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ORIGINAL ARTICLE

Investigation of naproxen drug using mass spectrometry, thermal analyses and semi-empirical molecular orbital calculation

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Abstract Naproxen ($C_{14}H_{14}O_3$) is a non-steroidal anti-inflammatory drug (NSAID). It is important to investigate its structure to know the active groups and weak bonds responsible for medical activity. In the present study, naproxen was investigated by mass spectrometry (MS), thermal analysis (TA) measurements (TG/DTG and DTA) and confirmed by semi empirical molecular orbital (MO) calculation, using PM3 procedure. These calculations included, bond length, bond order, bond strain, partial charge distribution, ionization energy and heat of formation (ΔH_f). The mass spectra and thermal analysis fragmentation pathways were proposed and compared to select the most suitable scheme representing the correct fragmentation pathway of the drug in both techniques. The PM3 procedure reveals that the primary cleavage site of the charged molecule is the rupture of the COOH group (lowest bond order and high strain) which followed by CH_3 loss of the methoxy group. Thermal analysis of the neutral drug reveals a high response to the temperature variation with very fast rate. It decomposed in several sequential steps in the temperature range 80–400 °C. These mass losses appear as two endothermic and one exothermic peaks which required energy values of 255.42, 10.67 and 371.49 J g^{-1} respectively. The initial thermal ruptures are similar to that obtained by mass spectral fragmentation (COOH rupture). It was followed by the loss of the methyl group and finally by ethylene loss. Therefore, comparison between MS and TA helps in selection of the proper pathway representing its fragmentation. This comparison is successfully confirmed by MO-calculation.

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1. Introduction

Naproxen (NAP) has an IUPAC name, 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (s)-(+)-(s)-6-methoxy-α-methyl-2-naphthaleneacetic acid (States Pharmacopoeia, 2004; Haque

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et al., 2010) and a general formula ($C_{14}H_{14}O_3$). It belongs to a group of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). It works by reducing hormones that cause inflammation and pain in the body. Naproxen is used to treat pain or inflammation caused by conditions such as arthritis, ankylosing spondylitis, tendinitis, bursitis, gout, or menstrual cramps (Mura et al., 2002; Kosaka et al., 1994; Larsen and Mc Ewen, 1998).

Mass spectrometry (MS) is one of the most powerful analytical techniques, particularly for pharmaceutical analysis, where good selectivity and high sensitivity are often needed. In the pharmaceutical industry measurements of drugs and their metabolites in plasma are essential for drug discovery and development. The more accurate and rapid measurements, is the more quickly a drug can progress toward regulatory approval. Time-of-flight mass spectrometer (TOF-MS) delivers high sensitivity, resolution, and exact mass measurements. A variety of ion source and software options makes MS a versatile choice for a range of analytical challenges (Karatasso et al., 2007; Jayasimhulu et al., 2006; Han et al., 2006; Delong et al., 2001; Koivusalo et al., 2001).

Thermal analysis techniques can provide important information regarding storage and stability of pharmaceuticals. Thermal analysis methods have thus become important tools for the development of modern medicines (Kulp et al., 2004; Barbas et al., 2007; Sovizi, 2010; Picker-Freyer, 2007; Santos et al., 2008). These are precise and accurate techniques with low sample requirements, and can provide detailed information about new chemical entities even at the very earliest stages of discovery and development of the new compositions and drugs (Michalik et al., 2008; Cooks et al., 1973; Lever and Papadaki, 2004; Levsen, 1978). Thermogravimetric TG/DTG analysis is used to provide quantitative information on weight losses due to decomposition and/or evaporation of low molecular materials as a function of time and temperature. In conjunction with mass spectrometric analysis (Bourcier and Hoppiliard, 2003; Fahmey et al., 2001; Zayed et al., 2010, 2012a), the nature of the released volatilize may be deduced, thus greatly facilitating the interpretation of thermal degradation processes. On the other hand, computational quantum chemistry can provide additional information about the atoms and bonds, which can be used successfully in an interpretation of experimental results (Somogyi et al., 1991). Application of computational quantum chemistry in addition to experimental results (MS and TA) gives valuable information about the atoms and bonds which helps in the description and prediction of primary fragmentation site of drug cleavage and the subsequent one (Zayed et al., 2005, 2006, 2007, 2012b).

The aim of the present work is focusing on further application of our previous work (Zayed et al., 2005, 2006, 2007, 2012b) in the case of naproxen drug. This work includes a correlation between, mass spectral fragmentation and thermal analysis degradation of the drug and comparing these experimental data with the theoretical molecular orbital (MO) calculation to identify the weakest bonds ruptured during both mass and thermal studies. Consequently the choice of the correct pathway of such fragmentation knowing this structural session of bonds can be used to decide the active sites of the drug responsible for its chemical, biological and medical reactivity.

2. Experimental

2.1. Materials

All chemicals used were of analytical reagent grade (AR), and of highest purity available. They included naproxen (NAP, M.wt = 230.26 g mole), as an authentic sample which was kindly supplied by the Egyptian Drug Control Authority (EDCA), Cairo (Egypt).

2.2. Mass spectrometry (MS)

Electron ionization (EI) mass spectrum of naproxen is obtained using Thermo Finnegan TRACE DSQ quadruple mass spectrometer with electron multiplier detector equipped with GC–MS data system at the Cairo University micro-analytical center. The direct probe (DP) for solid material was used in this study. The sample was put into a glass micro vial, by a needle (≈1 μg max), the vial was installed on the tip of the DP containing heating cable and inserted into the evacuated ion source. The sample was ionized by an electron beam emitted from the filament, the generated ions being effectively introduced into the analyzer by the focusing and extractor lenses system. The MS was continuously scanned and the obtained spectra were stored. Electron ionization mass spectra were obtained at ionizing energy value of 70 and 12 eV, ionization current of 60 μA and vacuum is better than 10^{-6} torr.

2.3. Thermal analyses (TA)

The thermal analyses of naproxen drug were performed using conventional thermal analyzer (Shimadzu system of DTA-50 and 30 series TG-50) at the Cairo University micro-analytical center. The mass losses of 5 mg sample and heat response of the change of the sample were measured from room temperature up to 600 °C. The heating rate, in an inert argon atmosphere, was selected as 10 °C min^{-1}. These instruments were calibrated using an indium metal as a thermal stable material. The reproducibility of the instrument reading was determined by repeating each experiment more than twice.

2.4. Computational method

The MO calculations were performed using semi-empirical molecular orbital calculation. The method used in these computations is the parametric method (PM3) described by Stewart (1989). The default criteria for terminating all optimizations were increased by a factor of 100 (keyword PRECISE). Vibrational frequencies were computed for the studied structures (keyword FORCE) so as to check whether the newly designed geometries are local minima. All the molecular orbital calculations were carried out at the restricted Hartree–Fock level (RHF) for the neutral molecule of naproxen while the unrestricted Hartree–Fock level (UHF) was carried out for its cation by using the PM3 method followed by full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles), without any symmetry constraint. All structures were optimized to a gradient norm 0.01–0.05, using the eigenvector following the EF routine (Baker, 1986). All the semi empirical MO calculations were performed with the

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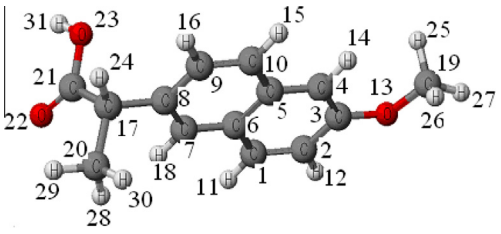


Figure 1 The geometrical structure of Naproxen and its numbering system.

MOPAC2000 software package (Stewart, 1999) implemented on an Intel Pentium IV 3.0 G Hz computer.

3. Results and discussion

It is of great interest to study the chemistry and reactivity of naproxen drug because of its importance in medicine. The geometrical structure of NAP and its numbering system is shown in Fig. 1.

Knowledge obtained from thermal decomposition mechanisms of the neutral drug is very important to understand the chemical process that is shared in biological systems. It is difficult to establish the exact major fragmentation pathway in EI using conventional MS. With combining the above two techniques and the data obtained from the MO calculation, it is possible to understand the following topics:

1. Stability of the drug under thermal degradation in solid state and mass spectral fragmentation in gas phase.
2. Prediction of the primary site of fragmentation and subsequent bond cleavage.
3. The correct pathway in both techniques.
4. Understanding what actually happened in biodegradation of the drug or its derivatives in vivo system and metabolites.
5. Thermal stability of the drug was a required information for handling, strength and shelf life.

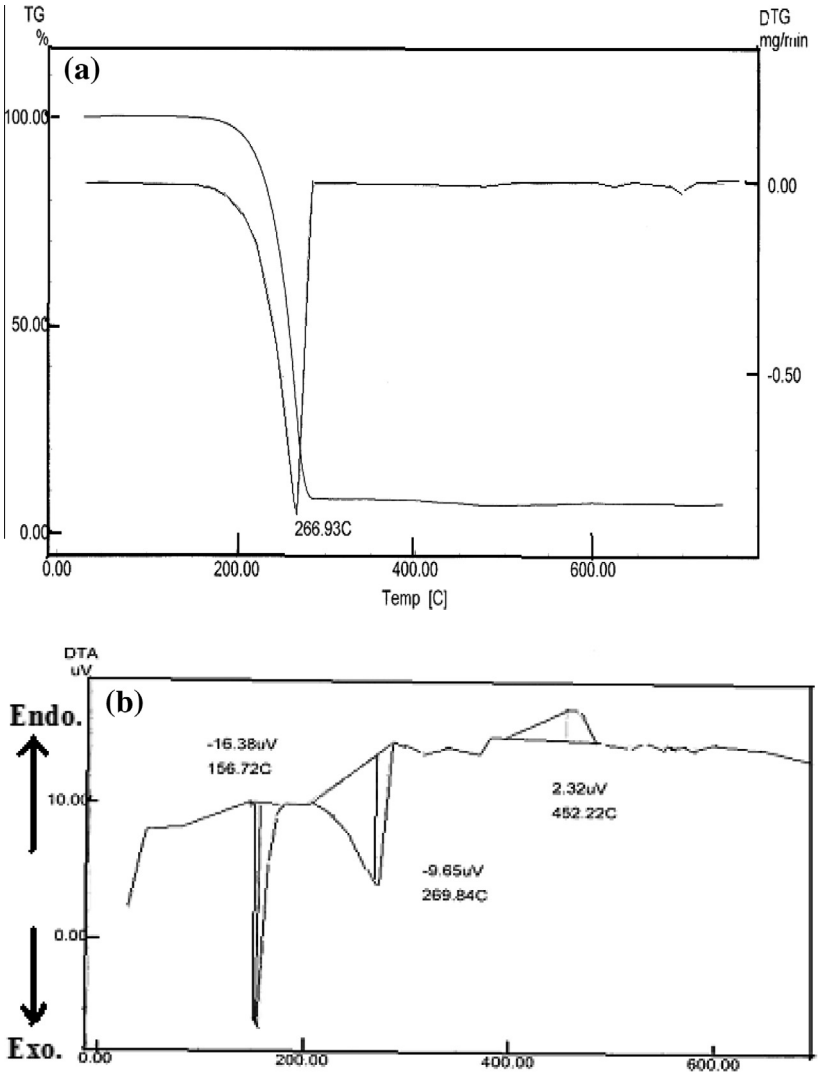


Figure 2 Thermal analyses of standard NAP drug: (a) TG/DT and (b) DTA.

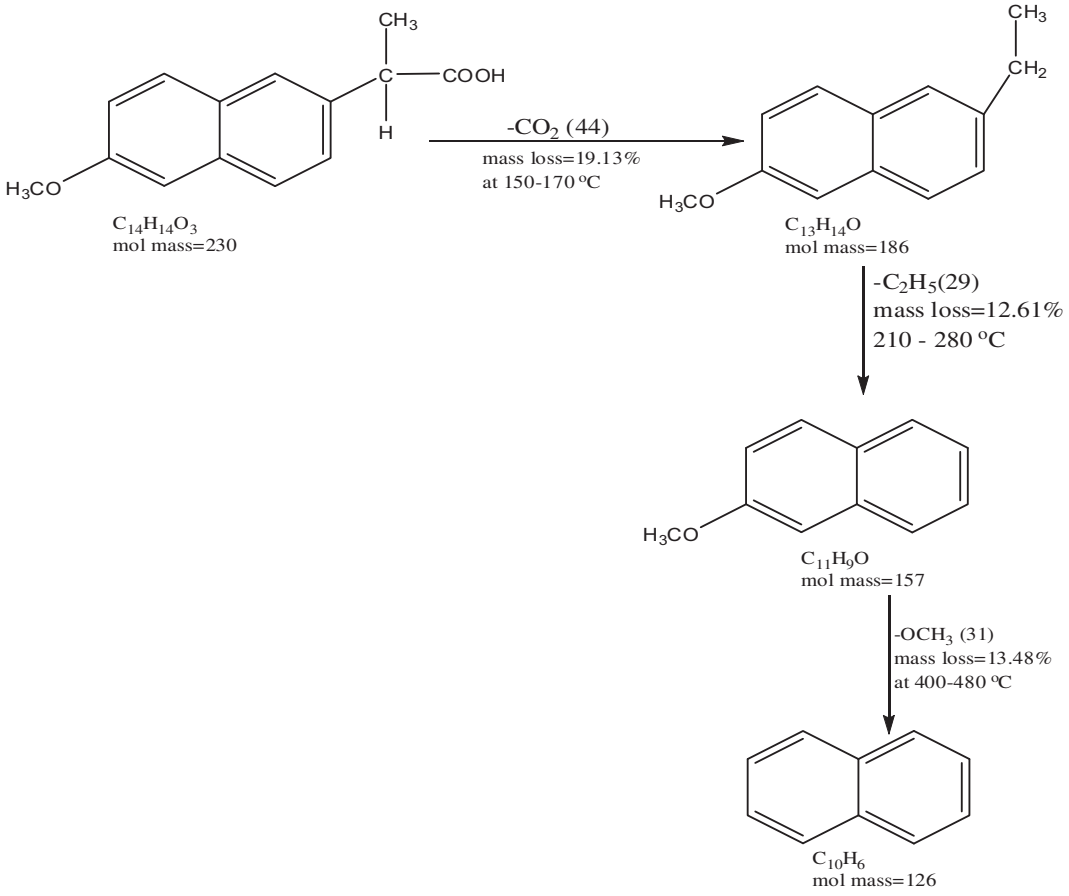
3.1. Thermal analysis

The TA data of naproxen (NP) are illustrated in Fig. 2a and b. It is clear from TG/DTG curves (Fig. 2a) that, this compound decomposed completely within the temperature range of 80–480 °C (mass loss = 99.0%). The main mass loss of this compound occurs at 266.93 °C as shown by DTG curve (Fig. 2a). From DTA curve (Fig. 2b) it is clear that thermal decomposition of NAP occurs in two main endothermic regions and one exothermic region: 150–170, 210–280 and 400–480 °C which cannot easily be described by TG technique. These endothermic and exothermic mass losses required energy values of 255.41, 10.67 and 371.45 kJ mol^{-1} at 157.0, 270.0 and 452.0 °C respectively. Therefore, the proposed thermal decomposition of NAP can be carried out in three consecutive steps as shown in Scheme 1.

3.2. Mass spectral (MS) fragmentation of Naproxen drug

The electron ionization (EI) mass spectrum for NAP drug measured at 70 and 12 eV was recorded (Fig. 3a and b) and investigated. The spectrum of NAP drug at 70 eV (Fig. 3a) is characterized by many competitive and consecutive pathways, thus forming many intense fragment ions (Scheme 2). The main fragmentation pathways for NAP after ionization of neutral molecule at 8.764 eV consist of three principal pathways (path 1–3) as rationalized in Scheme 2. The signal that appears at m/z = 230 (RI = 100%) refers to the appearance of the main molecular ion $[C_{14}H_{14}O_3]^+$. The high intensity reflects the stability of the molecular ion of NAP. The fragment ion at signal m/z = 185 (Scheme 2, path 1) represents the second most prominent ion $[C_{13}H_{13}O]^+$ (RI = 90.42%) and is mainly due to the rupture of COOH molecule from main molecular ion. Also, its high stability is due to the presence of the lone pairs of electrons of oxygen atom with two aromatic rings. Two important fragment ions are observed in the mass spectra at m/z = 170 (RI = 26.65%) and at m/z = 154 (RI = 12.85%). These fragment ions may be due to the rupture of CH_3 and OCH_3 radicals, respectively. The fragment ion observed at m/z = 139 may be due to the formation of $[C_{11}H_7]^+$. Comparison of TA (Scheme 1) and MS path 1 (Scheme 2) refers to the coincidence between TA scheme and MS of NAP drug metabolites (vitro fragments).

At the low energy value of 12 eV (Fig. 3b), the base peak is observed at molecular ion m/z = 230, IR = 100%. It is noted that the peaks corresponding to the secondary process (m/z = 185) were observed at RI < 10%. Comparison of the data in Fig. 3a to that in Fig. 3b, refers to the fact that 70 eV is sufficient energy for fragmentation of NAP (mole mass 230) to give its daughter fragment ion $[C_{13}H_{13}O]^+$ (m/z = 185, RI = 90.42%), but 12 eV the lower energy is insufficient to give this fragment from its parent drug molecule. This also confirms the proposed mass Scheme 2, which indicates that the path 1 is the only possible way to form $[C_{13}H_{13}O]^+$ at 70 eV. This is also confirmed by the full scan MS/MS spectrum (Fig. 4) (da-fang



Scheme 1 The proposed thermal decomposition pathway of NA.

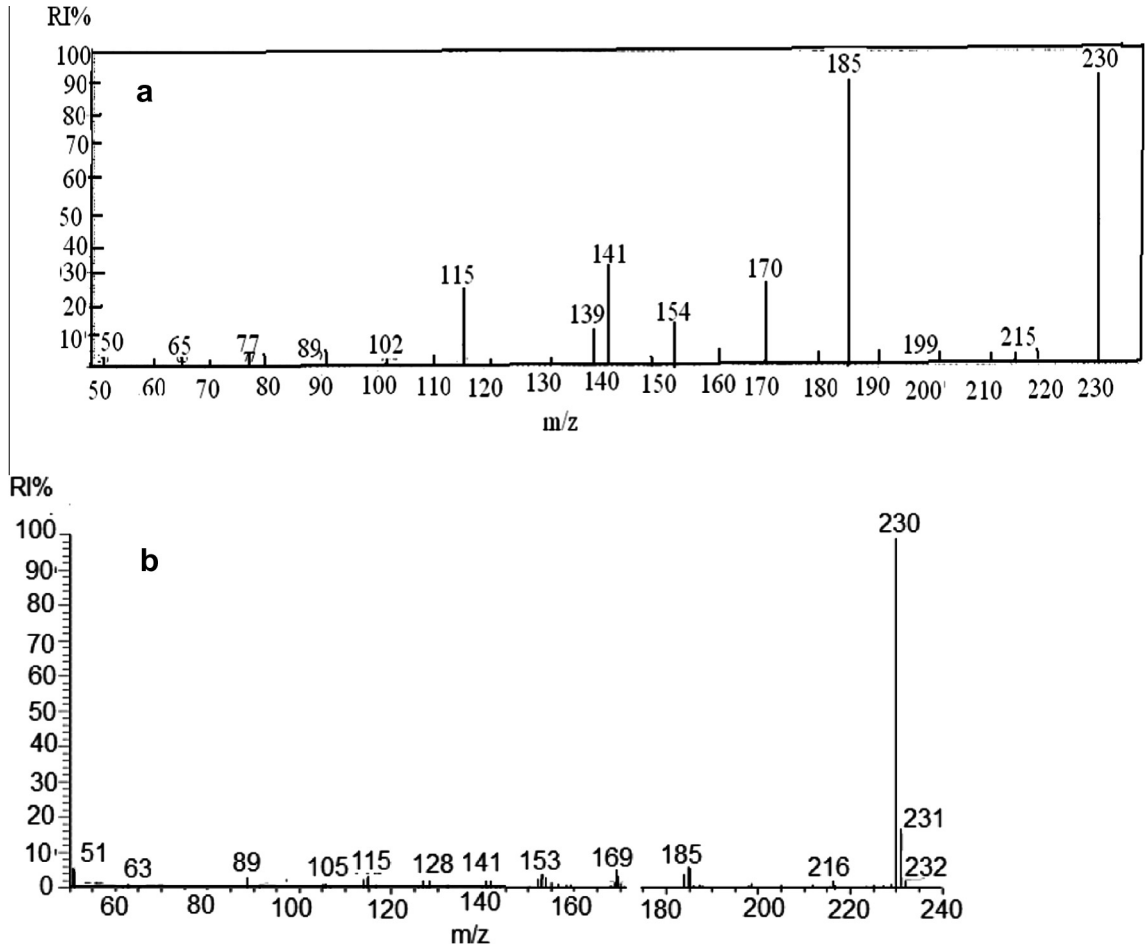


Figure 3 Mass spectrum of NAP at: (a) 70 eV and (b) 12 eV.

et al., 2003) of NAP that showed a molecular ion at m/z = 229.1 of very low intensity, whereas its daughter fragment ion $[C_{13}H_{13}O]^+$ (m/z = 184.9, RI = 100%) appeared as base peak.

3.3. Computational molecular orbital (MO) calculation

Molecular orbital (MO) calculation gives valuable information about the structure and reactivity of the molecules, which actually are used to support the experimental evidences (Fahmey et al., 2001; Zayed et al., 2005, 2006, 2007, 2010, 2012a,b). The most important parameters calculated using MO calculation includes bond orders, bond length, charge distribution, bond strain, and heat of formation and ionization energy. In the present work, the calculations have been carried out on NAP neutral molecule (related to TA decomposition) and charged molecular ion (related to MS fragmentation) which is used for prediction of weakest bond rupture to follow the fragmentation pathways in both techniques.

Fig. 1 shows the numbering system of NAP skeleton that helps in ordering the calculated parameters Table 1 presents the values of bond length (Å), bond order and bond strain (kcal mol^{-1}) of NAP drug in both neutral and in cationic forms. One can conclude the following from Table 1:

1. Small differences in bond length in NAP system upon ionization indicate that no appreciable change in the geometries upon ionization.
2. The lowest bond order (important for prediction of primary site of cleavage) observed at bond C17–C21 for both neutral (0.919) and positive species (0.932).
3. Upon ionization the stability of the molecule decreased by 180.53 kcal mol^{-1} (ΔH_f (−97.79) − ΔH_f^+ (92.74)).

The charge distribution on different atoms (C and O) and heats of formation; ΔH_f (kcal mol^{-1}) for neutral and charged NAP species are summarized in Fig. 5. Significant changes in the electron distribution with given system often takes place during the ionization.

3.4. Correlation between thermal analysis (TA) decomposition and MO-calculation

As indicated, the determination of initial bond rupture would be an important first step in using this calculation in predicative manner. MO calculation and PM3 procedure revealed that the C17-C12 bond has the lowest bond order at 0.919 and large bond length = 1.521 Å and bond strain = 0.032 kcal mol^{-1}. Experimental TA curves (Fig. 2) of naproxen reveal that the

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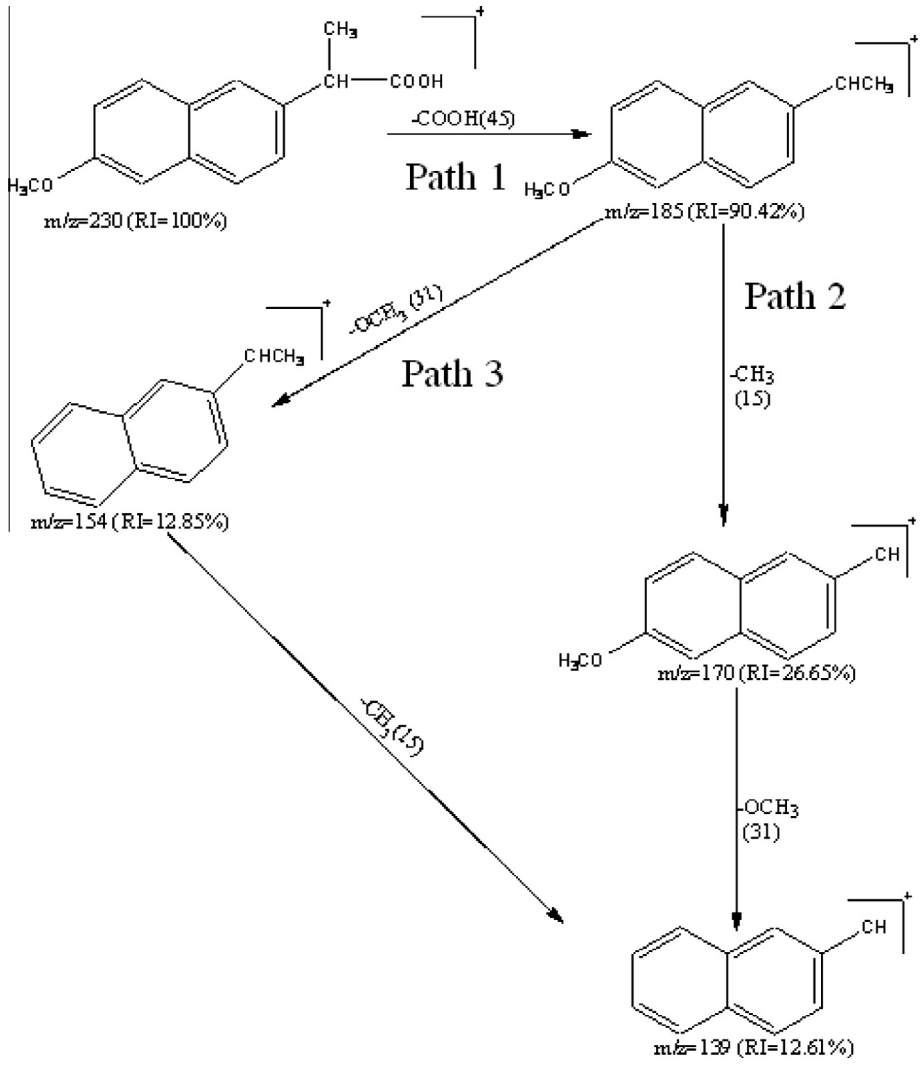

Scheme 2 Proposed mass fragmentation of NAP drug in cationic form at 70 eV.

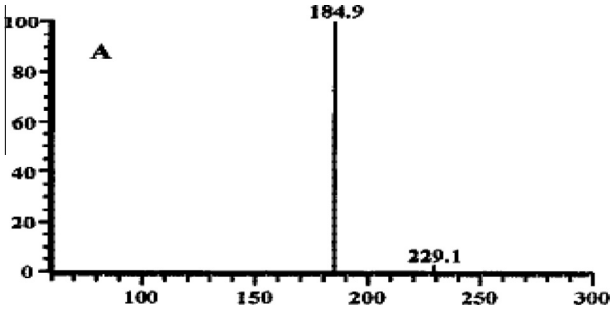

Figure 4 Full scan MS/MS spectrum of m/z = 230 of NAP (Aresta et al., 2006).

first weight loss equals to 19.56%. This weight loss corresponds to the rupture of COOH (lowest bond order) at temperature 157 °C of range 150–170 °C, followed by the rupture of C3–O13 bond (bond order = 1.037, bond length = 1.364 Å, bond strain = 0.032 kcal mol^{-1}). The second weight loss of 13.65% occurs at temperature in the range 180–280 °C. This weight loss is mainly due to rupture of OCH_3 ($O + CH_3$). This wide range of temperature may be due to slow fragmentation with small half life time (Pourmortazavi et al., 2008), since in TA decomposition of the molecules is continuously energized and determined by gas evolution and the distribution of energy can be described by energy (Hosseini et al., 2005).

On the other hand, the electrostatic repulsion between C17 (−0.012) and C21 (−0.386) for neutral molecule facilitates the rupture of this bond (C17–C12), than the second rupture of C3 (0.100) and O13 (−0.187) atoms, indicating that the COOH loss is more easy than O–CH_3 loss.

3.5. Correlation between mass spectral (MS) fragmentation and MO calculations of charged molecule

The scope of this investigation is restricted to a search for prediction of the first and subsequent bond ruptures during the course of fragmentation of NAP drug in MS technique. The subsequent fragmentation in MS is determined to a large extent by the initial bond rupture of molecular ion (Zayed et al., 2007; Stewart, 1989, 1999; Baker, 1986). A number of mass spectrometric techniques have utilized helping in rationalized the correct pathways of the

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Table 1 Comparison between computed bond length (in Å), bond order and bond strain (kcal mol^{-1}) using the PM3 method for neutral and molecular cation of NAP drug.

Bond	Bond length (Å)		Bond order		Bond strain (kcal mol^{-1})	
	Neutral	Cation	Neutral	Cation	Neutral	Cation
C1–C2	1.365	1.396	1.634	1.639	0.008	0.009
C2–C3	1.428	1.397	1.197	1.215	0.014	0.013
C3–C4	1.377	1.400	1.548	1.223	0.037	0.036
C4–C5	1.420	1.399	1.218	1.437	0.026	0.024
C5–C6	1.409	1.398	1.334	1.190	0.018	0.017
C6–C1	1.424	1.397	1.201	1.130	0.015	0.013
C6–C7	1.418	1.398	1.232	1.444	0.021	0.018
C7–C8	1.375	1.398	1.577	1.305	0.025	0.020
C8–C9	1.419	1.398	1.241	1.331	0.025	0.020
C9–C10	1.368	1.396	1.607	1.545	0.008	0.009
C10–C5	1.421	1.398	1.220	1.165	0.019	0.021
C3–O13	1.379	1.364	1.037	1.207	0.032	0.032
C8–C17	1.504	1.513	0.973	0.995	0.089	0.083
O13–C19	1.406	1.405	0.985	0.958	0.006	0.005
C17–C20	1.522	1.535	0.983	0.966	0.052	0.043
C17–C21	1.521	1.520	0.919	0.932	0.032	0.037
C21–O22	1.218	1.209	1.807	1.778	0.001	0.001
C21–O23	1.354	1.342	1.053	1.105	0.005	0.005

Dipole moment (Debye)	Electron affinity (eV)	Heat of formation (kcal mol^{-1})	Ionization potential (eV)
(a) 2.44	0.526	−97.78709	8.764
(b) 5.96	4.982	92.74	12.999

(a) Neutral form values and (b) cationic form values.
The order of the bond strength: C21–O22 > C1–C2 > C9–C10 > C7–C8 > C3–C4 > C5–C6 > C8–C9 > C6–C7 > C10–C5 > C4–C4 > C6–C1 > C2–C3 > C21–CO23 > C3–O13 > O13–C19 > C17–C20 > C8–C17 > C17–C21.

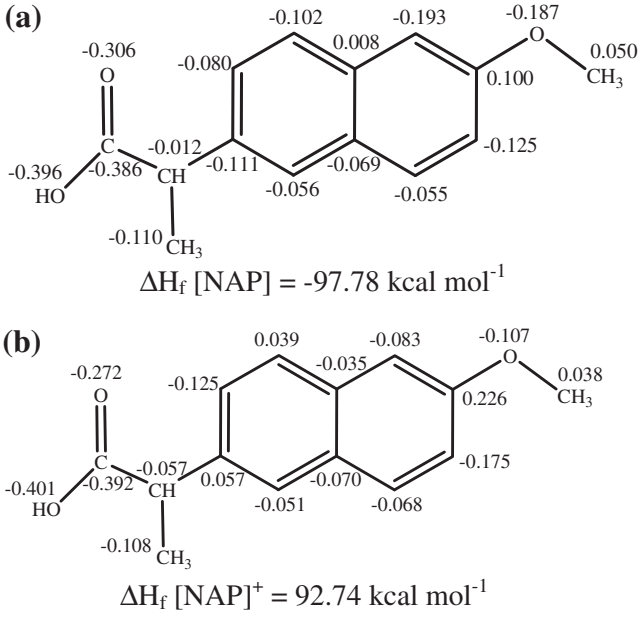

Figure 5 Charge distribution on different atoms for NAP: (a) neutral molecule and (b) molecular cation.

molecules, among which are: threshold measurement and metastable abundance ratios (Cooks et al., 1973). On the other hand, computational process can provide important information which can be used successfully in description of primary site of cleavage. The theoretical data obtained can be considered valuable for MS; because they were studied in gas phase species, which can be handled much more easily by quantum chemistry (Stewart, 1989, 1999; Baker, 1986). Mass spectrum of NAP reveals (Scheme 2) three competitive and consecutive fragmentation pathways.

PM3 procedure on cationic form (Table 1) reveals that the C17–C21 bond is the first site of bond cleavage (lowest bond order = 0.932, large bond length = 1.520 Å, bond strain = 0.037 kcal mol^{-1}). This bond cleavage accompanied by rupture of COOH molecule forms the fragment ion $[C_{13}H_{13}O]^+$ at m/z = 185 and relative intensity = 90.42%. Further loss is a rupture of CH_3 molecule from this fragment at m/z = 170 $[C_{12}H_{10}O]^+$ (Scheme 2, path 1). On the other hand, the electrostatic repulsion between the charge localized on C17 (−0.057) and C21 (−0.392) atom (Fig. 5) facilitates the loss of COOH molecule.

The MO calculation data of fragment ion $[C_{13}H_{13}O]^+$ at m/z = 185 are shown in Table 2. These data refer to the ordering of its bond strength; which is given by C9–C10 > C1–C2 > C3–C4 > C8–C17 > C7–C8 > C6–C7 > C4–C5 > C2–C3 > C5–C6 > C6–C1 > C10–C5 > C8–C9 > C3–O13 > C17–C20 > O13–C19. This means that, the first ruptured bond is O13–C19 leading to the formation of fragment ion m/z = 170 $[C_{12}H_{10}O]^+$ via the loss of CH_3 group. It was followed by the rupture of the bond C17–C20; which leads to the formation of m/z = 154 (RI = 12.85%) via the loss of CH_3O and finally to the rupture of the bond C3–O13 leading to the formation of fragment ion $[C_{11}H_7]^+$ that observed at m/z = 139. This means that all fragment ions are coming from the daughter m/z = 185 not from the parent drug m/z = 230. This is also is in good agreement with the proposed thermal and mass schemes (1 and 2) and MS/MS data (da-fang et al., 2003).

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Table 2 Comparison between computed bond length (in Å) and bond order using the PM3 method for neutral and molecular cation of $[C_{13}H_{13}O]^+$ at $m/z = 185$ system.

Bond	Bond length (Å)		Bond order	
	Neutral	Cation	Neutral	Cation
C1–C2	1.380	1.360	1.484	1.679
C2–C3	1.422	1.436	1.222	1.165
C3–C4	1.394	1.400	1.389	1.364
C4–C5	1.413	1.394	1.252	1.394
C5–C6	1.424	1.435	1.218	1.167
C6–C1	1.421	1.437	1.206	1.131
C6–C7	1.410	1.381	1.256	1.489
C7–C8	1.412	1.429	1.257	1.174
C8–C9	1.430	1.448	1.164	1.089
C9–C10	1.376	1.355	1.510	1.729
C10–C5	1.424	1.436	1.184	1.138
C3–O13	1.379	1.347	1.033	1.158
C8–C17	1.406	1.373	1.274	1.562
O13–C19	1.406	1.415	0.986	0.958
C17–C20	1.700	1.464	1.022	1.055

The order of the bond strength: C9–C10 > C1–C2 > C3–C4 > C8–C17 > C7–C8 > C6–C7 > C4–C5 > C2–C3 > C5–C6 > C6–C1 > C10–C5 > C8–C9 > C3–O13 > C17–C20 > O13–C19.

3.6. Correlation between TA and MS

It is important to make a discussion between results of TA and MS of NAP, to see the behavior of the drug in both techniques. This comparison shows the agreement between mass path 1 and TA. In both TA and MS techniques, it is proved that the C17–C21 bond is the first site of rupture. In TA, COOH rupture is followed by OCH_3 (O + CH_3) (Scheme 1). In MS fragmentation it is initiated by COOH rupture and followed by CH_3 group rupture in path 1 (Scheme 2). The obtained fragment ions in MS are $m/z = 230$, 185, 170, 154 and 139, that are confirmed by TA. This can be considered as a vitro metabolites of NAP drug; which are very similar to vivo urinary metabolites of naproxen obtained by liquid chromatography–electro-spray mass spectrometry (Aresta et al., 2006).

4. Conclusion

The aim of this study is concerning with the applicability of experimental TA and MS techniques and theoretical investigation MO calculations, using the PM3 procedure on NAP drug.

From correlation between MS and MO calculations, it is clear that the C17–C21 bond is the first site of bond cleavage. This refers to lowest bond order, large bond length and less bond strain. This bond cleavage accompanied by the rupture of COOH molecule forming the fragment ion $[C_{13}H_{13}O]^+$ at $m/z = 185$ and relative intensity = 90.42%. Further loss is a rupture of CH_3 molecule from this fragment at $m/z = 170$ $[C_{12}H_{10}O]^+$. On the other hand, the electrostatic repulsion between the charges localized on C17 and C21 atoms facilitates the loss of COOH molecule. Therefore, this investigation concluded that the correlation between both practical and theoretical techniques helps in the selection of the proper pathway representing the decomposition of this drug to give its vitro metabolites.

From the obtained data of both practical (TA, MS) and theoretical (MO) techniques in this investigation, it is proved that, the C17–C21 bond is the first site of rupture in TA, COOH followed by OCH_3 (O + CH_3), while in MS the rupture was initiated by COOH rupture and followed by CH_3 group. MO calculations reveal that the C17–C12 bond has the lowest bond order, large bond length and bond strain. Also, the electrostatic repulsion between C17 and C21 for neutral and cationic NAP forms facilitates the rupture of the bond (C17–C12). The charges on atoms C3 and O13 make the second bond C3–O13 rupture less possible. This indicates that the COOH loss is easier than O–CH_3 loss. Naproxen can be completely thermally dissociated in the temperature range of 80–480 °C (mass loss = 99.0%).

The obtained fragment ions in MS of $m/z = 230$, 185, 170, 154 and 139, are confirmed by TA and can be considered as vitro metabolites of NAP drug. These vitro metabolites are suggested and confirmed by MO calculation and are very similar to vivo urinary metabolites of naproxen obtained by liquid chromatography–electro-spray mass spectrometry (Aresta et al., 2006).

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