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A pseudoreceptor docking study of 4,5-α-epoxymorphinans with a range of dielectric constants

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SUMMARY

Thirteen 4,5-epoxymorphinan μ agonists with established analgesic action were docked into an Asp-Lys-His-Phe pseudoreceptor complex under a range of distance-dependent dielectric conditions. The number of compounds with potential energies of the docked complexes that agreed in rank order with corresponding analgesic potencies was determined for each condition. Two dielectric conditions, *n*-decane (1.991) and ethanol (24.3), enabled the greatest number of compounds to relate to their pseudoreceptors with each having 9 and 8 successes respectively. Both of these conditions demonstrated unique influences on the types of structures that were successfully docked. For example, the morphine stereoisomer α-isomorphine, the geometric isomer B/C *trans*-morphine, and the 8-position-substituted γ-isomorphine were successes in the *n*-decane condition, whereas the ethanol condition produced the substituted codeine derivatives dihydrocodeinone and dihydroxycodeinone. These findings emphasize the importance of dielectric influence when developing force-field modeled quantitative structure–activity relationships for a closely related homologous series.

INTRODUCTION

Mechanisms of pharmacological action of drug molecules are related to their unique ability to interact at key receptor sites presumed to be responsible for their desired (specific) effects. Although there have been many successful studies which have investigated ligand-active site interactions from crystallographic and NMR data, for the vast majority of cases of bio-active compounds, exact conformational knowledge of their receptor complexes is unknown. With the advent of large-scale computational power afforded by supercomputers, a diversity of molecular mechanics and dynamics experiments are now possible, towards the goal of fitting an active molecule to either known or unknown receptor pharmacophores. There are already numerous techni-

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ques concerning receptor fitting, all of which attempt to determine the essential three-dimensional coordinates of functional groups involved with an active ligand which when in some optimal state, produces a desired effector system response. Some of the approaches designed to employ structural data information for these pursuits include the 'active analog' approach [1], and distance geometry applications [2,3].

Although the concept of receptor–ligand steric-fit is certainly a fundamental principle of drug action, the effective binding of an active ligand to its receptor is also an electrostatic event [4]. Receptor–ligand interactions are most likely to be characterized by changes in the nonbonded and electrostatic terms of the potential energy function [5]. For example, the Lennard–Jones 6–12 potential and Coulombic electrostatic energies can be used to measure the interaction energy (E_{inter}) between a ligand and a receptor which consists of:

$$E_{inter} = \sum_{i} \sum_{j>i} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{\varepsilon r_{ij}} \right]$$

The first two terms of the above equation correspond to the van der Waals repulsion and van der Waals dispersion energies respectively, where A_{ij} and B_{ij} are nonbonded constants and r_{ij} is the distance between nonbonded atom pairs. The last term is the Coulombic electrostatic energy where q_i and q_j are atom charge pairs and εr_{ij} is the dielectric function.

Successful implementation of these and other types of molecular mechanics simulations with free energy thermodynamic perturbation methods, has also enabled investigators to approximate experimentally derived binding constants, predict structurally favorable interaction of molecular species with macromolecules, and to help postulate carcinogenic structure–activity relationships [6–8].

A continuing effort exists in the modeling of opiate structure which has contributed markedly to the understanding of ligand chemistry on a theoretical level. Belleau et al. [9–11] established the crucial relationship between the orientation of the lone pair on the tertiary amine nitrogen and opiate activity. Extensions of this 'clastic binding hypothesis' have provided mechanistic insight into proton transfer of the amine [12] revealing critical interatomic distances and proton transfer potentials [13,14] from semiempirical calculations. A comprehensive evaluation of structure–activity relationships of four chemical classes of opiates was contributed by Cheney [15], who employed ab initio level calculations to develop a statistically determined free energy model of agonist/antagonist binding based on stability of the drug–receptor complex. These computational investigations were concerned with the derivation of key intramolecular properties from a molecular orbital perspective.

Generally, active opiate agonists consist of a benzene ring and a tertiary amine that are assumed to be in a spatially favorable orientation. B/C *cis*-morphine (5R, 6S, 9R, 13S, 14R) (CMOR), the naturally occurring, prototypical μ agonist, has a well-known and established use in

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Abbreviations: Asp, aspartate; CMOR, B/C *cis*-morphine; CODN, codeine; CPU, central processing unit; DCOD, dihydrocodeinone; DHCO, dihydroxycodeinone; DHMO, dihydromorphinone; DDOM, dihydrodesoxymorphine-D; GISM, γ-isomorphine; His, histidine; ISOC, isocodeine; ISOM, α-isomorphine; K, Kelvin; Lys, lysine; MACM, 6-acetylmorphine; METP, 5-methyldihydromorphinone; NMR, nuclear magnetic resonance; PCOD, pseudocodeine; Phe, phenylalanine; TMOR, B/C *trans*-morphine.

clinical analgesia. Isomeric 4,5-α-epoxymorphinans, including morphine, are interesting to model because chemically, they constitute a fairly rigid sample of compounds with established pharmacological action. Our model attempts to define an energetically, spatially favorable orientation of a group of morphine-related ligands within a hypothetical abbreviated 'pseudoreceptor' pocket. The homologous series employed in this study has previously been pharmacologically investigated [16–18]. Using thirteen 4,5-epoxymorphinans we performed a comparative study with a stereoselective pseudoreceptor design of the QSAR at a force-field level of computation. Because of the unavailability of in vitro data for this specific set of compounds, we used in vivo analgesic potencies as our pharmacological measurement. Although the modeling of pseudoreceptor architecture would be more straightforward with in vitro binding affinity data, at least for opiates it is generally accepted that binding affinity curves seem to correspond quite well with the in vivo potency and efficacy classifications [19–24]. Without knowledge of the actual receptor structure, our pseudoreceptor architecture was constructed with pharmacophoric substituents that present chemical complementarity with the ligands' functional groups. We have previously presented this receptor design [25] along with analytical data [26]. Pseudoreceptor construction consisted of a phenylalanine-induced dipole interaction between the aromatic rings, a histidine-imidazole hydrogen bond with 4,5-α epoxy and the 3-hydroxy, a lysine-ε-amino hydrogen bond with the 6-hydroxy substituent, and a reinforced ionic bond (using ionized aspartate) with the protonated amine of the ligand.

The present study employed a distance constraint/energy refined docking procedure to provide a force-field characterization of the stereochemical interaction of 13 opiate agonists with a hypothetical pseudoreceptor. Specifically, our objectives in this research were:

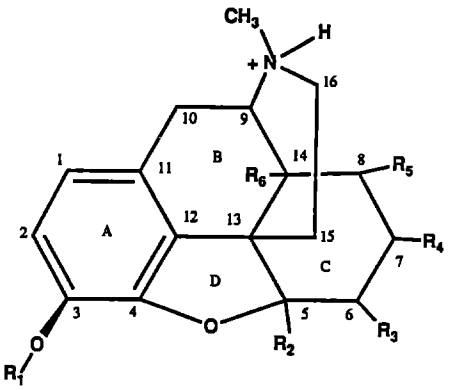
(1) to allow each molecule to assume its own 'preferred' docking conformation while using close starting geometry and maintaining identical docking conditions;
(2) to explore different electrostatic influences on the final total energy of docked complexes by using a range of distance-dependent dielectric constants from vacuum to water;
(3) to determine whether this force-field level of computation is sufficiently sensitive to model pharmacologically relevant discrepancies between this closely related homologous series.

METHODS

Starting geometry

The initial geometry of B/C *cis*-morphine (5R, 6S, 9R, 13S, 14R) (CMOR), was a previously determined crystal structure [27]. The additional agonists, 5-methyldihydromorphinone (METP), dihydrodesoxymorphine-D (DDOM), dihydromorphinone (DHMO), 6-acetylmorphine (MACM), α-isomorphine (ISOM), dihydrocodeinone (DCOD), dihydroxycodeinone (DHCO), γ-isomorphine (GISM), B/C *trans*-morphine (TMOR), codeine (CODN), isocodeine (ISOC), and pseudocodeine (PCOD), were constructed from the parent geometry of the CMOR crystal. Figure 1 presents the structures of these agonists in their progressive order of analgesic potency.

Pseudoreceptor architecture consisted of an Asp-Lys-His-Phe pocket. First, the four amino acids were positioned with their side chains oriented towards their eventual docking targeted bonds (see Fig. 2). Once these orientations were established, each amino acid was moved 10 Å from the fully minimized CMOR ligand. This movement was performed so that the amino acids were at maximal distances from each other. The resulting structure of the pocket served as a



Ligand	R_1	R_2	R_3	R_4	R_5	R_6
METP	H	CH_3	O =	H_2	H_2	H
DDOM	H	H	H_2	H_2	H_2	H
DHMO	H	H	O =	H_2	H_2	H
MACM	H	H	$COOCH_3$	H	H	H
CMOR	H	H	OH	H	H	H
ISOM	H	H	OH*	H	H	H
DCOD	CH_3	H	O =	H_2	H_2	H
DHCO	CH_3	H	O =	H_2	H_2	OH
GISM	H	H	H	H	HOH	H
TMOR	H	H	OH	H	H	H**
CODN	CH_3	H	OH	H	H	H
ISOC	CH_3	H	OH*	H	H	H
PCOD	CH_3	H	H	H	HOH	H

Fig. 1. Structures of the 4,5-epoxymorphinans, in protonated form. *the OH of ISOM and ISOC is R at the 6-position, **the 14-position pyramidal carbon inversion (H from R to S) forces the B and C rings into *trans*-geometry.

template to create the other 12 compounds' initial starting geometries for the docking experiments. This was accomplished by replacing the CMOR ligand in the template structure with each compound. The conformational proximity of the 13 pseudoreceptor complexes was evaluated by superimposition and a root-mean-square deviation calculation. The pseudoreceptor–ligand complexes resulted in almost identical (within 0.0017 Å) starting geometries for all complexes.

Docking procedure

Each compound was docked by applying distance constraints between specific target atoms in the ligand–amino acid complex. The consistent valence force field was used to mechanically represent the molecular models [28]. The range of distance-dependent dielectric constants employed during simulations in this study were: vacuum (1.0), *n*-decane (1.991), isopropyl ether (3.38), chlorobenzene (5.708), methyl ethyl ketone (15.8), ethanol (24.3), methanol (32.8), dimethyl sulfoxide (46.7), and water (80.0).

Computational modeling was performed on a CRAY-XMP24 with only one CPU enabled. The modeling software used in this study was INSIGHT II and DISCOVER 2.5 [29]. All calculations were performed without cutoff boundaries.

Each distance-constraining iteration began with a starting distance of 10 Å and annealed slowly

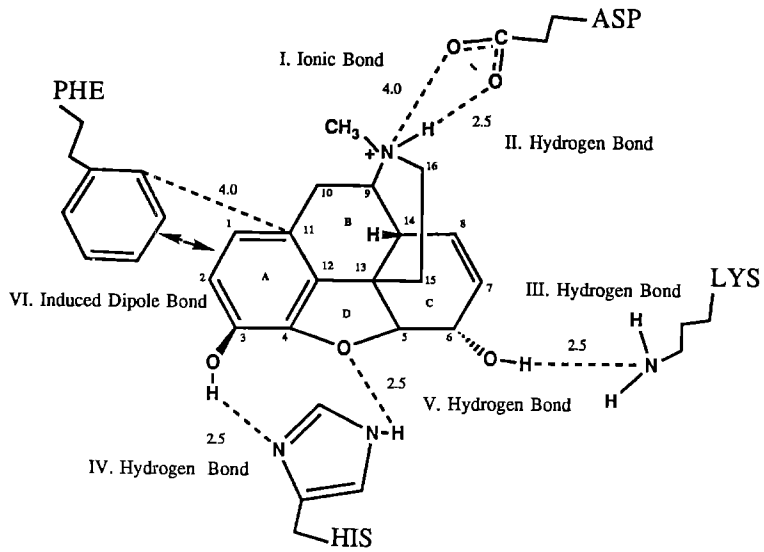


Fig. 2. Targeted geometry for the docking simulations.

(0.1 Å steps) to its targeted distance using a 50 kcal/Å constraint. Between each step, the molecular system was energy refined using steepest descents and conjugate gradients with harmonic oscillators and without cross-term energy calculations. Figure 2 illustrates the targeted conformation of the docking simulation.

A hypothetical reinforced ionic bond between the protonated amine of the morphine-related agonists was simulated by closing the distance between the Ns of the agonists and an O of an (Asp) side chain to within 4 Å. Each isomer was then brought to within a 2.5 Å distance between the H-bonded to the N and to the other side-chain O of Asp. Because the hydroxyl substitutions on the 8-position of GISM and PCOD placed these OHs into close enough proximity to be H-bonded to Asp, these targeted constraints were also enforced. Targeted bond formation for the 6-position O substituents (usually hydroxy or keto or acetyl carbonyl O) was a hypothetical hydrogen bond (H-bond) with a neutral ε-amino side chain of Lys. Although the Lys side chain is most likely protonated at physiological pH, we did not use the charged amino form in order to prevent ionic charge competition with the carboxylate anion of Asp. This type of ion-dipole bond would compete with the docking constraint forces applied to the free amino acids in this pseudoreceptor. A neutral Lys side chain enables the N to serve as only a hydrogen bond acceptor. The selected distance for either an OH–N or O–HN H-bond was also 2.5 Å. Compounds without a 6-substitution (DDOM, GISM, and PCOD) were constrained within an approximate distance of other substituted compounds (usually 3.8–4.0 Å). All ligands were also targeted for a 2.5 Å distance to H-bond between a 3-substituted OH (methoxy or hydroxy) and the lone-pair N of the His-imidazole, and to the 4,5-α epoxy and N–H of the His side chain. Finally, a targeted distance of 4 Å was achieved between the aromatic rings of Phe and the agonists to model an induced dipole interaction.

Each pseudoreceptor–ligand complex was minimized (until the norm of the gradient was < 0.001) once all targeted bonds were achieved.

Analysis

Within a dielectric condition, the number of docked, minimized ligand–pseudoreceptor complexes' total energies that agreed in rank order with their corresponding ED_{50} values represented the number of compounds that was successfully predicted by that model. Pearson products moment correlations were then calculated between the potential energy values and their corresponding natural log transformed ED_{50} values for the purpose of quantifying the relationship. A significant correlation was considered to exist at $\alpha = 0.01$. In the event that several different sets of compounds with the same number of successes existed within a dielectric condition, a particular set of compounds was chosen on the basis of this statistical criterion. If two sets with the same number of successes were correlated significantly, the set with the greater correlation was chosen.

RESULTS AND DISCUSSION

Table 1 illustrates the final energies of each minimized docked complex (ligands and amino acids) under each distance-dependent dielectric constant used. These results indicate that *n*-decane and ethanol, which had 9 and 8 successes, respectively, were the best dielectric conditions for associating analgesic response with pseudoreceptor docking energies. Interestingly, the stereoisomer ISOM and geometric isomer TMOR of CMOR, ranked successfully in the *n*-decane medium, whereas DCOD and DHCO (modified codeine derivatives) were successes when the ethanol constant was employed. Between the two media, 11 out of 13 compounds related to their pseudoreceptors.

METP and DDOM were consistently underestimated for analgesic action regardless of dielectric influence. Our pseudoreceptor architecture was not appropriate for these analogues. Perhaps their greater analgesic potency is largely due to better bilayer transport capabilities. If this is the case, the greater lipophilicity of METP and DDOM could account for greater in vivo potency which is not necessarily represented in a mechanical pseudoreceptor model. On the other hand, METP is the 5-methylated analogue of DHMO. Since both compounds possess six receptor contact points, spatial arrangements may suggest that factors other than electronic effects may be important in this docking experiment. The additional methyl group near the 6-carbonyl oxygen has contributed about 10 kcal/mol greater energy for the METP analogue in the docked complex. On examination of the energies under the *n*-decane condition, it was found that the greatest discrepancy between the METP and DHMO complexes was the electrostatic energy (METP = −20.5 kcal/mol, DHMO = −12.8 kcal/mol). Spatially, METP's 5-methyl group was found to be almost in van der Waals contact with one of the hydrogens of the Lys ε amino group. Thus, the position of the 5-methyl group has placed additional similarly charged atoms near the methylene portions of the Lys side chain which contributed to a more unfavorable electrostatic energy. The influence of steric differences on the architecture of this pseudoreceptor model can also be seen in compounds that do not possess all of the six binding contact points. A good example in this study was PCOD which was correctly predicted 8/9 times from the docking experiments. PCOD had the spatial and electrostatic disadvantages of the codeine derivatives' 3-methoxylation as well as the alcoholic 8-OH group (similar to GISM), and consequently was predicted to be least potent.

In these pseudoreceptor simulations, the amino acids were 'free floating'; that is to say, each compound was able to determine a preferred amino acid placement about its binding contacts. This means that differences in steric fit between ligands in this pseudoreceptor model can be

TABLE 1
POTENTIAL ENERGIES OF THE DOCKED PSEUDORECEPTOR COMPLEXES FOR A GIVEN DIELECTRIC CONDITION

	1.00	1.991	3.38	5.708	15.8	24.3	32.8	46.7	80.0	ED_{50}
1 METP	144.8[a]	157.7[a]	169.7[a]	165.9[a]	169.7[a]	168.7[a]	168.9[a]	169.1[a]	171.0[a]	0.07
2 DDOM	142.0[a]	157.2[a]	167.4[a]	171.6[a]	173.2[a]	173.8[a]	174.1[a]	174.3[a]	174.6[a]	0.08
3 DHMO	132.9[a]	147.5	158.2	161.1	162.2	164.6	165.6[a]	165.6[a]	165.8[a]	0.17
4 MACM	129.2	147.6	158.9	163.9[a]	169.1[a]	164.7	165.0	165.3	165.6	0.18
5 CMOR	133.2	150.0	159.0	162.2	168.8	170.2	170.5	170.7	170.9	0.75
6 ISOM	131.8[b]	152.0	156.3[b]	160.6[b]	164.3[b]	165.5[b]	165.8[b]	166.1[b]	166.3[b]	0.80
7 DCOD	145.5[a]	164.4[a]	168.5[a]	171.7[a]	173.4[a]	174.5	174.2	173.2	173.9	1.28
8 DHCO	152.5[a]	166.0[a]	172.9[a]	175.5[a]	176.0[a]	176.4	176.6	176.7	175.5	1.34
9 GISM	123 .4[b]	152.3	164.3	168.2	172.1	172.9[b]	173.2[b]	173.5[b]	173.8[b]	7.09
10 TMOR	139.7	152.7	164.1[b]	167.0[b]	170.8[b]	171.4[b]	171.7[b]	171.9[b]	172.2[b]	7.5
11 CODN	144.9[a]	161.8	170.1	173.2	179.9	180.5	181.5	181.7	182.0	8.04
12 ISOC	141.1	163.3	171.3	173.4	180.2	181.4	180.9	175.6[b]	180.6[b]	13.0
13 PCOD	136.3[b]	167.2	175.9	178.0	183.7	182.5	182.8	183.1	184.0	17.8

Vacuum (1.00)	$r=0.99$	$n=4$
n-Decane (1.991)	$r=0.84$	$n=9$
Isopropyl ether (3.38)	$r=0.91$	$n=7$
Chlorobenzene (5.708)	$r=0.93$	$n=6$
Methyl ethyl ketone (15.8)	$r=0.94$	$n=6$
Ethanol (24.3)	$r=0.98$	$n=8$
Methanol (32.8)	$r=0.97$	$n=7$
Dimethyl sulfoxide (46.7)	$r=0.98$	$n=6$
Water (80)	$r=0.99$	$n=6$

Potential energies (kcal/mol) of the docked pseudoreceptor complexes for a given dielectric condition; the last column corresponds to the ED_{50} values of the analgesic response. Only compounds with energies that agreed in rank order with their ED_{50} values were considered as successes and included in a correlation analysis. Below the energies, the correlation coefficients are listed for each condition with the number of compounds (n = number of successes) that rank ordered. All correlations were significant at the 0.01 criterion level.

[a] The energy was overestimated predicting that the structure is less potent.

[b] The energy was underestimated predicting that the structure is more potent.

shown by the spatial disposition of the amino acids themselves (as opposed to the ligands) after docking. Examination of all of the superimposed docked complexes in comparison to the DHMO complex revealed that the His and Phe components deviated slightly (total range = 1.6 Å) amongst the complexes. This was not suprising since most differences between the structures occur in the C ring. By contrast, the range of deviation for Lys between complexes was 5.34 Å with the highest for TMOR (6.1) and the lowest for DHCO (0.76). Figure 3 illustrates the effect of the B/C ring trans geometry on the spatial dispositions of the amino acids in comparison to DHCO. From Fig. 3, it can be seen that the trans geometry of the B and C rings imposes the 7,8-dedihydro bonds between the Lys and Asp residues. This imposition favors completely different orientations for these amino acids in comparison with the much more energetically favorable DHMO com-

plex. These steric differences in this pseudoreceptor model may translate to a steric hindrance in the real receptor in vivo. Additionally, the orientation of the DHMO complex favors greater electronic communication between the Asp, Lys and protonated amine of the ligand compared to the TMOR complex.

Asp deviations ranged at 2.28 Å with the greatest for GISM (2.6) and the least for PCOD (0.33). This finding was particularly interesting given that both compounds contain the 8-OH substituent which placed an additional H-bond donor in the vicinity of the carboxylate anion of Asp.

These findings illustrate several points. Most importantly, investigators developing QSAR models from mechanical force fields may wish to consider a range of dielectric influences on the electrostatic terms. In docking experiments, the dielectric influence on the electrostatic potential may influence steric components of the molecules. For example, the *n*-decane very low polarizable attenuation of electrostatic influence favored the stereoisomeric and geometric isomeric analogues ISOM and TMOR. However, a moderately polarizable (ethanol) influence on the Coulombic-like electrostatics seems to favor substituted species such as DCOD and DHCO. A possible explana-

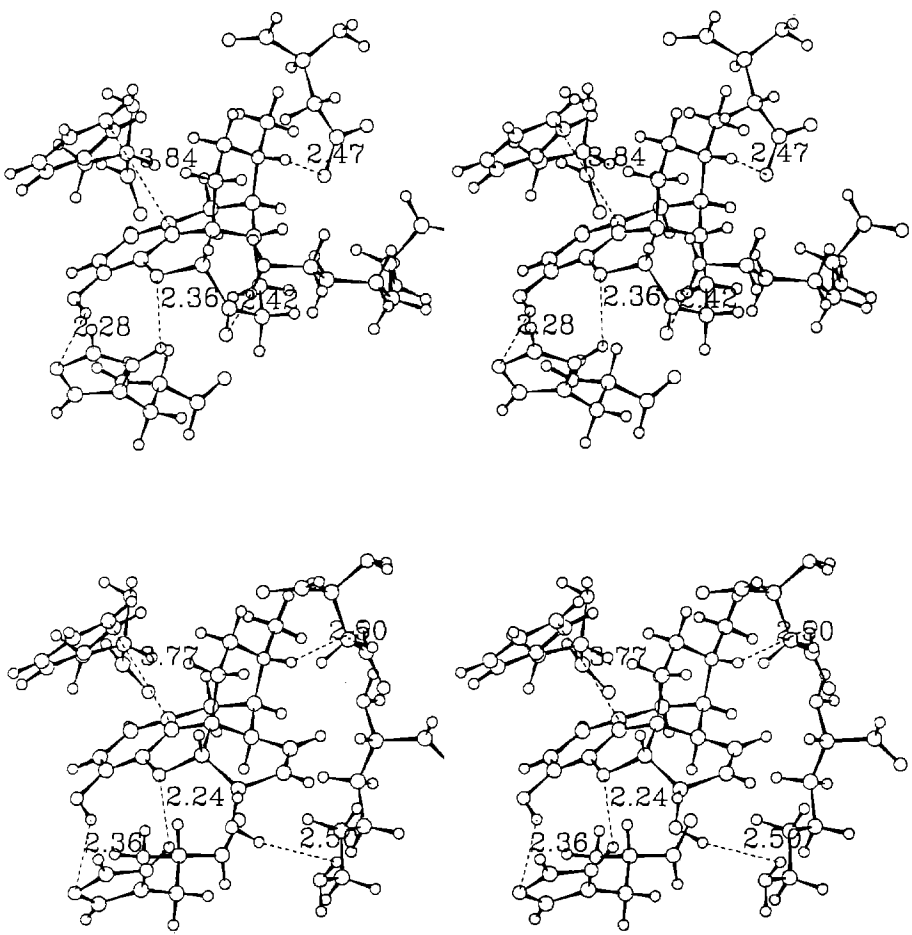


Fig. 3. Stereoview of DHMO (top) and TMOR (bottom) in Asp-Lys-His-Phe (top right, clockwise order) fully minimized pseudoreceptor pocket after docking.

tion for this finding can be reasoned if one first considers that a simple inversion (from R to S) of the OH group at the 6-position converts CMOR to ISOM. At a force-field level, the steric energies of these two compounds are equivalent. However, surrounding each ligand (during docking) by a pocket of amino acids, would tend to amplify intramolecular steric and electrostatic properties of compounds thereby enabling each to participate differently in nonbonded and electrostatic interactions. In a low polarizable medium such as *n*-decane, the attenuation of electrostatic influence between any two charged species is slight (compared to ethanol), which sensitized discrepancies between CMOR and ISOM. However, in substituted species that contain more polar hydrogens in various positions (such as DCOD and DHCO) perhaps a moderately polarizable dielectric prevents under- or overexaggerated interaction energies.

Implicit to these distance-dependent influences on the electrostatic terms of the nonbonded energy expression is a generalizable relationship that embodies many features of pharmacological action (e.g., kinetics, transport, diverse receptor subtype activation). Although our model related to the in vivo measurements of this congeneric series, future investigations employing this type of pseudoreceptor strategy may have greater success when specific receptor systems are modelled with corresponding in vitro binding affinity data. Since one of the main goals of the QSAR science is to develop predictable models, a pseudoreceptor model seems applicable, especially if it represents some of these generalizable properties. Moreover, our results indicate that force-field level molecular QSAR models would benefit from the fine-tuning of a specific dielectric influence. For example, Table 1 indicates that a blind acceptance of a vacuum distance-dependent dielectric would have been less productive. Further, although it is widely accepted that most protein interiors or active sites lie in a dielectric range between 2 to 5, it is clear that an a priori notion of these constants for electrostatic attenuation may not have been optimal. In this study, using an ethanol dielectric, which is well-placed between water and lipid, perhaps retained electrostatic influences of both solvents.

CONCLUSIONS

QSAR molecular mechanically based docking experiments depend heavily on nonbonded and electrostatic components of their molecular energy expressions. Of key importance to the steric and electronic components of ligand–pseudoreceptor interactions are the contributions due to electrostatic repulsion or attraction. Proper attenuation of these electrostatic properties by dielectric and distance-dependent influences may be one of the most critical features an investigator may employ to enhance the physicochemical relationship between the model and the pharmacological action.

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