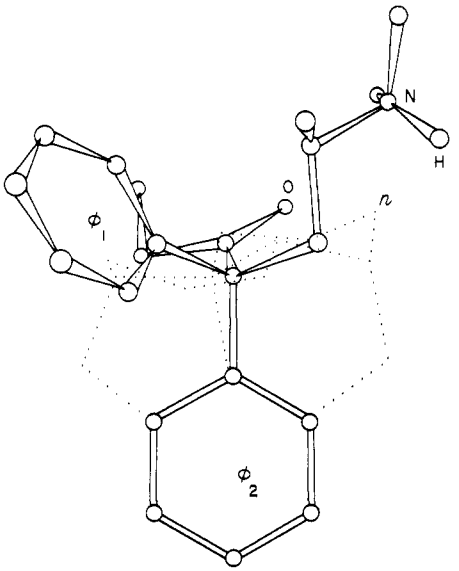

Figure 1. Optimized x-ray structure of methadone hydrobromide with a phenyl ring superimposed on that of morphine.

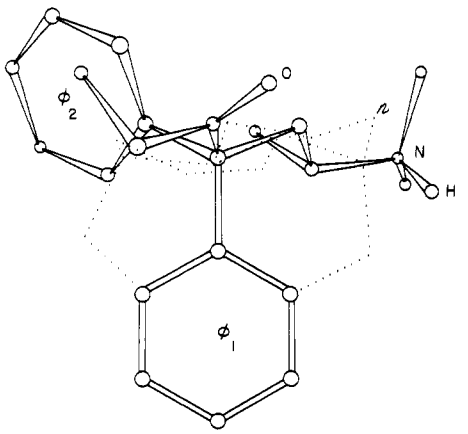

Figure 2. Optimized extended chain structure of protonated methadone with a phenyl ring superimposed on that of morphine.

as planarity of the phenyl rings. The regularized geometries gave the lower energy for both forms and were used for all the other candidate structures.

Results

Table I summarizes the results obtained from conformational analysis of all candidate structures of the (−)-methadone isomer. Conformational energies for protonated and nonprotonated methadones (ΔE) are relative to their respective minimum energy conformers. The relative energy ordering in this table provides some indication of the accessibility of each conformation in an environment devoid of solvent effects. Values of ΔE are subject to some error from the sensitivity of the overall geometry (and thus the energy) to small changes in bond lengths and angles which were not taken into account in this study. One would expect intuitively that a full optimization of each geometry would decrease the energy of the higher energy structures more than the lower, thus reducing the energy spread.

The conformers described in Table I are shown in Figures 1–11, except for the nonprotonated extended chain II which resembled the protonated form. All conformers are drawn to scale and shown in the plane of a reference Ph ring. This ring was chosen in each case to orient the molecule with maximal overlap relative to the Ph and

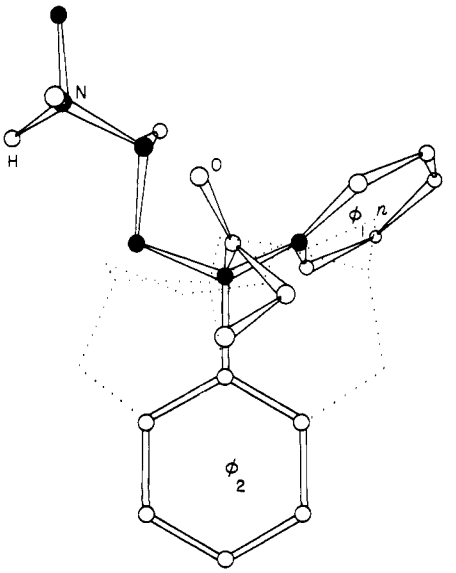

Figure 3. Optimized structure (2) of protonated methadone with a phenyl ring superimposed on that of morphine.

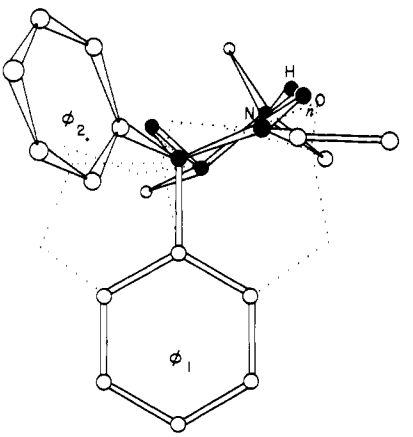

Figure 4. Optimized structure (3a) of protonated methadone with a phenyl ring superimposed on that of morphine.

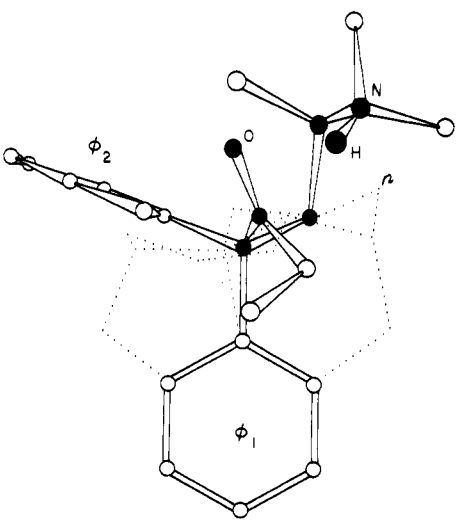

Figure 5. Optimized structure (3b) of protonated methadone with a phenyl ring superimposed on that of morphine.

piperidine rings of morphine (shown as a dotted line in each figure). Those atoms most closely approximating the piperidine ring of morphine are shown as darkened

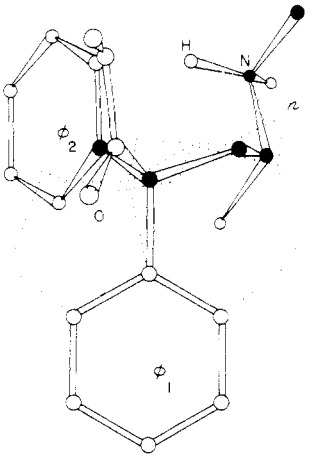

Figure 6. Optimized morphine-like structure of protonated methadone with a phenyl ring superimposed on that of morphine.

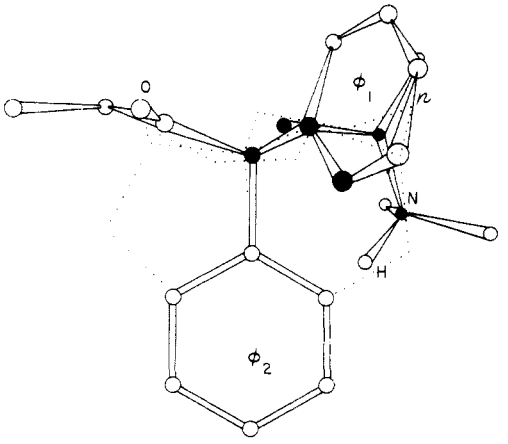

Figure 7. Optimized morphine-like structure of protonated methadone with a phenyl ring superimposed on that of morphine.

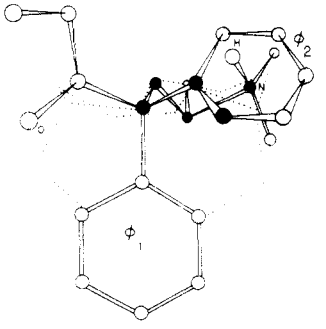

Figure 8. Structure with maximum morphine-like features (not energy optimized) with a phenyl group superimposed on that of morphine.

spheres. Figure 12 shows a similar scale drawing for morphine obtained from a recent crystal structure[23] with the methyl and hydroxyl groups in minimum energy positions.[21]

The salient feature of rigid opiates which appears necessary for analgesic activity is a piperidine ring with a phenyl substituent at the γ-axial position. A recent synthesis of 6,7-benzomorphan with no phenolic OH retaining codeine-like agonist activity in rats[29] indicates that contrary to previous indications, the 3-OH group may not be necessary for agonist activity but definitely enhances it. Polar oxygen groups at other positions appear vital to both methadone and meperidine type opiate agonism and

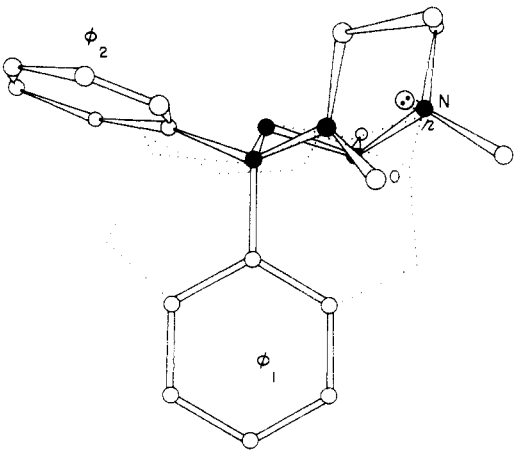

Figure 9. Optimized x-ray structure of methadone base with a phenyl group superimposed on that of morphine.

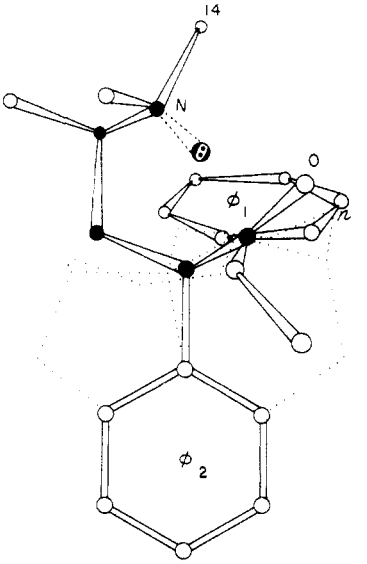

Figure 10. Optimized structure (4) of methadone base with a phenyl group superimposed on that of morphine.

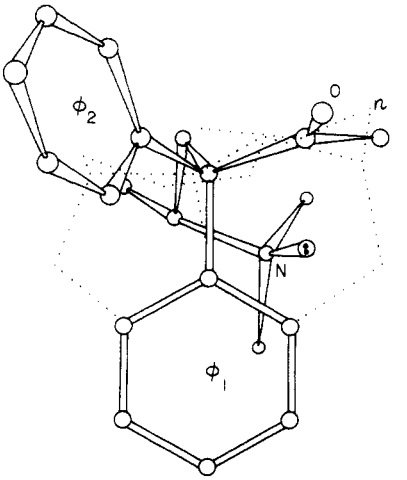

Figure 11. Optimized morphine-like structure of methadone base with a phenyl group superimposed on that of morphine.

for rigid opiates generally provide additional enhancement of activity. As indicators of similarity to morphine structure we have chosen to monitor the following parameters: the distance of the amine N atom to atom C_{10}

Table I. Minimum Energy Conformers of Candidate Methadone Structures

Defining atoms[i]	τ_i[j]	Protonated conformers								Nonprotonated conformers			
		1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[f]	8[g]	I[a]	II[b]	III[h]	IV[f]
C_{Ph_1}[k]-C_{10}-C_4-C_3	1	95.0	86.0	176.0	168.0	101.0	65.0	70.0	20.0	143.0	86.0	37.0	166.0
C_{10}-C_4-C_5-C_6	2	189.0	50.0	312.0	309.0	190.0	79.0	317.0	310.0	296.0	51.0	296.0	354.0
C_5-C_6-N-H[l]	3	321.0	72.0	315.0	46.0	315.0	303.0	46.0	30.0	158.0	45.0	27.0	37.0
C_{10}-C_4-C_{16}-C_{Ph_2}[k]	4	32.0	160.0	36.0	16.0	98.0	6.0	50.0	55.0	95.0	161.0	69.0	19.0
C_4-C_5-C_6-N	5	230.0	197.0	221.0	259.0	73.0	93.0	263.0	285.0	292.0	192.0	301.0	287.0
C_5-C_6-C_7-H	6	58.0	54.0	71.0	49.0	76.0	82.0	50.0	60.0	52.0	33.0	55.0	51.0
C_6-N-C_9-H	7	76.0	57.0	69.0	50.0	71.0	63.0	50.0	60.0	58.0	44.0	60.0	51.0
C_4-C_3-C_2-C_1	8	159.0	260.0	251.0	154.0	259.0	200.0	203.0	225.0	192.0	260.0	100.0	109.0
C_{10}-C_4-C_3-C_2	9	69.0	299.0	272.0	291.0	28.0	182.0	211.0	170.0	180.0	299.0	188.0	79.0
C_6-N-C_8-H	10	67.0	80.0	55.0	60.0	60.0	38.0	61.0	60.0	49.0	59.0	55.0	68.0
C_3-C_2-C_1-H	11	60.0	60.0	64.0	60.0	60.0	60.0	60.0	60.0	63.0	60.0	65.0	61.0
ΔE,[m] kcal/mol		9.8	11.6	4.3	0.0	12.8	29.5	12.1	120.1	11.4	4.2	0.0	3.6

[a] X-Ray structure of conjugate acid 1[16] and base I.[15] [b] Extended chain. [c] Structure 2. [d] Structure 3a. [e] Structure 3b. [f] Morphine-like structure. [g] Morphine-like structure not energy optimized. [h] Structure 4. [i] Angles tabulated are defined (τ_{ABCD}) by clockwise rotation of atom A into D along B → C axis. Values given in degrees. [j] Axis number as shown in structure 1. [k] C_{Ph_i} is either Ph carbon atom once removed from pivoting atom (C_{10} or C_{16}) on Ph_i. [l] C_5-C_6-N-lone pair for nonprotonated conformers. [m] Energy relative to minimum energy protonated or nonprotonated structure.

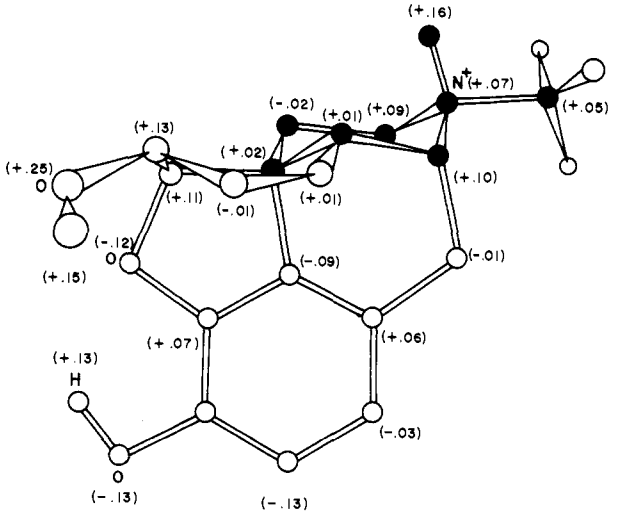

Figure 12. Structure of morphine based on x-ray data[23] and net atomic charges from previous calculations.[21]

Table II. Key Structural Features of Methadone Compared to Morphine

Conf	$R_{Ph\text{-}N}$[a]	$R_{N\text{-}O}$[b]	Z_N[c]	$R_{A\text{-}B}$[d]	A-B[e]
1	4.85	3.17	−0.25		
2	4.08	4.95	−2.41		
3	4.90	3.27	0.48	5.09	C_9-C_{16}
4	3.98	2.46	−2.94	1.58	H_N-O
5	4.31	3.47	0.51	1.76	H_N-O
6	4.26	5.50	−2.26	2.40	C_{10}-C_8
7	3.27	5.69	−2.14	4.40	N-C_{11}
8	2.67	5.42	−1.41	4.01	N-C_{21}
I	3.71	2.97	−1.24	2.58	N-C_3
II	4.12	4.97	−2.41		
III	3.56	2.65	2.81	2.46	N-C_3
IV	2.84	4.73	−2.70	2.91	N-C_{11}
M[f]	3.49	7.07	−0.90	1.54	

[a] Distance from nitrogen atom to central carbon atom (C_{10} or C_{16}) of reference phenyl ring (in Å). [b] Nitrogen-oxygen distance (in Å). [c] Distance of nitrogen atom to reference phenyl ring plane (in Å). [d] Pseudoring closure distance where appropriate (in Å). [e] Ring closure defining atoms. [f] Comparable parameter values in morphine.

(or C_{16}) of the reference phenyl ring, the O–N atom distance, the distance of the nitrogen atom from the reference Ph plane, and the pseudopiperidine ring closure distance where appropriate. These results are summarized in Table II which also lists comparable parameters in morphine.[23]

Discussion

The results of this work support experimental evidence that methadone has several low-energy conformers and provides further indication that the conformational equilibria possible in the acid and base forms are qualitatively different.

The protonated, minimum energy conformer (Figure 4) exhibits some N–H···O=C interaction as proposed by Portoghese (**3a**), although the H bond is far from ideal. The minimum energy base conformation (Figure 10) possesses some N···C=O interaction as proposed by Beckett (**4**) and is consistent with a mechanism used to explain the rapid deuterium–hydrogen exchange rate on C_2 when dissolved in CD_3OD.[14] A comparison of the energy difference between each of these minimum energy conformers and their lowest energy, noninteracting (extended chain) counterparts provides an indication of the stabilization energy with respect to protonation. In the acid this difference is higher (Table I, conformer 2–conformer 4 = 11.6 kcal/mol) than in the base (Table I, conformer II–conformer III = 4.2 kcal/mol) indicating an increase in the dissociation energy ($MH^+ \rightarrow M + H^+$) due to intramolecular interactions between the amine and carbonyl groups. This result is consistent with the increased pK_a of methadone over deoxymethadone.[11]

The cited energy differences are also consistent with the reversal of sign of the Cotton effect in the circular dichroism spectra observed in the base when it is dissolved alternately in chloroform (or hexane) and methanol. Competition between intramolecular interaction and interaction with H-bonding solvent would enhance the presence of the extended chain conformer in CH_3OH much more readily in the base than in the acid form where the reversal is not seen. The observed solvent effect on the NMR spectra of the base is also consistent with the relatively small energy difference between an internally associated conformer and one in which such association does not occur.

Our results also indicate that conformational equilibria can occur in the acid form as well but between conformers with different types of intramolecular interactions. For example, both conformer **3** and **4** of Table I (structures **2** and **3a**) could be in equilibrium to different extents in "inert" and H-bonding solvents. The relatively small energy difference obtained is in keeping with some evidence in both circular dichroism and NMR results for different types of and less drastic conformational changes

in the acid form than in the base. However, given the 13 kcal/mol difference between conformers 4 and 5 (corresponding to structures 3a and 3b) these do not appear to be the most likely candidates for conformational equilibrium as previously suggested.[14]

Both the acid and base crystal structures were very close to local minima as calculated with PCILO using standard bond lengths and angles and our minimization procedure for determining torsion angles. This result is some indication that the use of standard geometries and of the PCILO method itself is justified in seeking to identify relative local energy minima. Moreover, the choice of a standard geometry does not seem to greatly alter the conformations corresponding to such minima.

It is important to note the distinct differences between the protonated and nonprotonated crystal structures (Figures 1 and 9) which emphasize the sensitivity of conformation to protonation. This sensitivity implies that structure–activity relationships for flexible opiates may be complicated by substantial intramolecular rearrangements caused by substituent variation.

While among the lowest in energy, none of the conformers based on previously proposed ideas of intramolecular bonding preserve the basic axial 4-phenylpiperidine structure of rigid opiates. In fact, if the phenyl rings of methadone and morphine are superimposed in any of these conformers (Figures 3–5, 10), other key positions of methadone, particularly the nitrogen atom, are significantly displaced from their position in morphine. While the "pseudopiperidine ring" closure distances (R_{A-B}) and characteristics given in Table II for these conformers (3–5, III) are indicative of some weak interaction, it is not unreasonable to believe that they are as much an indirect result of steric hindrance in other parts of the molecule as of direct, attractive interactions.

Our calculations on conformers designed specifically to mimic the axial 4-phenylpiperidine structure of morphine further emphasize the difficulty in obtaining reasonable conformational similarity for protonated methadone; closest overlap is obtained (conformer 8, Figure 8) at the expense of a large energy destabilization. Relaxation of the geometry (conformer 7, Figure 7) or altering the type of overlap (conformer 6, Figure 6) produces conformers still not convincingly morphine-like. The remaining low-energy form of the base (conformer IV, Figure 11) is also not very morphine-like in structure.

One might also consider an alternative opiate analogy. If the minimum energy conformer of protonated methadone is placed so that its nitrogen atom is superimposed on that of morphine (Figure 12), implying a fixed cationic receptor site, then the quaternary carbon atom (C_7) is superimposed on the crucial C_4 position of the piperidine ring, a position which also carries the phenyl ring in the 4-phenylpiperidine class of opiate analgesics. The resulting orientation of methadone greatly resembles the minimum energy conformer we have recently obtained for meperidine,[24] shown in Figure 13 with its piperidine ring superimposed on morphine. The ester chain in meperidine and the carbonyl chain of methadone would occupy similar positions at the receptor site, reinforcing the possibility that the receptor can to some extent accommodate a polar group in this vicinity.

Also given in Figures 12–14 are the net atomic charges calculated from PCILO for morphine, meperidine, and methadone. The cationic head atoms (nitrogen and the atoms bonding to it) have similar charges in all three compounds, as does the C=O group in methadone and meperidine, reinforcing the idea that these two types of

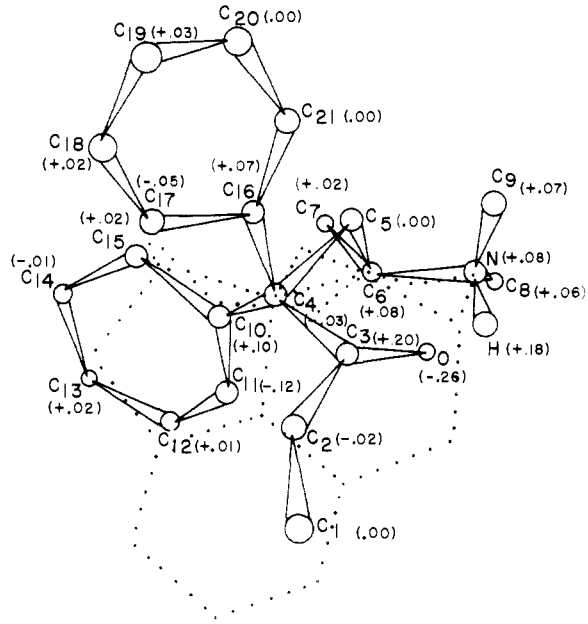

Figure 13. Minimum energy conformer of protonated methadone with net atomic charges shown with a nitrogen atom superimposed on that of morphine.

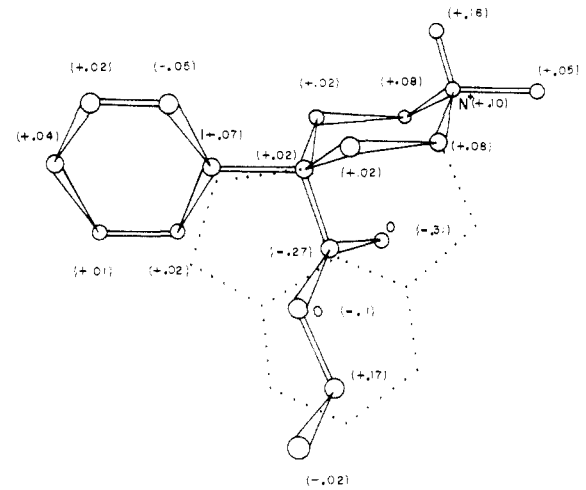

Figure 14. Minimum energy conformer of meperidine with calculated net atomic charges[24] shown with piperidine ring superimposed on that of morphine.

analgesics could act in a similar fashion at the opiate receptor. While there may be some structural similarities between them, there is no a priori reason to expect similar SAR behavior by parallel variation of N substituents of methadone and meperidine. The nonparallel behavior observed is understandable in the light of the different effect such substituent variation would have on the overall conformation of each type of analgesic.

Conclusion

In these results we have demonstrated different types of conformational flexibility in the acid and base forms of methadone. In keeping with pK_a results and solvent effects on circular dichroism and NMR spectra, the base form is less stabilized by intramolecular interactions than is the acid, while the acid has several low-energy conformers capable of intramolecular interaction.

None of the low-energy intramolecularly associated conformers in either base or acid form could be superimposed on the main structural features of the prototype rigid opiate morphine. Protonated conformers designed

specifically to mimic the morphine structure did overlap more with it, but none were energetically favored. The minimum energy protonated conformer resembled calculated low-energy conformers of meperidine in several key respects.

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Structure–Activity Studies on Sulfamate Sweeteners

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The structure–activity relationships governing sulfamate sweeteners are reviewed under the headings: size of the reduced ring, changes in the sulfamate function, substitution of hydrogen in the ring, and substitution of carbon in the ring and open-chain compounds. Fifteen compounds have been synthesized with a view to testing the limitations on structural changes which may be made within these categories without loss of sweetness. The presence of the grouping $>CHN(R)SO_3^-$ is suggested as a necessary but not a sufficient condition for a compound to be sweet-tasting. Thus, the B center of the Shallenberger A–H,B theory of sweetness is best regarded as being $-SO_3^-$ rather than $-SO_2-$ for sulfamates. Threshold levels and relative sweetness have been determined for seven sulfamates.

Following the accidental discovery of the sweetening properties of cyclamate (**1d**) by Sveda in 1937, Audrieth and Sveda[1] carried out a limited structure–activity study, synthesizing and screening for sweetness a number of compounds containing the sulfamate functional group. From this study they concluded that the groups essential for sweetness were "(a) a cyclohexyl ring which may or may not be substituted and (b) a free hydrogen on the nitrogen of the sulfamate function $-NHSO_3X$, where X may be almost any salt-forming group". In succeeding years many groups[2-12] have synthesized sweet-tasting sulfamates, many of which require qualification of the rules formulated by Audrieth and Sveda and, in some cases, require an extension or are at variance with them. Clearly then a reappraisal of the structure–activity relationships of sulfamate sweeteners is necessary and we suggest that these relationships are best categorized under the headings: size of the reduced ring, changes in the sulfamate function, substitution of hydrogen atoms of the ring and of carbon atoms of the ring, and opening of the reduced ring (i.e., aliphatics). In this present study the 15 sulfamates which we have synthesized and characterized have been designed to test some of the limitations on structural changes which may be made within these categories without loss of sweetness.

Chemistry. All primary sulfamates, i.e., those containing the $-NHSO_3^-$ group, were synthesized by reaction of the corresponding amine with chlorosulfonic acid.[1] Secondary sulfamates were prepared from the appropriate primary amines by methylation[13] followed by sulfamation with chlorosulfonic acid. Cyclohexylsulfamyl chloride was prepared by reaction of cyclohexylsulfamic acid with phosphorus trichloride.

Structure–Activity Relationships and Discussion. Size of the Reduced Ring. Variation in the size of the reduced ring is an obvious starting point in a probe of the