# Structures, Lipophilicity, Dipole Moments, Acidity and Spectroscopic Properties of Non-Steroidal Anti-Inflammatory Drugs Diclofenac, Bromfenac and Amfenac: A Theoretical Study

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## Abstract

This work is a contribution of theoretical chemistry to the classification of some non-steroidal anti-inflammatory drugs (NSAIDs). Indeed, research on the efficacy of NSAIDs has shown that no NSAID is recognized as the most efficient anti-inflammatory drug. We have made a theoretical study of diclofenac, bromfenac and amfenac, in order to compare their efficacy from some physicochemical properties. To do this, we used the DFT and TD-DTF methods at the B3LYP/6-311+G(d, p) level theory. The lipophilicity study shows that diclofenac and bromfenac are very lipophilic. Acidity study shows that diclofenac is more acid than bromfenac and amfenac. The results from molecular orbital and the TD-DFT calculations reveal that for the three NSAIDs, the lowest energy transition is due to the excitation from HOMO to LUMO. The absorption energy corresponding to H→L transition is comparable with the energy gap value. Our findings have shown that bromfenac is more reactive than amfenac, which is more reactive than diclofenac.

## 1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a set of molecules that have anti-inflammatory, antipyretic and analgesic properties [1] [2]. They are often indicated for treating postoperative pain for surgeries with a predominant

inflammatory component such as dental surgery, stomatological surgery, maxillofacial surgery, orthopedic surgery and ocular surgery [3] [4] [5] [6]. Indeed, postoperative inflammation is a common condition that can lead to significant complications and to avoid these complications, ophthalmologists commonly use non-steroidal anti-inflammatory drugs. Particularly, in the processes of angiogenic retinal diseases including age-related macular degeneration (AMD) [7], inflammation plays a substantial role. In the field of the treatment of these diseases, NSAIDs are associated with anti-vascular endothelial growth factor (VEGF). That combination of NSAIDs with anti-VEGF significantly reduces the treatment burden of anti-VEGF agents.

Bromfenac, diclofenac and amfenac are the commonly used NSAIDs. Bromfenac is 2-amino-3-(4-bromobenzoyl) phenylacetic acid. It is an NSAID that is widely used as an ophthalmic solution for the treatment of ocular inflammation and pain after cataract surgery and inflammatory diseases of external eye segments [8] [9]. Recent studies have shown that bromfenac inhibits laser-induced choroidal neovascularization in rats [10]. Gomi *et al.* have reported in humans that the use of topical bromfenac may reduce the frequency of intravitreal injections of Ranibizumab [11]. Although bromfenac has good intraocular penetration in humans [12], the relationship between its efficacy and pharmacokinetics has not been determined [13]. This led Tetsuo et al to determine the drug levels of bromfenac, diclofenac, and amfenac in the retinochoroidal tissues of rabbits by liquid chromatography-tandem mass spectrometry (LC-MS/MS) [14]. Their studies' findings showed that bromfenac has a stronger inhibitory activity on COX-1 or COX-2 than amfenac or diclofenac. However, there is no theoretical data that can confirm these results.

Verification of these experimental results remains at the center of our team's concerns. The present research aims to investigate the structure, lipophilicity, dipole moment, stability, acidity, and spectroscopic properties of diclofenac, bromfenac and amfenac. This would allow to know their mode of action and to design derivatives with more efficacies. To do this, we use DFT [15] [16] and TD-DFT [17] [18] methods with the B3LYP functional.

## 2. Methods of Calculation

Calculations on the ground state geometries are carried out with DFT (B3LYP functional) using 6-311+G(d,p) basis set [15] [16]. The absorption spectrum are calculated using TD-DFT method at B3LYP/6-311+G(d,p) level of theory [17] [18]. The ground state optimization and spectral calculations are carried out in gas and aqueous phases and using Tomasi's conductor-like polarizable continuum model (CPCM) [19]. The Gibbs free energies are obtained from the calculation of the frequencies. Frequency analyses were proceeded to confirm the structure being a minimum or a transition state (*i.e.* without or with solely an imaginary frequency). These calculations are carried out with the GAUSSIAN-09 program [20]. The freeware ACD/ChemSketch is used for LogP calculation.

## 3. Results and Discussions

Generally, the absorption of drugs through the cornea is dependent upon their physicochemical properties. The results concern the lipophilicity, the dipole moment, the acidity, and the spectroscopic properties of diclofenac, bromfenac and amfenac. Previously, they focus on their structures. These results will allow making a comparison of their efficacy.

### 3.1. Structures

The important structural parameters of diclofenac, bromfenac and amfenac are those of the carboxylic group (Figure 1). The calculated values are in Table 1.

In the gas phase, the length of the O-H bond is 0.970 Å in all the molecules. The single C-O bond is 1.355 Å in bromfenac. It is 0.001 Å longer in amfenac and 0.003 Å longer in diclofenac. The length of the C=O double bond is 1.204 Å in the three molecules. The bond angle HO-C=O, is 122.6° in bromfenac and amfenac; it is 0.2° shorter in diclofenac. In the aqueous phase, the O-H and C=O bonds remain identical for the three molecules. The O-H bond is 0.971 Å and the C=O bond is 1.210 Å. They increase by 0.001 Å and 0.006 Å respectively compared to the gas phase. The C-O single bond is 1.347 Å in bromfenac and amfenac and 1.348 Å in diclofenac. This bond is thus shortened in the aqueous phase. The bond angle HO-C=O, increases in the aqueous phase; it is 122.7° in bromfenac and amfenac and 122.6° in diclofenac. The chemical structures of bromfenac and amfenac are structurally identical with the exception of a bromine atom at the C4 position (Figure 1); the structural parameters are not affected by the substitution.

### 3.2. Lipophilicity and Dipole Moments

Lipophilicity is important in the design of a drug. It allows knowing if the molecule is more likely to be hydrophilic, or more likely to be lipophilic. It has often been used as a criterion for comparing several drugs [21] [22] [23]. We have used the freeware ACD/ChemSketch to calculate the LogP. Calculated lipophilicity (LogP) parameters and dipole moments are shown in Table 2.

The LogP value of diclofenac is 4.06, that of bromfenacis 2.73 and that of amfenac is 1.78. The three NSAIDs are lipophilic; however diclofenac and bromfenac are very lipophilic. The values of the dipole moment in the gas phase show
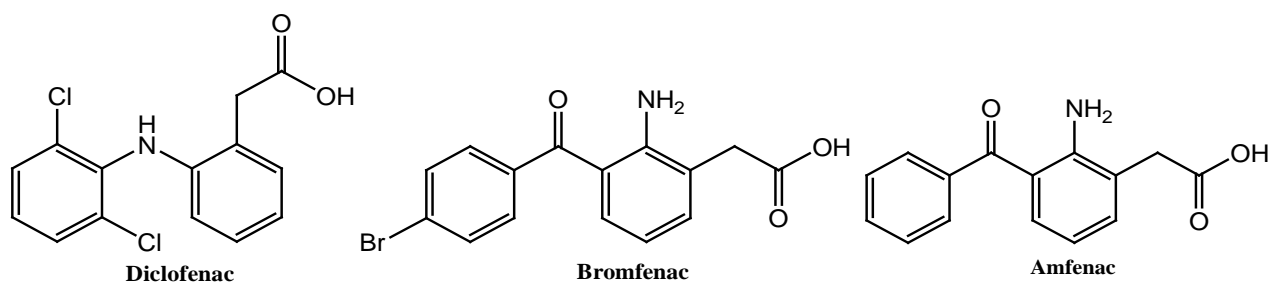


**Figure 1.** Chemical structures of diclofenac, bromfenac and amfenac.

Table 1. Geometrical parameters (bond length in Å, angle in degrees) in gas and aqueous phases.

| Parameters | Gas phase | | | Aqueous phase | | |
|:---:|:---:|:---:|:---:|:---:|:---:|:---:|
| | Diclofenac | Bromfenac | Amfenac | Diclofenac | Bromfenac | Amfenac |
| O-H | 0.970 | 0.970 | 0.970 | 0.971 | 0.971 | 0.971 |
| C-O | 1.358 | 1.355 | 1.356 | 1.348 | 1.347 | 1.347 |
| C=O | 1.204 | 1.204 | 1.204 | 1.210 | 1.210 | 1.210 |
| HO-C=O | 122.4 | 122.6 | 122.6 | 122.6 | 122.7 | 122.7 |

Table 2. Calculated and experimental lipophilicity (LogP) parameters and dipole moments ($\mu$).

| Compounds | LogP | $LogP_{Exp}$ | $\mu_{gas}$ (D) | $\mu_{aqueous}$ (D) |
|:---:|:---:|:---:|:---:|:---:|
| Diclofenac | 4.06 ± 0.41 | 4.51[a] | 2.65 | 3.97 |
| Bromfenac | 2.073 ± 0.61 | 3.4[b] | 2.25 | 3.35 |
| Amfenac | 1.78 ± 0.59 | | 1.39 | 2.25 |

[a] https://www.drugbank.ca/drugs/DB00586; [b] https://www.drugbank.ca/drugs/DB00963.

that diclofenac, possess the highest value of dipole moment (2.65 D) and bromfenac with a dipole moment of 2.25 D is more polar than amfenac (1.39 D). Thus the substitution of bromine at the C4 position of amfenac increases the dipole moment. These values increase clearly in aqueous phase. This result is in good agreement with that of the lipophilicity. The preceding results make it possible to discuss the acidity of NSAIDs because lipophilicity, polarity and acidity are related.

## 3.3. Acidity

It is known that most of the anti-inflammatory drugs are carboxylic acids in which the carboxylic group is available for metal-ligand interactions [24] [25]. Indeed, the carboxylic acid group is ionizable at physiological pH. The anionic charge allows anchoring of the NSAID in the catalytic site by establishing an electrostatic interaction with a positively charged cox enzyme residue. It is important to know their acidic characteristics. The gas phase energy $\Delta G$ of the proton abstraction can helps to evaluate the acidity [26]. It may be calculated from the following equations:

$$AH \rightarrow A^- + H^+. \tag{1}$$

$$\Delta G = G(A^-) + G(H^+) - G(AH) \tag{2}$$

In gas phase, $G_g(H^+) = 2.5RT - T\Delta S = 1.48 - 7.76 = -6.28$ kcal/mol [27] [28]. This method has been used to determine the acidity of several molecules [29] [30] [31] [32]. **Table 3** presents the results of the calculations. The weaker $\Delta G$ is, the more the oxygen atom is acidic. Under these conditions, in the gas phase, diclofenac is more acid than bromfenac and amfenac. This result agrees with lipophilicity and dipole moments.

Table 3. Gas phase acidity: ΔG (kJ/mol).

| Compounds | $G_g$ (au) | $\Delta G_g$ (KJ/mol) |
|---|---|---|
| Diclofenac | −1665.80756 | |
| Diclofenac (O-anion) | −1665.144766 | 1712.2 |
| Bromfenac | −3433.469536 | |
| Bromfenac (O-anion) | −3432.805887 | 1714.5 |
| Amfenac | −859.913231 | |
| Amfenac (O-anion) | −859.250338 | 1712.5 |

## 3.4. Spectroscopic Properties

In this part, we analyzed the frontier molecular orbitals and absorption properties.

### 3.4.1. Frontier Molecular Orbitals (FMOs)

Frontier molecular orbitals (FMOs) known as highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) respectively, plays a vital role in chemical reactions of any molecule, as well as absorption spectra [33] [34]. According to Koopman's theorem [35] associated within the framework of HF self-consistent field molecular orbital theory, the ionization energy (I) and electron affinity (A) can be stated through HOMO and LUMO orbital energies as:

$$I = -E_{HOMO} \tag{3}$$

$$A = -E_{LUMO} \tag{4}$$

Higher HOMO energy is corresponds to the more reactive molecule in the reactions with electrophiles, while lower LUMO energy is essential for molecular reactions with nucleophiles [36]. Therefore, hardness of any materials is corresponds to the gap between the HOMO and LUMO orbitals. It clearly indicates that if the HOMO-LUMO energy gap is larger than molecule will be harder [37] [38]. The Hardness ($\eta$) of a molecule is calculated by:

$$\eta = \frac{1}{2}\left(E_{LUMO} - E_{HOMO}\right) = \frac{1}{2}\left(\Delta E\right) = \frac{1}{2}\left(I - A\right) \tag{5}$$

The calculated values of $\Delta E$ and $\eta$ are presented in Table 4. In gas phase, the energy gap of bromfenac is 3.93 eV followed by amfenac at 4.00 eV and diclofenac at 4.91 eV. Bromfenac is therefore more reactive than amfenac followed by diclofenac. Indeed more $\Delta E$ is small more the molecule is reactive. The energy gap values decrease in aqueous phase for the three molecules. These molecules are more reactive in aqueous solution. Furthermore, bromfenac has a chemical hardness value of 1.96 eV followed by amfenac with a value of 2.00 eV and diclofenac with a value of 2.45 eV. These values suggest that bromfenac is less hard than amfenac followed by diclofenac. The same observations are made in aqueous phase. In general, halogenation enhances the potency of medicinal compounds ($Br^- \sim I^- > Cl^- > F^- > H$) [39]. This confirms our results.

**Table 4.** Molecular orbital energies ($E_{HOMO}$, $E_{LUMO}$), energy gap $\Delta E$ and hardness $\eta$ (eV).

| Compounds | Gas phase | | | | Aqueous phase | | | |
|---|---|---|---|---|---|---|---|---|
| | $E_{HOMO}$ | $E_{LUMO}$ | $\Delta E$ | $\eta$ | $E_{HOMO}$ | $E_{LUMO}$ | $\Delta E$ | $\eta$ |
| Diclofenac | −6.092 | −1.187 | 4.91 | 2.45 | −6.109 | −1.128 | 4.980 | 2.49 |
| Bromfenac | −6.149 | −2.215 | 3.93 | 1.96 | −6.112 | −2.232 | 3.880 | 1.94 |
| Amfenac | −6.038 | −2.038 | 4.00 | 2.00 | −6.091 | −2.152 | 3.940 | 1.97 |

### 3.4.2. Absorption Properties

The spectral studies of diclofenac, bromfenac and amfenac have been performed using TD-DFT at B3LYP/6-311+G(d,p) level of theory in gas and aqueous phases. TD-DFT is a reliable method for the excited state computation [40] [41] that provide accurate results. To obtain the nature and energy of the singlet-singlet electronic transition, the prediction of the first 3 excited states are performed. The calculated absorption energy, corresponding oscillator strength and orbital coefficients are summarized in Table 5. The results show that for all the molecules, the lowest energy transition is due to the excitation of electron from HOMO to the LUMO. The absorption maxima ($\lambda_{max}$) of the three molecules, diclofenac, bromfenac and amfenac correspond to the H→L transition. In gas phase, the absorption maxima ($\lambda_{max}$) of bromfenac is 7 nm greater than that of amfenac. This means that replacing a hydrogen atom with a bromine atom is accompanied by a bathochromic effect that decreases the absorption energy. Thus for the absorption maxima, the energy of bromfenac (3.36 eV) is smaller than that of amfenac (3.42 eV) which is smaller than that of diclofenac (4.20 eV).

The absorption intensity is directly related with the dimensionless oscillator strength and the dominant absorption bands are the transitions with higher oscillator strength value [36]. Figure 2 shows the variation of the absorption energies in gas and aqueous phases as a function of the oscillator strength. In gas phase, the absorption spectrum of diclofenac has one peak observed at 4.36 eV (284 nm), it is associated with the H(HOMO)→L+1(LUMO+1) transition. The absorption spectrum of bromfenac has two peaks, the maximum peak is observed at 4.39 eV (282 nm) associated with H-1→L transition and second peak at 3.36 eV (369 nm) corresponding to H→L transition. For amfenac, the absorption spectrum has one peak observed at 3.42 eV (362 nm), is associated with the H→L transition. It has been observed that for all the studied molecules, the absorption wavelength calculated in gas phase and in aqueous phases is nearly similar and the maximum variation is only around 9 nm. Thus the solvent influences little the absorption spectrum. For diclofenac and bromfenac, we observe the same number of peaks with the same transitions. For amfenac we can observe a second peak at 4.479 eV (277 nm) which is associated with the H-2→L transition. In general, the absorption energies of bromfenac are lower than those of amfenac, which are themselves lower than those of diclofenac. It is interesting to note that the absorption energy corresponding to H→L transition is comparable with the energy gap value. The molecule with a small H→L energy gap possess

**Table 5.** Absorption energy (nm and eV) and oscillator strengths f (a.u.) of diclofenac, bromfenac and amfenac calculated at TD-B3LYP/6-311+G(d,p) level of theory in gas and aqueous phases.

| Compounds | Gas phase | | | Aqueous phase | | |
|---|---|---|---|---|---|---|
| | Orbital transitions | Absorption energy | Oscillator strength | Orbital transitions | Absorption energy | Oscillator strength |
| | | nm | eV | f (a.u.) | | nm | eV | f a,u. |
| Diclofenac | H→L (0.678) | 295 | 4.200 | 0.015 | H→L (0.659) | 291 | 4.257 | 0.019 |
| | H→L+1 (0.690) | 284 | 4.363 | 0.282 | H→L+1 (0.672) | 286 | 4.339 | 0.331 |
| | H→L+2 (0.639) | 262 | 4.739 | 0.007 | H→L+2 (0.617) | 265 | 4.687 | 0.024 |
| Bromfenac | H→L (0.695) | 369 | 3.362 | 0.153 | H→L (0.698) | 377 | 3.291 | 0.194 |
| | H-3→L (0.438) | 328 | 3.775 | 0.002 | H-1→L (0.440) | 323 | 3.834 | 0.007 |
| | H-1→L (0.513) | 282 | 4.394 | 0.261 | H-1→L (0.499) | 283 | 4.374 | 0.291 |
| Amfenac | H→L (0.691) | 362 | 3.423 | 0.133 | H→L (0.697) | 371 | 3.343 | 0.175 |
| | H-1→L (0.590) | 328 | 3.781 | 0.001 | H-1→L (0.567) | 323 | 3.840 | 0.001 |
| | H→L+1 (0.557) | 274 | 4.520 | 0.006 | H-2→L (0.579) | 277 | 4.479 | 0.035 |
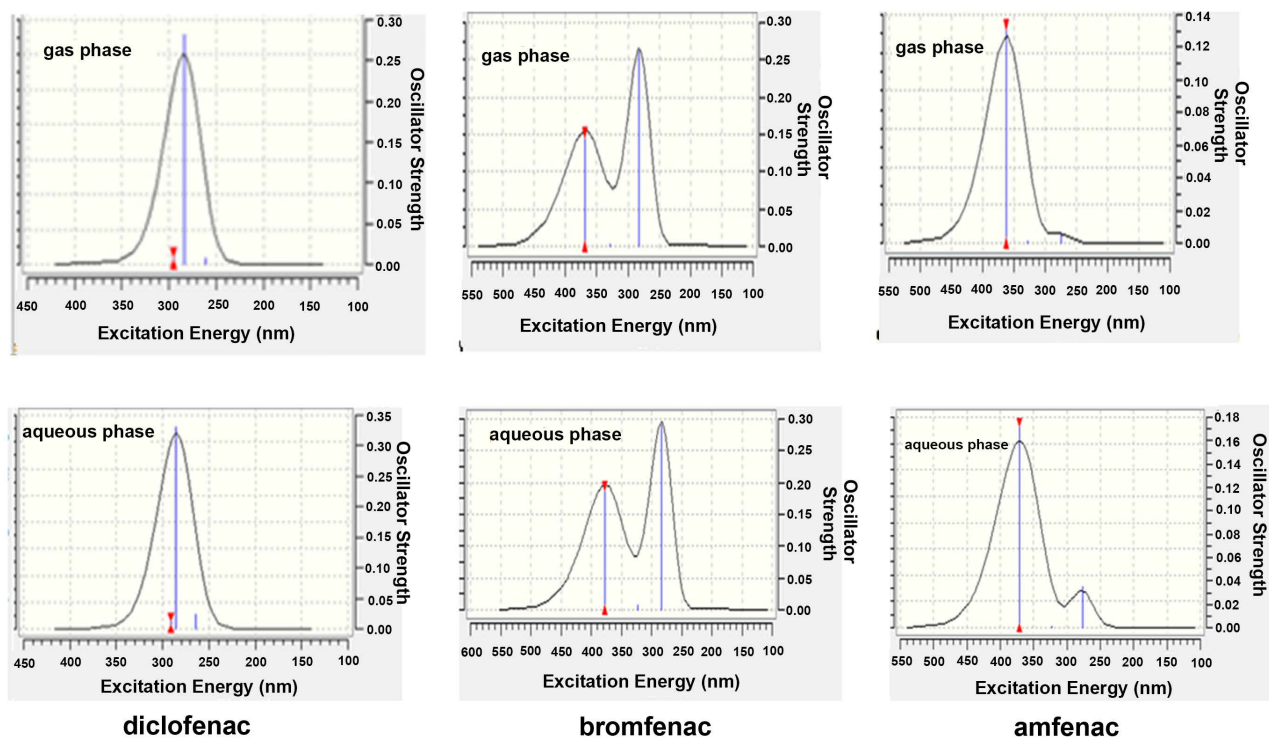


**Figure 2.** Absorption spectra of diclofenac, bromfenac and amfenac.

maximum absorption wavelength. This means that bromfenac is effectively more reactive than amfenac followed by diclofenac. This result is in agreement with experimental studies of Led Tetsuo *et al.* that have shown that bromfenac had a stronger inhibitory activity on COX-1 or COX-2 than amfenac or diclofenac [14]. It is also compatible with earlier reports [42] [43] [44] [45].

## 4. Conclusion

We have studied some physicochemical properties of diclofenac, bromfenac and amfenac using the DFT and TD-DFT methods. The study of the structures of diclofenac, bromfenac and amfenac reveals a slight variation in the values of the geometrical parameters of the carboxylic group. The lipophilicity study shows that, diclofenac and bromfenac are very lipophilic. The evaluation of the polarity through the dipole moment shows that diclofenac is more polar than bromfenac followed by amfenac. The dipole moments increase with the polarity of the medium. In terms of acidity, research establishes that in the gas phase, diclofenac is more acid than bromfenac and amfenac. The energy gap indicates that bromfenac is more reactive than amfenac followed by diclofenac. This result is confirmed by that of TD-DFT calculations. Indeed TD-DFT calculations show that for the three NSAIDs, the lowest energy transition is due to the excitation from HOMO to LUMO. The absorption energy corresponding to H→L transition is comparable with the energy gap value. Moreover, this work opens new perspectives; in particular, its results could help to establish a classification of efficacy of NSAIDs.

## Acknowledgements

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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