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Conformation of six fentanyls revisited

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ABSTRACT

Conformation of fentanyl and its five derivatives was studied at the B3LYP/6-31G** level. Two stereoisomers for α-methyl-β-hydroxy fentanyl and four for the ohmefentanyl were taken into account. Conformation in the gas phase and water, simulated using the IEF-PCM and SMD implicit models of solvents, was independently optimized using 27 starting structures resulted from rotations about the most important three torsion angles. The role of the Grimme's D3 correction for the dispersion forces was additionally considered for each medium. The correction appeared to influence more the gas phase than water dissolved structures. Moreover, the correction influences more the conformations of N-phenylpropionamide group than those of the modified phenylethyl substituent. In water solution simulated by the IEF-PCM and SMD solvation models, the conformers connected to the phenylethyl moiety, are substantially different only for the two derivatives, for which indications coming from different computational variants are the most vague. However, for the conformers connected to the N-phenylpropionamide group, the IEF-PCM model favors the *t* conformation for three derivatives while SMD prefers sum of the g^+ and g^- conformations for the other three derivatives. For the ohmefentanyl stereoisomers, irrespectively, the solvation or presence of the D3 correction, all the methods concordingly predict the N-phenylpropionamide group conformation twisted by either −120° or to 120°.

1. Introduction

The fentanyl family of anesthesia-related drugs had been developed by Janssen and co-workers since early 1960s [1–7]. Fentanyl itself (N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylpropanamide) is a synthetic opioid analgesic, ca. 50–100 times more potent than morphine. It has a rapid onset [8] and short duration of action [9]. Its high lipid solubility enables a quick and efficient blood–brain barrier penetration accounting for its high potency. Compared to most opioids, it is a potent μ-opioid receptor agonist exhibiting relatively little effect on δ-and κ-opioid receptors [10].

Fentanyl is a core system for a class of synthetic opioid analgesic-medicines. Fentanyl, sufentanil [2], and alfentanil [3] are used in high doses as primary anesthetic agent in cardiac surgery, while in low doses they are used as supplements to general anesthesia in various surgical procedures [8]. Carfentanil [11] is an animal tranquilizer, 10,000 times more potent then morphine, used in ZOOs and wildlife management environments to rapidly incapacitate large hoofstock [12]. Remifentanil is a short-acting analgesic [13,14] used for release of intense pain of short duration, e.g., in patients undergoing electroconvulsive therapy.

Not all fentanyls are highly μ-selective, and could produce actions through δ- and κ-opiate receptors [15]. The highest μ-affinity analog, lofentanil, was found to be among the least selective, while another high affinity analog, carfentanil, was the most μ-selective [16]. Its ^{11}C isotopolog is used in positron emission tomography to quantify the μ-opioid receptors [17], yet, it has recently been shown that the carfentanil binding is preferential for μ_1 compared to μ_2 *in vitro* and *in vivo* [18]. Ohmefentanyl, with its three chiral centers, is a very potent and highly selective agonist for the μ-opioid receptors [19]. The (3*R*,4*S*,2′*S*)-(+)-*cis* stereoisomer is ca. 13,000 times more potent than morphine [19]. However, introduction of the isothiocyanato group reduced its activity and affinity to the μ- but enhanced selectivity for the δ-opioid receptors. The highest selectivity analgesic potency was exhibited by the (3*R*,4*S*,2′*R*)-ohmefentanyl isothiocyanate [20]. Also, the other chiral derivatives of ohmefentanyl exhibit significant stereospecificity [21].

Numerous different simple chemical modifications of fentanyl do not dramatically change the pharmacological profile of the derivatives. This property of the fentanyl core makes it attractive

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for new drug synthesis, but, simultaneously has aroused great interest of clandestine laboratories producing designer drugs [22]. The clandestinely produced designer drugs are now a worldwide problem. Among designer drugs the fentanyl derivatives represent a significant part. They belong to the piperidine class, together with pethidine, ketobemidone, and picenadol, but, with their 4-anilinopiperidine moiety are the most potent in the class [22]. The illicit use of fentanyl and its analogs is associated with risk of fatal overdose of substances of high, and sometimes even not characterized, potency.

One of key features determining interaction of a non-rigid ligand with receptor is ligand conformation. A change of conformation of a flexible molecule induces a change in most of the molecular parameters which are further affected by the environmental factors such as physical state, temperature, pressure, solvent and presence of other species. Therefore, importance of conformational studies cannot be overemphasized. This is especially true for biomacromolecules such as DNA, carbohydrates, lipids, and proteins but also shorter oligo-biopolymers and small but flexible bioactive ligands. Fentanyls, with their at least six single bonds may have ca. 10^6 of conformations. Therefore, the problem of building a reliable fentanyl pharmacophore and selecting bioactive fentanyl conformations have repeatedly focused research interest since mid 1980s [23–33]. Analysis of the conformational landscape often leads to discussion of a few conformers energetically close to the global minimum and, when experimental structural information on the appropriate receptor is missing, they are taken for building a pharmacophore, i.e., spatial distribution of molecular moieties important for a specified bioactivity. However, the conformation of a molecule at a biological target usually differs from that in the crystal structure and in calculated global minimum [34–36].

In this study we consider the same six fentanyl derivatives as studied twenty years ago by Došen-Mićović et al. [26] by using molecular mechanics (MM) followed by some PM3 calculations. The studied fentanyls differ in the N-phenylethyl moiety attached to the piperidine N-atom (Scheme 1). The MM study suggested that in all active fentanyl analogs, the phenylethyl side chain adopted only an extended conformation [26]. The flexibility of the phenylethyl side chain, was restricted by the presence of the hydroxyl group (**βOH**, **αMeβOH-I**, **αMeβOH-II**, Scheme 1). Moreover, after the hydroxyl substitution, the energetic distance between the global minimum and the receptor-recognized conformation was decreased. On the other hand, activities of the compounds substituted by an alkyl in the phenylethyl side chain (all but **FENT**, Scheme 1) correlated with their hydrophobicities. Water is the native environment for both medicines and receptors, therefore, here, its role was taken into account. In our work two implicit water models, IEF-PCM and SMD, were used. Dispersion forces play an important role for both molecular conformation and ligand-receptor recognition. Therefore, for the gas phase and water media role of the Grimme's D3 dispersion correction was examined, too.

2. Calculations

For each considered fentanyl derivative, a set of 27 starting conformations was generated by rotating θ_1 and θ_2 torsion angles by 120.0° and setting θ_3 to one of three values: −150.0°, 180.0° and 150.0° (Scheme 2). Conformations with θ_3 values ranging from 0.0° to 90.0° were not considered since it was previously found that they are energetically unstable and do not significantly contribute to fentanyls populations [23,26,27].

The conformers were minimized at the B3LYP/6-31G** level by using Gaussian 09 suite of programs [37]. The minimizations were performed with or without consideration of the Grimme's D3 empirical dispersion correction [38], and the solvent model in the IEF-PCM [39,40] or SMD [41] version. The following variants of the calculations were applied:

(a) vacuum (**VAC**),
(b) vacuum combined with D3 correction (**VAC-D3**),
(c) IEF-PCM water model (**PCM**),
(d) IEF-PCM water model with D3 correction (**PCM-D3**),
(e) SMD water model (**SMD**),
(f) SMD water model with D3 correction (**SMD-D3**).

The 27 starting structures were used for each type of calculations independently, so for each structure 162 independent optimizations were performed. All computational variants were followed by harmonic frequencies calculations to assure the true minima at the potential energy surface were obtained. In the case of convergence to the same minimum a duplicate structure was excluded. So were the transition structures indicated by imaginary frequencies. For every six computational variants, the Boltzmann populations of fentanyl derivatives were determined from the Gibbs free energies (25 °C, 1 atm).

It is known that most of routine DFT methods fails in estimating weak intermolecular dispersion interactions being a manifestation of electron correlation effects. A variety of approximations to the exchange–correlation term proposed in the last three decades increased the effectiveness and applicability of DFT methods to most chemical problems. However, local and gradient corrected local (semilocal) DFT fails to properly describe the dispersion interaction near the equilibrium geometry [42]. The strength of dispersion interactions decreases with ca. R^{-6}, where R is the distance between the interacting systems. They may be crucial not only for protein folding and intermolecular interactions but also for conformation of molecules in both protic and aprotic solvents.

A simple description of dispersion within DFT, the DFT-D scheme, relies on adding a constant, a pairwise additive, and an isotropic dispersive term accounting for the long range attraction which diminishes with R^{-6}. To overcome deficiencies of this oversimplified scheme, in 2006, Grimme published the DFT-D2 scheme in which the dispersion coefficients are connected to ionization potentials and the static polarizabilities of isolated atoms [43]. Next, the DFT-D2 method was improved in the DFT-D3 scheme of Grimme et al. [38]. In the DFT-D3 scheme, the coefficients to the R^{-6} term are dependent on the neighborhood of each atom and during optimization they continuously change along with environment changes. The DFT-D3 approach is satisfactorily accurate at practically the same computational cost as pure DFT [44].

The solute–solvent interactions, in the IEF-PCM method the solvent are mimicked by a dielectric continuum with dielectric constant ε surrounding a cavity with shape and dimension adjusted on the real geometric structure of the solute molecule. The latter polarizes the solvent which, as a response, induces an electric field (the reaction field) which interacts with the solute. In the IEF-PCM, the electrostatic part of such an interaction is represented in terms of an apparent charge density spread on the cavity surface.

In the SMD Solvation Model [41], where the "D" stands for "density" to denote that the full solute electron density is used without defining partial atomic charges, treatment of bulk electrostatics involves a cavity dispersion–solvent-structure protocol for the non-electrostatic contribution to the free energy of solvation. The SMD model employs a single set of parameters optimized over six DFT electronic structure methods. In the SMD model applicable to any solvent for which macroscopic descriptors may be estimated, water is treated as a special solvent that is given its own set of surface tension coefficients. It is important that the SMD parameters do not depend on charges, hybridization states, or classifications of other atoms as attached or unattached and thus there are no discontinuities when the model is applied along reaction paths.