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Structure–Activity Relationships of Eseroline and Morphine: *Ab Initio* Quantum-Chemical Study of the Electrostatic Potential and of the Interaction Energy with Water

ALESSANDRO AGRESTI,* FRANCA BUFFONI,* JOYCE J. KAUFMAN† AND CARLO PETRONGOLO‡

* *Dipartimento di Farmacologia dell'Universita, Viale Morgagni 65, 50134 Firenze, Italy,* † *Department of Anesthesiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, and Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218, and* ‡ *Laboratorio di Chimica Quantistica ed Energetica Molecolare del C.N.R., Via Risorgimento 35, 56100 Pisa, Italy*

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SUMMARY

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Ab initio SCF-MO-LCAO calculations of the electrostatic potential and analytical calculations of the interaction energy with water have been performed for two analgesic molecules: eseroline and morphine. The nature of the calculations and the structure-activity relationships have been discussed and the theoretical results have been compared with the experimental binding affinities to the opiate receptor. The calculations show that the reactivity properties of the aminic N of eseroline and morphine are very similar, while significant differences were found for the electrostatic potential and water affinity of N_5, benzene, and phenolic OH. These results can explain the lower binding affinity of eseroline to the receptor with respect to that of morphine, they agree with experimental data on the binding affinity of analgesics to the receptor, and they confirm a molecular model of the analgesic-receptor interaction which has been suggested on the basis of experimental data.

INTRODUCTION

Bartolini *et al.* (1)[1] have recently reported that the loss of the methylcarbamic group in physostigmine gives rise to a new compound, eseroline (Fig. 1), devoid of anticholinesterase activity but endowed with a strong analgesic activity which is antagonized by naloxone. It appears, therefore, that the direct interaction of eseroline with the opiate receptor is a fundamental step in the mechanism of its biological activity. In particular Galli *et al.* (2), using the inhibition of ^{3}H-naloxone binding to rat brain homogenates, have shown that the binding affinity of eseroline to the opiate receptor is equal to one-tenth that of morphine.

As a part of our *ab initio* quantum-chemical study of analgesics (3-5), in this paper we report the results of a SCF-MO-LCAO study of eseroline and we compare the molecular-orbital structure, the electrostatic molecular potential, and the interaction energy with water of eseroline and morphine. From such a theoretical description of th electronic structure and noncovalent reactivity of these molecules, we can also infer some details of the structural organization of water surrounding them and of possible biological binding sites, in order to obtain a possible explanation of their different binding affinities to the receptor.

The Roothaan SCF (6) calculations for eseroline have been performed by using the STO-3G basis set (7) and the X-ray geometry of physostigmine (8). The H_{13} atom of eseroline has been set 0.96 Å distant from O_{13} and along the O_{13}–carbonyl C bond of physostigmine (8). The electrostatic potential of morphine has been calculated from the SCF wavefunction of Ref. 3. As the STO-3G basis used here for eseroline is slightly different from that previously used for morphine (3), we have performed some test calculations on pyrrolidine, piperidine, and phenol, by pointing out that the two basis sets yield very similar electrostatic potentials.

EXPERIMENTAL PROCEDURES

The chemical and spatial structures of the active sites of the opiate receptor are still unknown, while it has been

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[1] Bartolini, A., G. Renzi, A. Galli, P. Malmberg-Aiello and R. Bartolini, unpublished observations.

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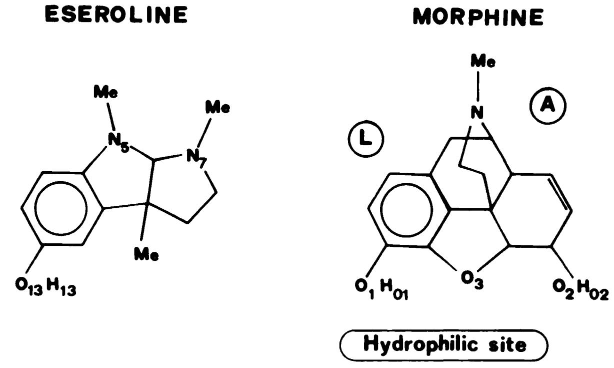

FIG. 1. *Eseroline and morphine*

For morphine we also report a portion of the molecular model of the opiate receptor suggested by Feinberg *et al.* (16) showing the amine A, the lipophilic L, and the hydrophilic binding sites of the receptor.

assumed that the analgesics–receptor interaction at the beginning of the biological response is mainly of the noncovalent type. In the portions of the interaction surface between two molecules where the polarization may be considered inessential to understand the phenomenon under study, the noncovalent interactions can be rather well investigated through the analysis of the electrostatic molecular potential (4, 5, 9–15), which is defined as

$$V(\underline{r}) = \sum_{\alpha}^{\text{nuclei}} Z_\alpha/|\underline{r}_\alpha - \underline{r}| - \int d\underline{r}_1 \rho(\underline{r}_1)/|\underline{r}_1 - \underline{r}|, \quad [1]$$

where Z_α and $\underline{r}_\alpha$ are the nuclear charges and coordinates, respectively, and $\rho(\underline{r}_1)$ is the electron-charge distribution which has been directly obtained from the calculated SCF wavefunction. Equation [1] clearly shows that $V(\underline{r})$ is the electrostatic interaction energy (i.e., at the first order of the perturbation theory) between the unperturbed charge distribution of a molecule and a positive unit charge (a proton) in the point $\underline{r}$. The calculation of $V(\underline{r})$ in the overall space surrounding a molecule thus provides an appropriate picture of the interactions between the considered molecule and ionic or polar reagents.

Of course, the electrostatic approximation gives only a simplified picture of the actual interaction, as polarization, charge transfer, and dispersion forces are neglected. Nevertheless, we note that "the electrostatic energy and electrostatic potential are very useful guides to qualitative and semiquantitative predictions of the energies and shapes of non-covalent complexes" (11), as the electrostatic energy is the largest term in several H-bond and other noncovalent interactions and V correlates rather well with the total SCF interaction energy (4, 9–12). Thus V can be used as a reactivity index of related compounds, with a great reduction of the computational effort with respect to the complete SCF calculations, so obtaining an approximate description of the molecular reactivity which is very useful if the considered molecules interact with an unknown receptor. The interested reader is referred to Refs. 4 and 9–12 for an extended discussion of the validity and limits of this approach. Here we limit ourselves to remember that this method has been successfully used to discuss the different biological activities of some morphine-like compounds (4, 5, 13), that the ordering of the minima of $V(\underline{r})$ of some conjugated systems (five-membered ring molecules, benzene, pyridine, pyrazine, and nucleic acid bases) is in agreement with the experimental reactivity toward electrophilic reagents (9, 12), and that the electrostatic-potential results for some adrenergic model compounds (15) are confirmed by more accurate calculations which also take into account the repulsive, polarization, and dispersion terms of the interaction. The results found for conjugated systems (9, 12, 15) indicate, in particular, that the polarization term of the interaction does not seem to modify substantially the electrostatic description of the interaction.

It has been suggested by Feinberg *et al.* (16) that "presumably all opiates bind to separate pharmacologically relevant hydrophobic and hydrophilic surfaces of the receptor." We have thus performed a quantitative study of the hydrophilic and hydrophobic properties of eseroline and morphine by computing the interaction energies between these analgesics and a molecule of water placed in a very large number of positions and orientations around the biomolecule. The usefulness of this approach is related to the following points: (i) It overcomes the limits of the electrostatic-potential method, as the interaction energy between two molecules is explicitly considered, also taking into account the nonelectrostatic forces; (ii) it gives useful information on the hydration of these molecules in the biophase, as its results are in reasonable agreement with those obtained by accurate Monte Carlo calculations of aqueous solutions of biomolecules at room temperature (17); (iii) the interaction energies and the positions of the preferred hydration sites, the volume of the hydrophilic regions, and the structural organization of water in these regions give a model of the hydrophilic interactions between polar groups of the analgesic and of the unknown receptor; and (iv) the shape and strength of the water-repulsive regions can indicate the presence of possible hydrophobic interactions between nonpolar groups of the analgesic and of the receptor, as water is pushed away from these groups.

The interaction energy ΔE between an analgesic molecule M and a water molecule W has been calculated by using the library of analytical potentials for the interaction between biomolecules and water, obtained by Clementi *et al.* (18–22) from *ab initio* SCF calculations, according to

$$\Delta E(\underline{r}_j) = \sum_{i \in M} \sum_{j \in W} (-\mathrm{A}_{ij}^{ab}/r_{ij}^{6} + \mathrm{B}_{ij}^{ab}/r_{ij}^{12} + \mathrm{C}_{ij}^{ab} q_i q_j/r_{ij}), \quad [2]$$

where A, B, and C are constants obtained by fitting *ab initio* SCF calculations, q are SCF atomic charges, r are interatomic distances, the sums run over the atoms i and j of M and W, respectively, and a and b are atomic class indices which distinguish between atoms of different atomic number and electronic environment in the molecule (18). In Eq. [2] the first two terms in r^{-6} and r^{-12} describe the nonelectrostatic attractive and repulsive interaction energies, respectively, and the last term in r^{-1} refers to the electrostatic term of the interaction.

Other authors (17–22) have previously discussed both the reliability of the numerical fit of A, B, and C to reproduce the SCF interaction energies and the transferability of A, B, and C to molecules not explicitly studied *ab initio*. Those results, and others we obtained for everal complexes with water, point out that the A, B, nd C constants are rather well transferable to new olecules, with an average error of the analytical potenials with respect to the SCF calculations of 1.5 kcal ol^{-1} for stabilization energies of up to 15 kcal mol^{-1}, nd with a saving in computer time of a factor of 10^4 with espect to the SCF calculations. Thus, through a careful omparison of the environments of the atoms of eseroline nd morphine with those of the molecules of Refs. 18–21, nd by performing test calculations on small molecules, e have divided the atoms of eseroline and morphine ito the classes shown in Table 1 (see Ref. 18 for the orresponding A, B, and C values).

Finally, with regard to the sensitivity of our results to pproximations and choice of parameters we made, we emember that the STO-3G electrostatic molecular potential agrees rather well, both in shape and in relative rdering of the minima, with that obtained by more ccurate basis sets (4), while the interaction energy with ater is of course more dependent on the choice of the arameters, as it is a linear function of A, B, and C.

ESULTS

We report in Table 2 the total SCF energy and the rbital energies and types of the highest occupied molecular orbitals (HOMOs) of eseroline. For a better comparison we also report the corresponding SCF results of orphine (3). These results show that the first and third IOMOs of eseroline are mainly π orbitals on the aromatic ring, so that they correspond rather well to the rst two HOMOs of morphine. Note also that of the two I lone pairs of eseroline, only the N_7 one is very close nergywise to the N lone pair of morphine and that the imilarity between the O_{13} lone-pair orbital of eseroline nd the O_1 one of morphine is rather affected by O_2 and O_3 of morphine.

We have calculated the electrostatic potential of eseroline and morphine in the benzene plane, in some planes arallel and perpendicular to the benzene one, and in lanes perpendicular to those of CNC and COH which bisect the CNC and COH angles. Our main results are reported in Figs. 2 and 3 and in Table 3. The potential maps in Fig. 3 and those reported for morphine in Refs. 4 and 5 (drawn in different planes) provide an overall view of the electrostatic potential of this analgesic.

TABLE 1

Atomic classes of eseroline and morphine[a]

Class	Eseroline	Morphine
2	H_6, H_8, H_9	H_5, H_6, H_9, H_{10}, H_{14}, H_{15}, H_{16}
3	H_{18}, H_{19}, H_{20}	H_{17}
4	H_{13}	H_{01}, H_{02}
6	C_{18}, C_{19}, C_{20}	C_{17}
7	C_8, C_9	C_{10}, C_{15}, C_{16}
8	C_6, C_{10}	C_9, C_{13}, C_{14}
15	N_5, N_7	N
16	H_2, H_3, H_{12}	H_1, H_2, H_7, H_8
17	C_1	C_3, C_4, C_5, C_6
18	C_2, C_3, C_{12}	C_1, C_2, C_7, C_8
19	C_{11}	C_{11}, C_{12}
20	C_4	—
27	O_{13}	O_1, O_2, O_3

[a] The class indices are those of Ref. (18), which also reports the alues of the A, B, and C constants. For the identification of the atoms e Figs. 2–4; the H atoms are labeled according to the heavy atoms to which they are bound.

TABLE 2

Eseroline and morphine: Total energies and types of the highest occupied molecular orbitals[a]

Eseroline[b]		Morphine[c]	
E_{tot}	−677.730	E_{tot}	−927.984
ϵ_{59}	−0.216 $\pi(C_1, C_4, C_{11}, N_5)$	ϵ_{76}	−0.244 $\pi(C_1, C_3, C_4, O_3)$
ϵ_{58}	−0.287 $lp(N_7)$	ϵ_{75}	−0.270 $\pi(C_2, C_3, C_{11}, C_{12}, O_1)$
ϵ_{57}	−0.289 $\pi(C_2, C_3, C_{11}, C_{12})$	ϵ_{74}	−0.280 lp(N)
ϵ_{56}	−0.338 $lp(N_5)$	ϵ_{73}	−0.303 $\pi(C_7, C_8)$
ϵ_{55}	−0.367 $lp(O_{13})$	ϵ_{72}	−0.360 $lp(O_2)$
ϵ_{54}	−0.393 $p(C_6, C_9, C_{10})$	ϵ_{71}	−0.379 $lp(O_1, O_3)$

[a] Energies in hartrees (1 hartree = 627.506 kcal mol^{-1}). For the identification of the atoms, see Figs. 2–4.

[b] This work, STO-3G basis set.

[c] Ref. 3.

The upper portions of Figs. 2 and 3 ($y > 0$) show that the potential is very similar in the space surrounding the pyrrolidine N_7 atom of eseroline and the piperidine N atom of morphine, in spite of the different nitrogen-containing rings. Indeed $V(\underset{\sim}{r})$ is strongly negative (i.e. proton attractive) in the lone-pair regions of N_7 and N, the potential minima correspond rather well, both in values and positions (see Table 3), and they lie in nearly tetrahedral arrangements with respect to the C atoms bound to N_7 or N.

On the other hand, the negative-potential region around N_5 of eseroline is unmatched in morphine and it is noticeably smaller and less attractive than that around N_7, owing to the strong repulsive potential due to the C_{18} and C_{19} methyl groups. The value of the N_5 minimum and its position rather distant from a tetrahedral arrangement (see Fig. 2 and Table 3) agree with the X-ray results (8) which evidenced a sp^2 hybridization of N_5.

The calculation of $V(\underset{\sim}{r})$ in other planes parallel and perpendicular to the benzene one[2] shows that in eseroline there is a wide region of negative potential which extends above and below the plane of the benzene and N_5-pyrrolidine rings and which is due to the conjugation of the N_5 lone-pair electrons with the benzene-π electrons. For instance, in the plane parallel to the benzene one with $z = 1.8$ Å (i.e., on the opposite side of C_{18} and H_{13}), we have found two minima equal to −29.4 and −28.7 kcal mol^{-1}, corresponding to O_{13} and N_5, respectively, and $V = -7.4$ kcal mol^{-1} above the midpoint of the C_4–C_{11} bond. The differences between eseroline and morphine are significant: The corresponding negative-potential region of morphine is strongly reduced (see the lower portion of Fig. 33 of Ref. 4) owing to the strong positive potential due to the its fused rings, so that V is equal to 1.9 kcal mol^{-1} above the midpoint of the C_{11}–C_{12} bond isosteric with C_4–C_{11} of eseroline) and it is strongly positive above the C_{10}-containing ring (isosteric with the N_5-pyrrolidine ring of eseroline).

Significant differences were also found in the phenolic region of the two molecules. The lower positions in Figs. 2 and 3 ($y < 0$) show indeed that the negative-potential

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[2] The corresponding potential maps are not reported here for the sake of brevity, but they are available upon request.

TABLE 3

Values and positions (in parentheses) of the minima of the electrostatic potential and of the interaction energy with water[a]

	Region	Eseroline	Morphine
Electrostatic[b] potential	N_7[c]	−83.4 (3.4, 2.1, 0.7)	−84.6 (3.4, 1.9, 0.6)
	N_5	−55.6 (0.1, 2.5, 1.1)	—
	O phenolic	−52.8 (−3.7, −2.2, 0.2)	−55.5 (−3.7, −2.5, −0.1)
	O_3	—	−35.6 (−0.2, −3.2, −0.2)
	O_2	—	−60.8 (1.3, −3.6, −3.6)
Interaction energy with water[d]	N_7	−7.7 (5.0, 1.4, 0.2)	−7.5 (5.1, 1.5, 0.2)
	N_5	−1.6 (−0.6, 5.2, 2.1)	—
	O phenolic	−4.1 (−4.4, −3.7, 2.2)	−4.0 (−4.5, −4.3, 1.0)
	O-H phenolic	−10.4 (−2.7, −4.0, −1.9)	−12.5 (−2.0, −3.9, −2.2)
	O_3	—	−5.2 (−0.9, −4.8, 0.0)
	O_2	—	−4.2 (1.1, −4.9, −4.8)
	O_2-H_{O2}	—	−7.3 (−1.3, −4.5, −1.1)

[a] Energies in kcal mol^{-1} and geometries in Å. See Figs. 2 and 3 for the coordinate system.

[b] STO-3G basis for eseroline and basis of Ref. 3 for morphine.

[c] N_7 for eseroline and N for morphine.

[d] Only the geometry of the O atom of H_2O is reported.

region is much wider in morphine than in eseroline, owing to the cooperative effect of the lone-pair electrons of O_1, O_3, and O_2. Thus the potential near the phenolic OH of morphine is noticeably affected by the neighbouring groups, like O_3, and the negative regions around O_3 and O_2 of morphine (see also Table 3) are unmatched in eseroline.

In conclusion, $V(\underline{r})$ is practically identical around the pharmacophorically significant N atoms of eseroline and morphine (N_7 of eseroline), whereas it is remarkably different around other significant groups of these molecules (N_5, benzene ring, phenolic OH, O_3, and O_2H_{O2}).

We have calculated the surfaces of the interaction energy of eseroline and morphine with water by placing the water oxygen in the same planes where we have calculated $V(\underline{r})$. For each plane we have placed O of H_2O in each point of a square grid (20 × 20; the grid interval is 0.4 Å) and the orientation of the H atoms has been optimized by minimizing the interaction energy (three simultaneous rotations of H_2O around to three orthogonal axes centered on O have been considered; the angular interval is 30°). Thus we have considered for each plane $\sim 7 \times 10^5$ positions and orientations of water, so as to completely scan the interaction energy surface without any a priori assumption on the preferred hydration sites.

The main results are reported in Figs. 4 and 5 and in

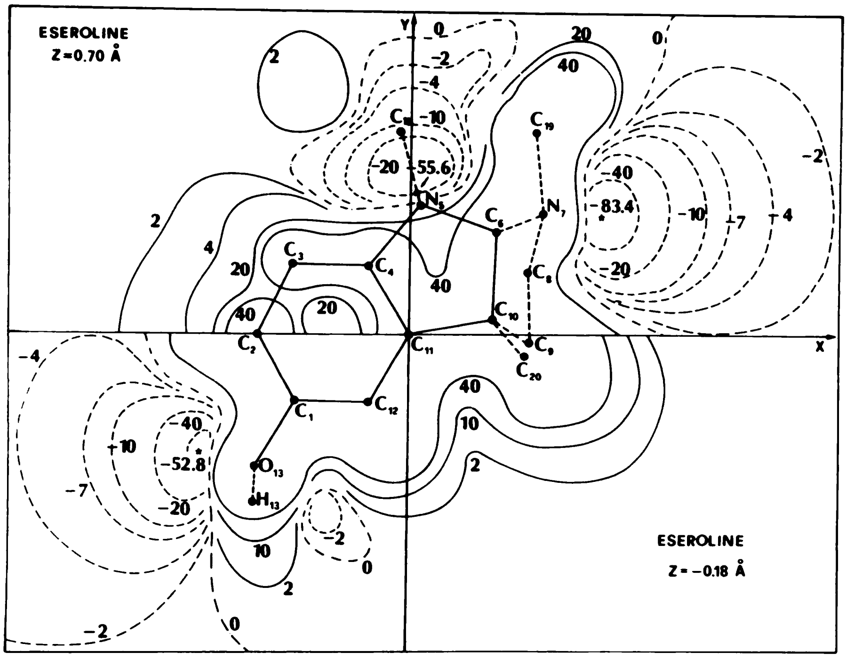

FIG. 2. *Eseroline*

Coordinate system and projection of the molecule on the (*x*, *y*) plane: The full bonds lie nearly in the (*x*, *y*) plane and the dashed bonds lie outside this plane. Isoenergy contour maps of the electrostatic potential (STO-3G basis) in parallel planes to the (*x*, *y*) one and containing the potential minimum near N_7 (above, $y > 0.0$ and $z = 0.70$Å) and near O_{13} (below, $y < 0.0$ and $z = 0.18$ Å). The stars indicate the minima and the potential values are in kcal mol^{-1}.

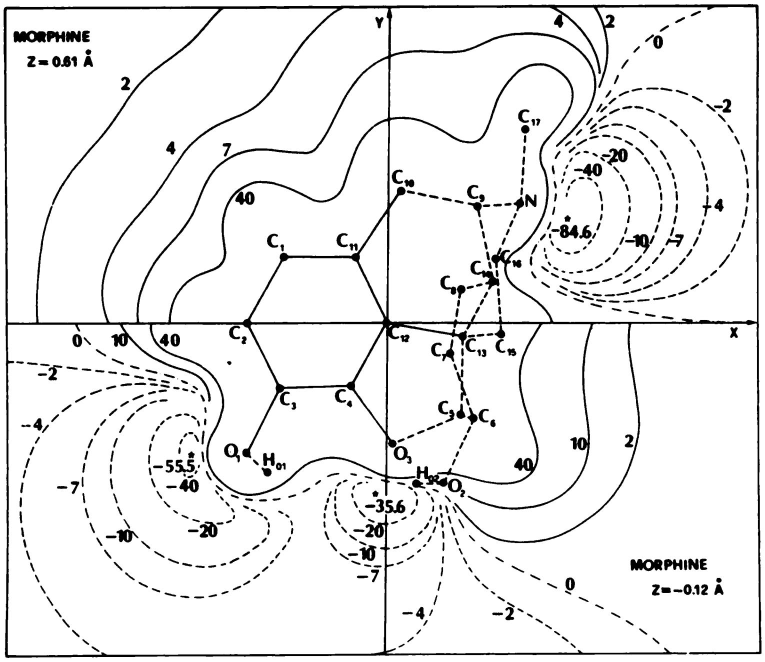

Fig. 3. *Morphine*

Coordinate system, projection of the molecule, and isoenergy contour maps of the electrostatic potential (basis of Ref. 3) in parallel planes to the (x, y) one and containing the potential minimum near N (above, $y > 0.0$ and $z = 0.61$ Å) and near O_1 (below, $y < 0.0$ and $z = 0.12$ Å). See Fig. 2 for other details.

Table 3. They refer to optimized water orientations and show that two strong hydrophilic regions characterize each molecule: The first surrounds N_7 of eseroline and N of morphine, and the second is due to the phenolic groups of both molecules and to O_3 of morphine. In addition, Table 3 shows that both N_5 of eseroline and O_2H_{02} of morphine are hydrated (the hydrophilicity of N_5 is however very small), while all the other groups are characterized by hydrophobic interactions.

The shape of the hydration surfaces near the pyrrolidine and piperidine groups points out that the reactivity properties of N_7 of eseroline and N of morphine are very similar, both for the values of the interaction energy and for the organization of water, and that the water affinity of the N_5 region of eseroline is very small, owing to the hydrophobic interactions due to the neighboring C_{18} and C_{19} methyl groups. The lower portions of Figs. 4 and 5 show that the interaction of water with the π electrons of the benzene ring of both molecules is prevented by the strong hydrophobic region surrounding all this ring.

The strongest hydrophilic interactions are due to the phenolic OH and, as expected, they correspond to a proton-acceptor organization of water. The preferred hydration sites are characterized by almost linear H bonds and by interaction energies of -10.4 and -12.5 kcal mol^{-1} for eseroline and morphine, respectively, while the interactions between the lone pairs of the phenolic oxygens and proton-donor water are decidedly weaker (-4.1 and -4.0 kcal mol^{-1} for eseroline and morphine, respectively; see Table 3). Figures 4 and 5 and Table 3 also show that the region of morphine containing the O_1H_{01}, O_3 and O_2H_{02} groups is decidedly more hydrophilic than the corresponding one of eseroline. Indeed the water-attractive region is much wider in morphine owing to the hydrophilic interactions due to the O_3 and O_2H_{02} groups which are unmatched in eseroline. In addition to this direct role, these groups also have an indirect and cooperative effect on the hydration of the phenolic one, as the O_1H_{01}-water interaction for morphine is ~2 kcal mol^{-1} stronger than the $O_{13}H_{13}$-water interaction for eseroline, and the optimum position of water is appreciably different in the two complexes.

To check to what extent the different orientations of the phenolic OH groups (see Figs. 4 and 5) determine these different reactivities of eseroline and morphine, we have also calculated the eseroline-water interaction with the orientation of the $O_{13}H_{13}$ group equal to that of the O_1H_{01} group of morphine. The optimum position of water is, in this case, more similar to that found for morphine, but the interaction energy lowers to -8.1 kcal mol^{-1}, owing to the repulsive effect of the H atom bound to C_{12} of eseroline (opposite to the attractive one of O_3 and O_2H_{02} of morphine), so that the reactivity characteristics are even more different in spite of the equal conformations.

Finally, note that the similarities and differences we have found between eseroline and morphine from the analysis of the electrostatic potential are completely confirmed from the analysis of the interaction energy with water.

DISCUSSION

The analyses of the electrostatic potential and of the interaction energy with water of eseroline and morphine complement each other by suggesting a model of their noncovalent reactivity, of their hydration properties, and of possible interactions with the receptor. For the first time perhaps, the hydrophilic and hydrophobic properties of analgesics have been quantitatively estimated, so that our results can be compared with a molecular model

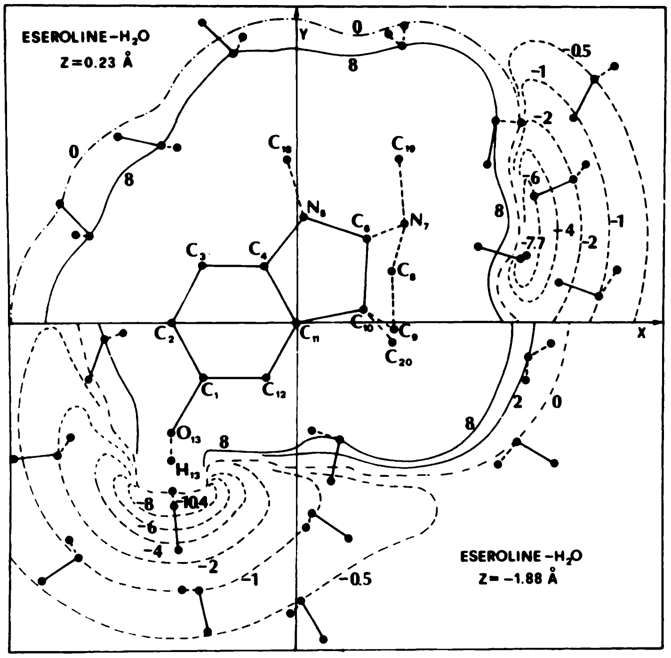

FIG. 4. *Eseroline*

Isoenergy contour maps of the interaction energy with water in parallel planes to the (x, y) one and containing the interaction-energy minimum near N_7 (above, $y > 0.0$ and $z = 0.23$ Å) and near $O_{13}H_{13}$ (below, $y < 0.0$ and $z = 1.88$ Å). The preferred hydration sites near N_7 ($\Delta E = -7.7$ kcal mol^{-1}) and near $O_{13}H_{13}$ ($\Delta E = -10.4$ kcal mol^{-1}) and other significant geometries of the surrounding water are also shown. The energy values are in kcal mol^{-1}.

of the analgesic-receptor interaction which has been obtained from experimental data (16) and is reported in Fig. 1 for the reader's convenience. Our results, and their possible relationships with the biological activity, can be summarized as follows.

The analyses of the molecular orbitals, of the electrostatic potential, and of the hydration surface concordantly show that the aminic groups N_7 of eseroline and N of morphine have equal electronic structures and reactivity properties. ESCA spectra (23, 24), *ab initio* (3-5), and CNDO (24) calculations show that this result also holds for other agonists, both in the neutral and in the N-protonated forms. While *ab initio* calculations show the charges on the N atom in certain congener pairs, such as morphine (a N-methyl agonist) and nalorphine (an N-allyl narcotic agonist-antagonist) are identical (3), the electrostatic molecular potentials around the N are identical in only one direction (4, 5), the lone-pair direction, which must be the agonist direction, and for agonists, at least, probably also the direction in which interaction with the receptor takes place. The electrostatic molecular potential maps around the N in morphine and nalorphine are quite different in all other directions (4, 5). Moreover, as the electrostatic-potential minima of piperidine and $(CH_3)_3N$ (−85.7 and −87.9 kcal mol^{-1}, respectively) do not change appreciably, we can infer that the features of this molecular region are mainly due to the common tertiary structure, sp^3 hybridization, and spatial arrangement of the nitrogen atoms and that the N reactivity of other analgesics, like 4-phenyl piperidines and methadone is probably the same. In conclusion our data indicate that the different binding affinities of eseroline and morphine to the receptor are not due to different reactivities of the aminic group, in agreement with the suggestion (16) that a receptor site A (Fig. 1) interacts in a similar way with the aminic group of different analgesics.

The negative electrostatic potential due to the N_5 lone-pair and π-benzene electrons of eseroline is replaced by a positive potential in the isosteric molecular region of morphine. By keeping in mind the lower binding affinity of eseroline to the receptor (2), this result suggests that the benzene group does not interact with an electrophilic site of the receptor (as *V* indicates that eseroline has a greater affinity for this site) and that N_5 probably lowers the binding affinity of eseroline. This hypothesis gives a rationale for the experimental finding (2) that profadol, which is devoid of the N_5-pyrrolidine ring and thus has *V* probably intermediate between that of eseroline and morphine, has a binding affinity greater than that of eseroline and equal to one-third that of morphine. Our calculations also show that the benzene ring of both molecules is strongly hydrophobic. This result is consistent with the model of Fig. 1 which indicates that a lipophilic receptor site L binds to the benzene ring of analgesics (16), probably through van der Waals dispersion forces which should be stronger in morphine owing to its fused rings, thus decreasing the interaction with the surrounding water.

Although the phenolic OH groups is not essential for the analgesic activity, experimental studies have clearly shown that this group interacts with the receptor, since its removal, as in 3-deoxymorphine (25), or its substitu-

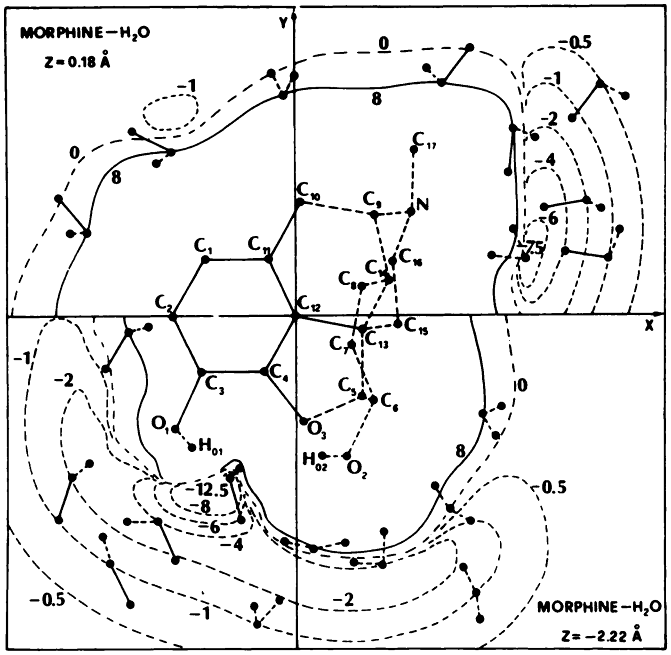

FIG. 5. *Morphine*

Isoenergy contour maps of the interaction energy with water in parallel planes to the (x, y) one and containing the interaction-energy minimum near N (above, $y > 0.0$ and $z = 0.18$ Å) and near O_1H_{01} (below, $y < 0.0$ and $z = -2.22$ Å). The preferred hydration sites near N ($\Delta E = -7.5$ kcal mol^{-1}) and near O_1H_{01} ($\Delta E = -12.5$ kcal mol^{-1}) and other significant geometries of the surrounding water are also shown. The energy values are in kcal mol^{-1}.

tion by other groups, as in physostigmine (2), codeine (26), and other analgesics (16), gives rise to a strong reduction of the binding affinity to the receptor (1/30 and 1/1154 for 3-deoxymorphine and physostigmine with respect to morphine). Both the electrostatic-potential results and the water-interaction results show that the reactivity characteristics of the phenolic OH of eseroline are different from those of the phenolic OH of morphine, owing to the cooperative effect of the O_3 and O_2H_{02} groups of morphine which, in addition, can directly bind to the receptor. On the whole, this molecular region of morphine is more reactive toward polar receptor sites and, in particular, it is more hydrophilic that the corresponding region of eseroline. This theoretical result is consistent with the experimental data for 3-deoxymorphine (25), physostigmine (2), and codeine (26) which pointed out the role of the phenolic OH of analgesics in the binding to the receptor, and it supports the suggestion (16) that this group and the neighboring polar groups interact with a hydrophilic site of the receptor (Fig. 1). Finally, the reactivity differences we found for the N_5, benzene, phenolic OH, O_3, and O_2H_{02} groups can explain the lower binding affinity of eseroline with respect to that of morphine (2).

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Send reprint requests to: Joyce J. Kaufman, Department of Chemistry, The Johns Hopkins University, Remsen Hall, Baltimore, Md. 21218.