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OXICAMS: COMPUTATIONAL THERMOCHEMICAL PARAMETERS AND SOLUBILITY

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ABSTRACT

The following eight oxicam structures were studied using theoretical methods, (DFT), and the Gaussian 09 program in the gaseous and aqueous phases: 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam. More specifically, the thermodynamic parameters, polarizability, and dipole moments of each molecule were studied. Molecules with higher amounts of unsaturated bonds and phenyl groups in their structures show increased electron delocalization, thereby increasing the diffusion of the electron clouds. 4-meloxicam, isoxicam, meloxicam, piroxicam,and normeloxicam presented μ values that equaled 2.8965, 3.2664, 2.1138, 2.6692, and 3.9705 Debye, respectively, and all of them share a formation of hydrogen bridges and lower values due to the dispersion of their charges as demonstrated by an increase in polarizability values. Furthermore, we observed that with an increasing solvent dielectric constant, the dipole moment of the molecules under study, both of which do not form hydrogen bonds, also increases. These increments are mainly seen in protic solvents, followed by aprotic solvents from most to least ε.

KEYWORDS: **Oxicams, Computational Nanochemistry, DFT**

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1. INTRODUCTION

Enol carboxamides with anti-inflammatory activity (i.e., also called oxicams) are a family of chemical compounds that belong to the non-steroidal anti-inflammatory drug (NSAID) group and are structurally characterized by a skeleton of 4-hydroxy-1,2-benzothiazines-3-carboxamide 1,1-dioxide. The anti-inflammatory activity of NSAIDs is based on the inhibition of prostaglan- din synthesis. Prostaglandins are substantially involved in the initiation and maintenance of the inflammatory process; more specifically, they increase vascular permeability and amplify the effects of other inflammatory mediators, such as kinins, serotonin, and histamine. Moreover, NSAIDs fight inflammation by also inhibiting cyclooxygenase (COX), i.e., a key enzyme in the pathway of prostaglandin synthesis and found in every tissue. NSAIDs cause inhibition of both forms of COX, i.e., COX-1 and COX-2. Because of their efficacy, NSAIDs are often the first drug of choice for treating mild inflammation [1–5]. Given the—previously described mode of action, the obvious principal targets for NSAIDs in terms of controlling inflammation are COX-1 and COX-2, which are membrane-associated enzymes. To bind with the targets these drugs must pass through the membrane, which constitutes the first level of interaction. Their interactions with membranes are expected to play a major role in guiding their interactions with COX [6]. NSAIDs also characteristically induce membrane fusion at a concentration relevant to the physiological concentration range [7]. The thermochemical and solubility parameters of NSAIDs are of fundamental interest because the pharmacological activity and ability to transfer through the membranes of cells depend on the respective thermochemical and solubility parameters [8–15]. In this work, the dipole moment, polarizability, thermochemical parameters, ΔGsolv, and solubility properties of a series of eight oxicams in different solvents were studied via Density Functional Theory (DFT) using M06 density functional and the CBSB7 and CBSB3 basis sets.

2. Theory and Computational Details

All computational studies were performed using Gaussian 09 [16, 17] series of programs with density functional methods as implemented in the computational package. The equilibrium geometries of the molecules were determined using the gradient technique. The vibrational frequencies and force constants were determined by computing the analytical frequencies on the stationary points that were obtained after the optimization to determine if they were the true minima. In order to calculate the molecular structure and properties of the studied systems, we have chosen the hybrid meta GGA density functional M06 [18], which consistently provides satisfactory results for several structural and thermodynamic properties [19, 20]. As previously mentioned, the basis sets used in this work are CBSB7 (i.e., equal to 6-311G(2d,d,p)) for the molecular structures and infrared spectra, and CBSB3 (i.e., equal to 6-311++G(2df,2p) on H-Ne, and 6-311++G(3d2f) on Na-Ar) [21, 22] for the other electronic properties. Solvation energies were computed using the SMD formalism [23], including the UAKS model and water, methanol, ethanol, 1,4- dioxane, dimethylsulfoxide (DMSO), and n,n-dimethylformamide (DMF) as solvents.

3. RESULTS AND DISCUSSION

The molecular structures of the eight oxicams considered in this study (i.e., 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxi- cam, piroxicam, and tenoxicam) are shown in Figure 1. The results for the calculation of the molecular dipole moments and the molecular polarizabilities of 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam in the gaseous phase with the M06 density functional and the CBSB3 basis set are presented in Table 1. Indeed, the atoms that constitute such molecules have different electronegativities such that when a covalent bond is created, the two bonding electrons are attracted to different strengths by atoms that share. The molecular

orbital loses its symmetry, and the probability of finding the electrons is greater in the vicinity of the more electronegative atom. Even so, it still retains the overall electrical neutrality; however, the more electronegative atom has a predominance of negative charge, and the less electronegative atom has a predominance of positive charge, which gives rise to the formation of a dipole. The magnitude of the dipole is defined by what is known as the dipole moment μ and is the product of the

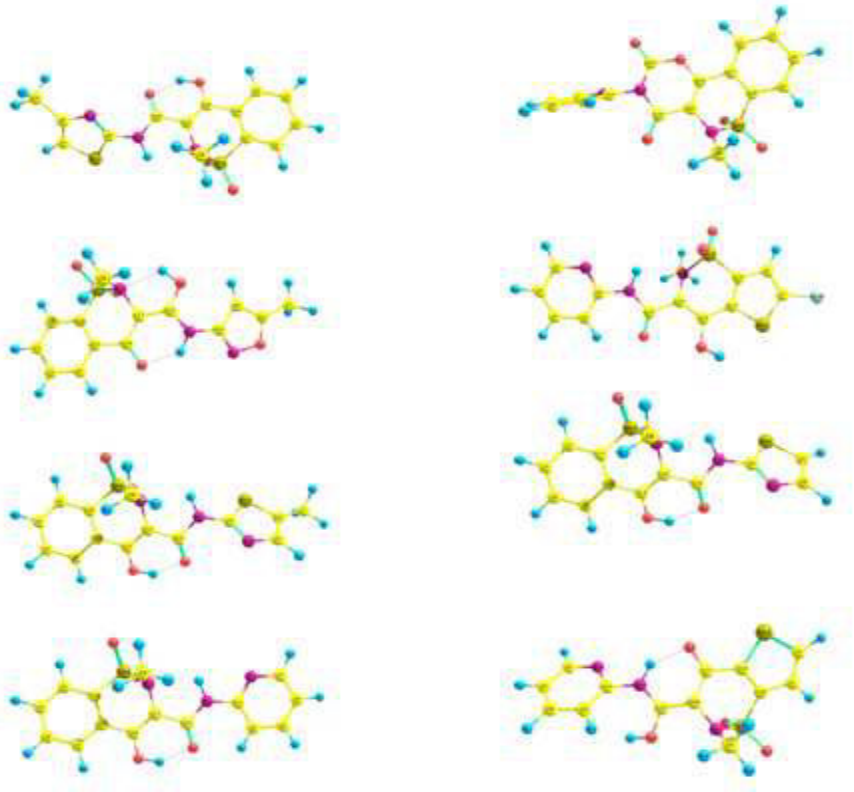

Figure 1

Molecular structures of the oxicams considered in this study: 4-meloxicam, piroxicam, isoxicam, lornoxicam, meloxicam, nomeloxicam, piroxicam, and tenoxicam

Table 1

Molecular dipole moments (in Debye) and molecular polarizabilities (in Bohr^3) for the oxicams in the gas phase calculated with the M06 density functional and the CBSB3 basis set

Molecule	Dipole Moment	Molecular Polarizability
4-meloxicam	2.8965	230.81
droxicam	5.4560	223.13
isoxicam	3.2664	216.36
lornoxicam	3.3696	240.52
meloxicam	2.1138	231.52
normeloxicam	2.6692	215.58
piroxicam	3.9705	225.41
tenoxicam	6.0761	226.58

fractional charge on each atom present and the distance that separates them. The charge separation in a covalent bond is greater as the difference in electronegativity between the atoms that form it, the polarity of the bond depends on the hybridization of the atoms making up the molecules under study as well as the molecular geometry. As previously mentioned, Table 1 shows the dipole moments of the molecules under study.The molecules that will not form hydrogen bonds are droxicam, lornoxicam and tenoxicam because they possess larger dipole moments (i.e., all the molecular charge contributes to the polarizabilities (α)). In contrast, 4- meloxicam, isoxicam, meloxicam, piroxicam,and normeloxicam have dipole moments (μ) of 2.8965, 3.2664, 2.1138, 2.6692, and 3.9705, respectively, and all of them demonstrate the formation of hydrogen-bonded bridges and lower values due to the dispersion of their charges as demonstrated by an increase in the polarizability values. This parameter expresses the ease with which the electron density of the molecule may be distorted by an external electric field. If the molecule has more unsaturated bonds and phenyl groups present in the structure, the electron density over those groups (i.e., electron delocalization) and the diffusion of electrons generally increases. A more diffuse electron cloud requires greater polarizability. The results for the calculation of the thermodynamic parameters of the 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam in the gaseous phase with the M06 density functional and the CBSB7 basis set are presented in Table 2. Note that the present study ranks the molecules in the following order according to their energy stability: lornoxicam, meloxicam and 4-meloxicam (i.e., they are equivalent in terms of energy stability), tenoxicam normeloxicam, droxicam, piroxicam, and isoxicam. Despite the unique pattern of stabilization, they all have only one electron delocalization stabilization and also π-type intermolecular forces for hydrogen-bonded bridges.The results for the calculation of the molecular dipole moments of the 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam in several solvents (i.e., water, methanol, ethanol, 1,4-dioxane, DMSO and DMF) with the M06 density

Table 2

Thermodynamic parameters (in Hartress) of the oxicams in the gas phase calculated with the M06 density functional and the CBSB7 basis set

Thermodynamic	4-Meloxicam	Droxicam	Isoxicam	Lornoxicam	Meloxicam	Normeloxicam	Piroxicam	Tenoxicam parameters (298.15 K)
SCF energy, E (Hartree)	-1802.42	-1554.41	-1479.39	-2222.69	-1802.42	-1763.12	-1442.33	-1763.10
Zero-point correction	0.263	0.256	0.266	0.226	0.263	0.236	0.270	0.235
(Hartree/particle)								
Thermal correction	0.283	0.276	0.286	0.246	0.284	0.254	0.288	0.254
to Energy								
Thermal correction	0.284	0.277	0.287	0.247	0.285	0.255	0.289	0.255
to Enthalpy								
Thermal correction to	0.212	0.207	0.217	0.175	0.212	0.187	0.289	0.187
Gibbs Free Energy								
Sum of Electronic and	-1802.16	-1554.16	-1479.13	-2222.46	-1802.15	-1762.89	-1442.06	-1762.86
zero-point Energies								
Sum of Electronic and	-1802.14	-1554.14	-1479.11	-2222.44	-1802.13	-1762.87	-1442.04	-1762.84
thermal Energies								
Sum of Electronic and	-1802.14	-1554.14	-1479.11	-2222-44	-1802.13	-1762.87	-1442.04	-1762.84
thermal Enthalpies								
Sum of Electronic and	-1802.21	-1.554.21	-1479.18	-2222.51	-1802.21	-1762.94	-1442.11	-1762.91
thermal Free Energies								

Table 3

Molecular dipole moments (in Debye) for the oxicams in several solvents calculated with the M06 density functional and the CBSB3 basis set

Molecule	Water	Methanol	Ethanol	1,4-Dioxane	DMSO	DMF
4-meloxicam	4.2623	4.2100	4.1452	3.3256	3.9188	3.9072
droxicam	8.5579	8.4128	8.2775	6.3511	7.9595	7.9226
isoxicam	5.1931	5.1000	5.0064	3.7706	4.7128	4.6916
lornoxicam	4.3470	4.3178	4.3011	3.6913	4.1607	4.1514
meloxicam	3.2808	3.2260	3.1638	2.4130	2.9763	2.9638
normeloxicam	4.0620	4.0077	3.9414	3.1155	3.7401	3.7278
piroxicam	5.8605	5.7803	5.7030	4.5087	5.4096	5.3905
tenoxicam	8.3545	8.2741	8.1886	6.8422	7.8836	7.8641

functional and the CBSB3 basis set are presented in Table 3.

The solvents used in this study can be divided into polar protic solvents and aprotic polar solvents. The polar protic solvents are water, methanol, and ethanol with dielectric constants (*e*) of 82, 33, and 24, respectively. The aprotic polar solvents are 1,4-dioxane; DMF, and DMSO with dielectric constants of 2.3, 47, and 38, respectively. We observed that as the solvent dielectric constant increases, the dipole moment of the molecules under study also increases, and both solvent dielectric constants and the dipole moments indicate that no hydrogen bonds will form. This increase in μ is seen mainly in protic solvents, followed by the aprotic solvents with the most to least *e*. The results for the calculation of the ΔGsolv of the 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam and tenoxicam as they are continuously updated with several solvents (i.e., water, methanol, ethanol, 1,4-dioxane, DMSO, and DMF) with the M06 density functional and the CBSB3 basis set are presented in Table 4. More specifically, Table 4 shows the free energy of solvation for the molecules under study with solvents with different dielectric constants, i.e., both protic and aprotic. One would expect a stabilization of molecules in solvents with a higher dielectric constant, but no clear pattern was observed. This can be attributed to the fact that solvation processes are thermodynamically favored only if the free energy of formation of the solution is less than the difference of ΔGsolvent - ΔGsolute. By comparing the dipole moments reported in Table 1, we can see that the molecule with the highest μ is tenoxicam. As such, tenoxicam can be involved in π-type interactions and hydrogen bonding electronic delocalization stabilization by changing the dielectric constant of the solvent. In fact, we observed that stabilization increases with protic solvents, such as water, methanol, and ethanol; yet, this trend is not observed in all cases.

4. CONCLUSIONS

The investigated molecules which have more unsaturated bonds and phenyl groups present in the structure show greater electron density over those functional groups (i.e., electron delocalization) and greater electron diffusion.

Table 4
∆Gsolv (in kcal/mol) for the oxicams in several solvents calculated with the M06 density functional and the CBSB3 basis set

Molecule	Water	Methanol	Ethanol	1,4-Dioxane	DMSO	DMF
4-meloxicam	-87.14	-89.08	-89.75	-83.43	-89.86	-91.47
droxicam	-93.10	-93.43	-94.37	-88.10	-95.74	-97.31
isoxicam	-86.94	-88.46	-89.29	-83.32	-89.51	-91.08
lornoxicam	-91.89	-94.22	-94.78	-86.95	-93.16	-94.74
meloxicam	-87.70	-89.50	-90.17	-83.83	-90.44	-92.03
normeloxicam	-86.06	-87.21	-87.85	-81.73	-88.36	-89.84
piroxicam	-81.37	-83.16	-84.03	-80.01	-85.00	-86.67
tenoxicam	-90.04	-90.61	-91.11	-82.54	-89.74	-91.20

A more diffuse electron cloud requires greater polarizability. Furthermore, 4 meloxicam, isoxicam, meloxicam, piroxicam,and normeloxicam have dipole moments (μ) of 2.8965, 3.2664, 2.1138, 2.6692, and 3.9705, respectively, and all of them form hydrogen bridges and have lower dipole moments due to the dispersion of their charges as demonstrated by the increase in their polarizability values. Note that the present study ranks the molecules in the following order according to their energy stability: lornoxicam, meloxicam and 4-meloxicam (i.e., they are equivalent in terms of their energy stability), tenoxicam, normeloxicam, droxicam, piroxicam, and isoxicam. They all have only one electron delocalization stabilization and also π-type intermolecular forces forming hydrogen-bonded bridges. We observed that as the solvent dielectric constant increases the dipole moment of the molecules under study increase as well, and neither indicated the ability to form hydrogen bonds. This increment in μ is seen mainly in protic solvents, followed by aprotic solvent followed from most to least *e*. Also, there is a trend to regulate the ∆Gsolv, which can be attributed to the fact that solvation processes are thermodynamically favored only if the free energy of formation of the solution is less than the difference of ∆Gsolvent - ∆Gsolute.

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