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Structure investigation of codeine drug using mass spectrometry, thermal analyses and semi-emperical molecular orbital (MO) calculations

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Abstract

Codeine is an analgesic with uses similar to morphine, but it has a mild sedative effect. It is preferable used as phosphate form and it is often administrated by mouth with aspirin or paracetamol. Therefore, it is important to investigate its structure to know the active groups and weak bonds responsible for its medical activity. Consequently in the present work, codeine was investigated by mass spectrometry and thermal analyses (TG, DTG and DTA) and confirming by semi-empirical MO-calculation (PM3 method) in the neutral and positively charged forms of the drug. Some results of studying the d-block element complexes of codeine were used to declare the relationship between drug structure and its chemical reactivity in vitro system. The mass spectra and thermal analyses fragmentation pathways were proposed and compared to each other to select the most suitable scheme representing the correct fragmentation of this drug. From EI mass spectra, the main primary cleavage site of the charged drug molecule is that due to β-cleavage to nitrogen atom in its skeleton. It occurs in two parallel mechanisms with the same possibility, i.e. no difference in appearance activation energy between them. In the neutral drug form the primary site cleavage is that occurs in the ether ring. Thermal analyses of the neutral form of the drug revealed the high response of the drug to the temperature variation with very fast rate. It decomposed in several sequential steps in the temperature range 200–600 °C. The initial thermal fragments are very similar to that obtained by mass spectrometric fragmentation. Therefore, comparison between mass and thermal helps in selection of the proper pathway representing the fragmentation of this drug. This comparison successfully confirmed by MOC. These calculations give the bond order, charge distribution, heat of formation and possible hybridization of some atoms in different position of the drug skeleton. This helps the successful choice of the weakest bond at which both mass and thermal fragmentation occurs. Therefore, the best fragmentation pathway of this drug is correctly selected. The effect of such fragmentation on the drug behavior in the human body can be expected as a result of comparing these data with that obtained on studying codeine metal complexes using mass and thermal fragmentation techniques.

Keywords: Codeine structure, mass spectrometry; Thermal analyses; MO-calculation

1. Introduction

Codeine (morphine 3-methyl ether) is an analgesic with uses similar to morphines, but it of much less effect, i.e. it has a mild sedative effect. Codeine usually used as the phosphate form and is often administrated by mouth with aspirin or paracetamol. The structural formula as in Fig. 1 of codeine was given by Gulland and Robinson [1] with general formula $C_{18}H_{24}NO_7P$.

The structural formula of this drug was thoroughly investigated by several authors using different techniques [2–12]. The mass spectra of morphine [13] and several closely related alkaloids [14–16] have been early studied. The assignment of individual peaks was made on the basis of the mass shift in the spectra of morphine derivatives. The mass spectrum of morphine is discussed as example of the skelated type [13].

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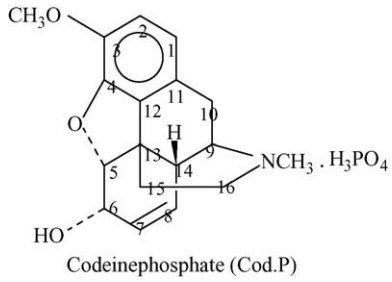


Codeinephosphate (Cod.P)

Fig. 1. The structural formula of codeine phosphate anhydrate.

The mass spectrometry has become a power tool for drug metabolism studies [17]. The technique is important because it provides a lot of structural information with little expenditure of the sample. In electron impact (EI) mass spectra, the fragmentation consists of competitive and consecutive unimolecular fragmentation pathways [18,19]. The fragmentation of ionized molecule depends mainly on their internal energy. The thermogravimetric TG/DTG analysis 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 [20,21], the nature of the released volatiles may be deduced, thus greatly help the interpretation of thermal degradation processes. On the other hand, computational quantum chemistry can provide additional information, which can be used successfully in an interpretation of experimental results [24] which can be used in the description and prediction of primary fragmentation processes.

Although, the literature is wealthy in information related to the biological activities of codeine and its derivatives; it seems lack of any correlation between the chemical behavior of this drug and its electronic structure, its tendency for complex formation and the stability of its d-block elements complexes in relation to its medical uses.

Recently, the complexing ability of this drug towards transition metals are investigated by Zayed et al. [22,23] using combined physico-chemical methods of analyses. They concluded the high stability of the formed complexes which are of the essential biological roles.

The aim of the present work is to make a correlation between, mass spectral fragmentation and thermal analyses degradation of codeine. Then these data are compared with theoretical 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 this drug responsible for its chemical, biological and medical reactivites. This biological role can be understand more on comparing the data obtained about the drug with that previously given about the prepared and studied d-block elements complexes of codeine phosphate [23].

2. Experimental

2.1. Mass spectrometry (MS)

Electron impact (EI) mass spectra of codeine and its complexes were obtained using Shmadzue-GC-MS-QP 1000 PX quadrupol mass spectrometer with electron multiplier detector equipped with GC-MS data system. The direct probe for solid material was used in this study. The sample was put into a glass sample micro vial by needle sample (≈1 μg max), the vial installed on the tip of the DP containing heating cable and inserted into evacuated ion source. The sample was ionized by electron beam emitted from the filament. The generated ions are introduced into the analyzer by the focusing and extractor lenses system. The mass spectra was continuously scanned and stored at 70 eV of ionizing energy values and emission current at 60 mA with vacuum better than 10^{-6} Torr.

2.2. Thermal analyses (TA)

The thermal analyses of codeine drug and its complexes were made using conventional thermal analyzer (Shimadzue system of DTA-50 and 30 series TG-50). 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 10 °C min^{-1}. These instruments were calibrated using indium metal as a thermal stable material. The reproducibility of the instrument reading was determined by repeating each experiment more than twice.

2.3. Quantum chemical calculations (MOC) of the codeine structural data

The calculations were performed using semi-emperical MO-calculation. The program used in these computations is the parametric PM3 method described by Stewart [25]. The geometries of all stable species studied were completely optimized with respect to all geometrical variables using the modified Davidson–Fletcher–Powell (DFP) [26] algorithm incorporated with the program. The program is run under the molecular orbital calculation package MOPAC2000 by Stewart [25] for microcomputers and E F routine eigen vector following Bakar method [27] and Waller [28].

3. Results and discussion

It is of great interest to study the chemistry and reactivity of codeine drug because of its importance in medicine similar to morphine drug. Knowledge obtained from thermal decomposition mechanisms of the neutral drug is very important to understand the chemical process that charred in biological systems. It is difficult to establish the exact major fragmentation pathway in EI using conventional MS. Combining the two above techniques and the data obtained from the MOC,

Table 1
The IR characteristics of codeine drug

ν (cm^{-1})	Assignment
3500, 3773	—OH
2500	—N^{t}H
1645	C_6=C_8 (alkenes)
1618, 1515	C=C (aromatic)
1280, 1090	C—O—C
1270	(CO) (O—Me)
890, 760	Two adjacent H aromatic

it is possible to understand the following topics:

(1) The stability of the drug under thermal degradation in solid state phase and mass spectral fragmentation in gas phase.
(2) Prediction of the primary site of the fragmentation which helps to rationalize subsequent bond cleavage.
(3) The correct pathways in both techniques.
(4) Effect of reactivity of the drug (charge localization of different atoms of the drug) to form complexes with transition elements.

3.1. Structure investigation of codeine ligand by IR, ^{13}C NMR and mass spectra

The IR spectrum of codeine as KBr-disc was recorded and assigned as bands in Table 1. It can be used in discussing qualitatively the relative strength of bonds during thermal and mass spectral fragmentation in comparison with the quantitative bond order and bond strain values coming from MOC.

EI mass spectrum of codeine drug was recorded and investigated. A typical mass spectrum (bargraph) of the drug is shown in Fig. 2 and in Table 2. Scheme 1 shows the possible main fragmentation pathways (path 1, path 2 and path 2′)

The mass spectrum of codeine obtained by electron impact (EI) ionization, shows a molecular ion peak M^+ at m/z = 299 of relative intensity 100%. The predominant fragments and their relative intensities are listed in Table 2.

Scheme 1 shows the possible main fragmentation pathways. The molecular ion of codeine drug ($C_{18}H_{21}NO_3$, m/z = 299) represent the base peak (i.e. RI = 100%) in the mass spectrum, indicating the high stability of the ion at 70 eV in the gas phase, which may be due to the presence of charge localization over the whole molecule.

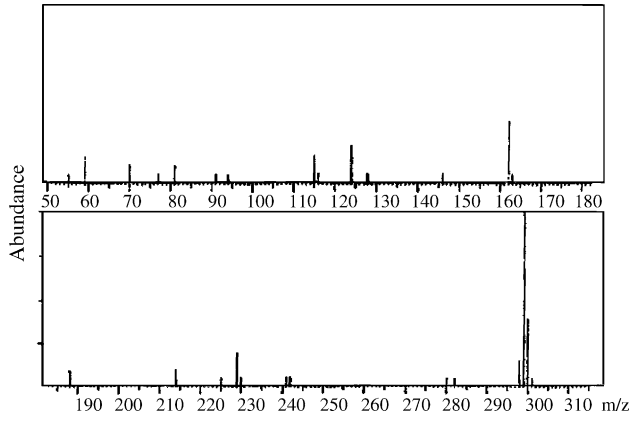


Fig. 2. EI mass spectral fragmentation of codeine drug at 70 eV.

Table 2
The mass fragments of codeine drug

m/z	Ion formula	Process	RI (%)
299	$C_{18}H_{21}NO_3$	M^+	100
298	$C_{18}H_{20}NO_3$	(M^+ −H)	14.3
282	$C_{18}H_{20}NO_2$	(M^+ −OH)	8.3
242	$C_{15}H_{14}O_2$	(M^+ −C_3H_7N)	9.3
229	$C_{14}H_{15}NO_2$	(M^+ −C_4H_6O)	25.0
188	$C_{12}H_{12}NO_2$	(M^+ −C_4H_6O—C_3HCN)	15.0
162	$C_{10}H_{12}NO$	(M^+ −$C_8H_9O_2$)	36.7
124	$C_7H_{11}NO$	(M^+ −$C_{11}O_2$)	21.7

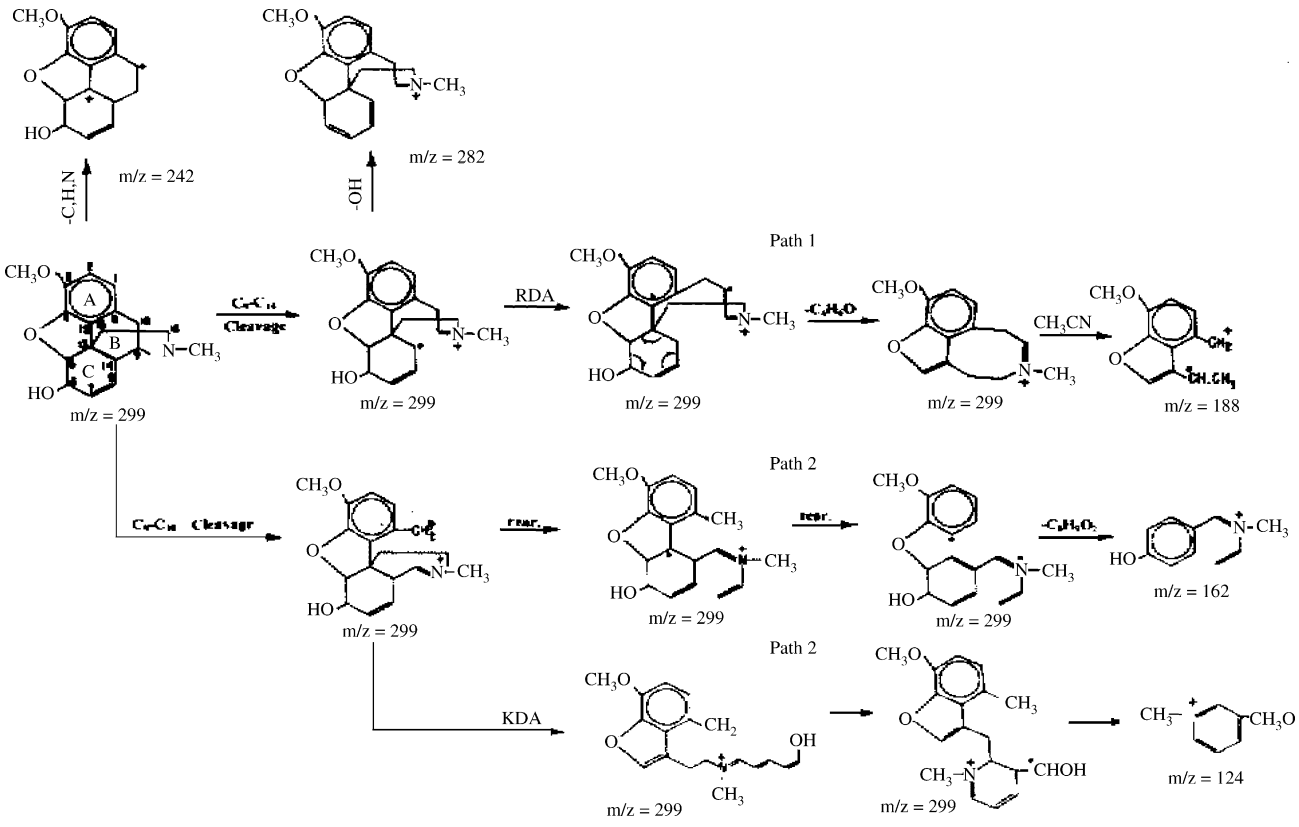
The most important mode of fragmentation at 70 eV of the drug is that due to the cleavage of the bond β- to the nitrogen atom, i.e. cleavage of C9–C14 and C9–C10 bonds The cleavage of these two bonds forms the two major competitively pathways (path 1 and path 2). Firstly, Scheme 1 path 1, the formation of the fragment ions at m/z = 188 ($C_{12}H_{12}O_2$, RI = 15%) was found to contain ring A. The formation of these fragment ions are explained by assuming an Retero Diol Alder (RDA) process [28] of C9–C14 bond cleavage (path 1) which in turn fragments to form ion at m/z = 229 by C_4H_6 loss. Further, the loss of CH_3CN molecule gives the fragment ion m/z = 188. On the other hand, the loss of OH gives the molecular ion of m/z = 282 ($C_{18}H_{20}NO_2$, RI = 8.3%) and can be ascribed to the removal of the C6 hydroxyl group. Also, the formation of the fragment ion at m/z = 242 ($C_{15}H_{14}O_2$, RI = 9.3%) is due to the elimination of the bridge C_3H_7N. Secondly, the formation of the fragments ion $C_{10}H_{12}NO$, RI = 36.7% is assumed to contain C-ring. This ion can be explained by visualizing the rearrangement after the C9–H10 cleavage by loosing $C_8H_9O_2$ (path 2). Thirdly, the fragment ion m/z = 124 ($C_7H_{11}NO$, RI = 21.7%) is formed from molecular ion after C9–C10 cleavage (path 2).

The ^1H NMR of codeine in deuterium oxide was recorded using tetra methyl silane as a reference standard and was assigned as given in Table 3

The ^{13}C NMR were recorded over 5000 Hz range. The values of chemical shift (δ) can be used in discussing the positions of protons (in plane and out of plane) on the carbon skeleton of codeine. These values can be compared with the type of hybridization of C atoms carrying these protons that

Table 3
NMR identification of codeine

Chemical shift (δ)	Assignment
6.78(d)	1H
6.95(d)	2H
5.78(d)	7H
5.40(m)	8H
4.40(m)	9H
3.87(s)	3-OCH_3
3.00(s)	N—CH_3



Scheme 1. Fragmentation pathways of codeine drug at 70 eV.

determined by MOC and the values of IR wave numbers corresponding to the strength of these bonds.

3.2. Quantum chemical calculations (MOC) of the codeine structural data in comparison with its mass, IR and ^{13}C NMR

The MOC were performed using semi-emperical molecular orbital procedure [25]. The program used in these computations is the parametric method (PM3) described by Stewart [25]. The geometries of all stable species studied were completely optimized with respect to all geometrical variables. The calculation was performed under the MOC package MOPAC2000 by Stewart [26] for microcomputers and optimized using eigen vector following E F routine [27].

Molecular orbital (MO) calculations give variable information about the structure and reactivity of the drug molecule. In our previous study, the fragmentation of some phenolic compounds [22,23,29] and their redox products [21] were investigated using MS and TA techniques and the comparative study has been succeeded in simple molecules identification. In large molecules as diazepam [30] and maloanilides [31], the comparative study needs particular information about the atoms and bonds using MNDO method [32]. In the present work, we used a more advanced semi-empirical MOC (PM3) method [25].

Investigation of the molecular structure of codeine drug with common formula $C_{18}H_{21}NO_3$ was interest in the present work aiming to help in illuminating experimental data, i.e. prediction of the weakest bond cleavage and the stability of the neutral (by TA) and charged molecules (by MS) and its reflection on the stability of the complexes with the transition elements.

Fig. 3 shows the charge density distribution localized on different atoms of neutral and charged species of codeine drug. Fig. 4 shows the bond order values for different bonds of the neutral and charged drug species. The computational results reveal some important notes:

(1) The charge density localized on the nitrogen atom increased from 0.088 to 0.480 from neutral to charge atom which reveals that the electron rupture upon ionization is surely occurs in nitrogen atom.
(2) Appreciable charge of the charge density localized on O21 and O22 upon ionization while not on the O23 atom.
(3) The lowest bond order for the neutral molecule is at the value 0.919 of C5–O22 bond while for charged molecular ion it occurs at the value 0.961.

From the MOC it is found that the H–C bonds of codeine drug appear as C1–H of bond order = 0.967 of C1 atom of SP^2 hyberdization that appear in ^1H NMR of chemical shift value (δ) = 6.78; C2–H of bond order = 0.962 of C2 of SP^2 and of chemical shift (δ) = 6.95; C7–H, of bond order = 0.961, of C7 of SP^2 and chemical shift (δ) = 578; and C8–H of bond order = 0.962, of C8 of SP^2 and chemical shift (δ) = 5.40.

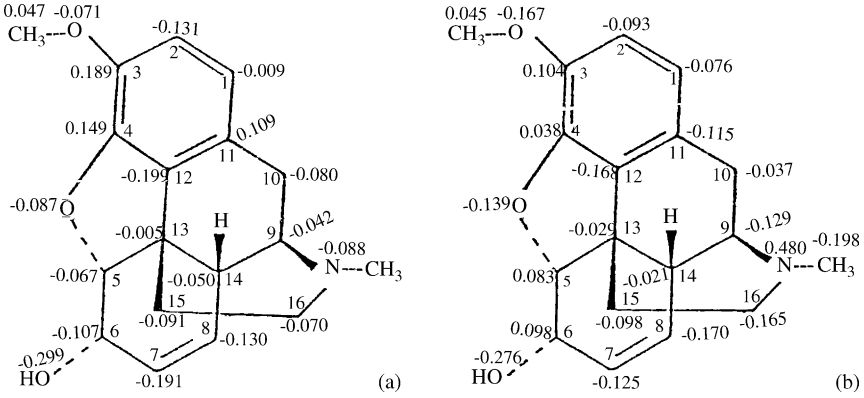


Fig. 3. Charge density distribution of codeine drug for neutral (a) and charge (b) species using PM3 method.

These values mean that all of these protons are strongly bonded to their carbon atoms in plane and then difficult to be ionized or loosed during mass and thermal fragmentation. They have the wave number in IR (Table 1) of values 3500 and 3773 cm^{-1} (s) for $\nu_{(OH)}$, 2500 cm^{-1} for ν_{NH}, 1645 cm^{-1} for alkenes, 1618 and 1515 cm^{-1} for aromatic rings and 1280 and 1090 cm^{-1} (sh) for $\nu_{(C–O–C)}$, 1271 cm^{-1} (sh) for $\nu_{(C–O)(O–ME)}$ and 1331–1348 cm^{-1} for ν_{CO} and 890, 760 cm^{-1} for adjacent aromatic hydrogens. These wave number values refer to the variation of strength of bonds of the protons to the C skeleton of this drug. These strength values depending upon the proton position in relation to the kind of proton, i.e. is that in aliphatic side chain or in aromatic ring or attached to functional groups like NCH_3, CH_3O, NH or C_2H_2. On the other hand, C9–H of bond order 0.965–0.964, of SP^3, (δ) = 4.4 the proton is out of plane may easily ionized or loosed during mass and thermal fragmentation. The C5–O22 of low bond order 0.919–0.976 and high bond strain = 0.979–1.026 KJ mol^{-1} and (δ) = 3.87 is easily fragmented in both thermal and mass fragmentation. The C9–NCH_3 of bond order = 0.964–0.978 of high bond strain = 0.659–1.026 KJ mol^{-1} and C16–NCH_3 of bond strain = 0.268–0.413 KJ mol^{-1} and bond order = 0.985–0.996 may reasonably account for the easily loosed side chain NCH_3 at C9–N20 bond rupture in both thermal and mass spectral fragmentation, but at high energy values than OCH_3 group. This conclusion agrees well with the chemical shift values of protons of CH_3 group of side chain OCH_3 ((δ) = 3.87) and that of protons of NCH_3 ((δ) = 3.30), which refer to the highly tited CH_3 aliphatic protons. It is concluded from this comparison that the MOC, IR, and NMR help the detection of the easily loosed groups and/or protons from the codeine drug skeleton during thermal and mass spectral treatment.

3.3. Comparison between TA, MS and MOC data of codeine drug and structure changes of its complexes obtained by MS and thermal treatments

The primary TA decomposition process of codeine drug is due to H_2O loss at temperature range 120–160 °C. IT followed by the loss of NCH_3 at 160–182 °C, C_2H_4 at 182–218 °C, $CH_2CH_2NH_2$ at 218–245 °C and OCH_3 at 245–400 °C. This is followed by the decomposition of the remaining ring system starting by ring B and ether oxide (OCH_3) at 400–538 °C leaving a stable biphenyl residue that volatile and completely loosed at high temperature value of 538–600 °C.

The H_2O loss is originated from the hydroyl group (C6–O23H) and hydrogen from the aromatic ring C [28] leaving a fragment of $C_{18}H_{19}NO_2$ (M–H_2O). This first loss can be

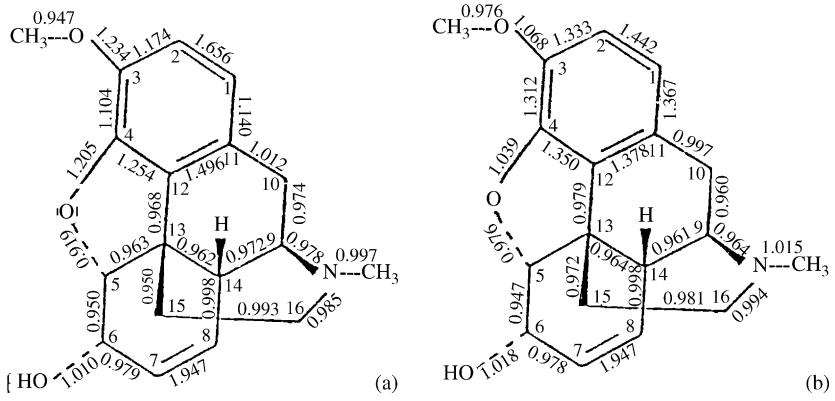


Fig. 4. Bond order of codeine drug for neutral (a) and charged (b) species using PM3 method.

Table 4
MOC properties of selected bonds and atoms (partial atomic charge, atomi hyberdization, bond order, and bond strain) for both neutral and positive codeine molecules

Bond list	Bond type	Bond strain	Bond order	Atom list	Hyberdization	Charge
C6—O23	Single	0.003[a]	1.010[a]	C3	SP^2	0.189[a]
		0.030[b]	1.018[b]			0.104[b]
C16—N20	Single	0.412[a]	0.985[a]	C4	SP^3	0.149[a]
		0.268[b]	0.994[b]			0.038[b]
C13—C15	Single	0.300[a]	0.950[a]	C5	SP^3	0.062[a]
		0.170[b]	0.972[b]			0.083[b]
C10—C11	Single	0.104[a]	1.012[a]	C6	SP^3	0.107[a]
		0.230[b]	0.997[b]			0.098[b]
C9—C14	Single	1.003[a]	0.972[a]	C9	SP^3	−0.042[a]
		0.709[b]	0.961[b]			−0.129[b]
C3—O21	Single	0.005[a]	1.234[a]	C10	SP^2	−0.080[a]
		0.176[b]	1.068[b]			−0.037[b]
C5—O22	Single	1.026[a]	0.919[a]	C11	SP^2	0.109[a]
		0.979[b]	0.976[b]			−0.115[b]
C4—O22	Single	0.045[a]	1.205[a]	C13	SP^3	−0.005[a]
		0.039[b]	1.039[b]			−0.029[b]
C5—C6	Single	0.729[a]	0.950[a]	C14	SP^3	−0.050[a]
		0.508[b]	0.947[b]			−0.021[b]
C9—N20	Single	1.026[a]	0.978[a]	C15	SP^3	−0.091[a]
		0.659[b]	0.964[b]			−0.098[b]
C13—C14	Single	0.162[a]	0.962[a]	N20	SP^3	−0.088[a]
		0.011[b]	0.964[b]			0.480[b]
C9—H	Single	0.020[a]	0.967[a]	O21	SP^2	−0.071[a]
		0.023[b]	0.965[b]			−0.167[b]
C5—H	Single	0.010	0.958[a]	O22	SP^3	−0.087[a]
		0.008[b]	0.965[b]			−0.139[b]
C6—H	Single	0.010[a]	0.956[a]	O23	SP^2	−0.299[a]
		0.006[b]	0.958[b]			−0.276[b]

[a] The values of neutral molecule used for thermal analyses fragmentation discussion.
[b] The values of charged molecule used for mass spectra fragmentation discussion.

explained by the rupture of O23 from C6–O23 bond of bond order 1.018 and bond strain = 0.003–0.030 kJ mole^{-1} to give a hydroxyl group combined with an aromatic proton obtained by rupture of C6–H bond of bond order = 0.956–0.958 and bond strain of 0.010 kJ mole^{-1}. In MS, the appearance of fragment ion at $m/z = 282$ is due to the OH^- loss obtained by (C6–O23H bond rupture, of bond order = 1.010 in a neutral drug molecule and =1.018 in a positively charged molecule (Table 4) due to the strain (0.030 KJ mol^{-1}) over this bond as given by MOC (Table 4). The initial molecular ion (of $m/z = 299$ $[C_{18}H_{21}NO_3]^+$) is stable at MS (RI = 100%) and stable in thermal analysis up to 160 °C. Subsequent fragmentation after H_2O loss in TA is due to the loss of the bridge C_3H_7N between C13 and N20 in two steps, by the loss of NCH_3 at (162–180 °C), this followed by the mass loss of C_2H_4 at 182–218 °C as a result of bond strain over C13–C15 = 0.170 KJ mol^{-1} of bond order = 0.950 obtained from MOC (Table 4). This is confirmed by the signal in MS at $m/z = 242$ (Scheme 1, path 1) due to the rupture of C_3H_7N molecular ion (RI = 9.3%, Table 2) in one step. Further fragmentation in TA is the loss of $CH_2CH_2NH_2$ at 218–245 °C due to the rupture of C10–C11 bond (bond order = 1.012 and bond strain = 0.237 KJ mol^{-1}, Table 4) and opening of ring B of the drug and rupture of C9–C14 (bond order = 0.961 and bond strain = 0.790 KJ mol^{-1}). This followed by the loss of OCH_3 at 245–400 °C, which is due the rupture of C3–O21 (bond order = 1.234) as a result of low bond strain = 0.005 KJ mol^{-1}, which required high temperature range. The opening of ring system by decomposition of ring B leaves the stable biphenyl system of rings A and C. This is followed by decomposition of unstable four membered ether oxide ring as a result of C5–O22 (of low bond order = 0.916 and high bond strain = 0.979 KJ mole^{-1}) and/or the rupture of the bond C4–O22 (of high bond order = 1.205 and low bond strain = 0.030 kJ mol^{-1}), which may required high temperature range 538–600 °C. In MS, the formation of the signals at $m/z = 229$, 188, 162 and 124 is due to the the loss of fragment C_4H_6O as a result of rupture of C5–C6 bond (bond order = 0.950 and high bond strain = 0.508 kJ mol^{-1}), followed by the loss of CH_3N as a result of rupture of C9–N20 bond (low bond order = 0.959 and high bond strain = 0.659 kJ mol^{-1}) as given by Scheme 1 path 1, or the loss of C_8H_9O (Scheme 1 path 2) due to the ruptur of the bond C4–O22 (bond order = 1.205 and low bond strain = 0.030 kJ mol^{-1}) of low possibility. This is explained by another low possibility due to the loose of $C_8H_{13}O$ part (Scheme 1 path 2′) as a result of C13–C14 rupture (of high bond order = 0.964 and low bond strain = 0.0011 kJ mol^{-1}). This mass fragmentation of Scheme 1 path 1 is more or less similar to that of TA possibilities, while that MS fragmenta-

tion represented by Scheme 1 path 2 and path 2′ are greatly different from TA fragmentation possibilities. The difference of TA fragmentation from MS fragmentation of codeine drug molecule can be explained by the fact that in MS, the molecular ions in gas phase undergoes many skeletal rearrangements (Scheme 1), which is related to its charge distribution in its positive form (Figs. 3b and 4b) differed from the neutral molecule (Figs. 3a and 4a) thermally decomposed and consequently difference in fragment possibilities between MS and TA techniques. TA and MS agree in loss of C_3H_7N, H_2O (in TA in case of there is no skeletal rearrangement) and differ in loss of $C_3H_7N + OH$ in MS (Scheme 1 path 1). This difference is due to skeletal rearrangements (Scheme 1, paths 2 and 2′). It is clear that if there is a charge distribution or skeletal changes due any reason like complex formation, the MA and TA fragmentation of the drug will changed. Therefore, it is important to note the MS and TA fragmentation behavior of the drug in its complexes formed with transition metal cations of essential biological roles like Fe(II), Fe(III), Co(II), Co(III), Ni(II), Cu(II) and Zn(II). It is also necessary to study the effect of complex formation of codeine with some transition d-block elements on the thermal decomposition of this drug, via studying the thermal decomposition behavior of these complexes in comparison with their mass spectra. The structures of these complexes were previously proposed and approved by Zayed et al. [22,23] and it take the formulae (Fig. 5).

From the formulae of these complexes in Fig. 5, it is clear that the strength of bonds (i.e. the stability) of drug to the metal cations depends mainly on the charge distributed on its atoms (Figs. 3 and 4) especially O21, O22 and O23 as donor centers, which actually changed during complex formation.

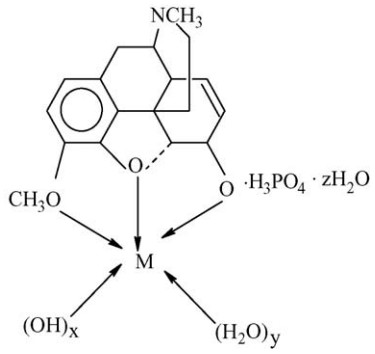


Fig. 5. The structural formulae of codeine phosphate complexes of d-block metals (M), M: Co(II), Ni(II) and Cu(II), $x = 1$, $y = 0$, $z = 0$; Fe(II), $x = 1$, $y = 2$, $z = 1$; Fe(III), $x = 2$, $y = 1$, $z = 0$; Co(III), $x = 0$, $y = 2$, $z = 1$; Zn(II), $x = 1$, $y = 0$, $z = 3$.

This change in charge and its redistribution in complexes, shall affect surely the thermal and mass fragmentation of the drug skeleton in the moiety of these complexes.

It is clear from Table 5 and detailed discussion of thermal behavior of these complexes in comparison with their mass spectra and the sequence of delivered fragments thermally decomposed from the drug skeleton depend upon the type of metal in the moiety of the complex. In this situation Fe(II)–Cod. complex loosed drug fragments as H_2O, CH_3N followed by C_2H_4, CH_3OH and $2H_2O$; Fe(III)–Cod. loosed CH_3N, C_2H_4, C_2H_2, CO_2, and CH_3O molecules; Co(II)–Cod. loosed CH_3N, $2C_2H_4$, C_2H_3 and CH_3O molecules; Co(III)–Cod. loosed CH_3N, CH_3O, $2NO_2$ and H_2O, NI(II)–Cod. loosed CH_3N, CH_3O, $2C_2H_4$ and OH^-; Cu(II)–Cod. loosed CH_3OCH_3, C_2H_4N and loosed OH^-; and Zn(II)–Cod. loosed of OH^-, and $3H_2O$ molecules.

Table 5
Thermal decomposition data of codeine phosphate complexes

Complex	Temperature range in TG (°C)	Peak temperature in TG (°C)	Mass loss (%)		Assignment
			Calculated	Found	
$[FeL(OH)2H_2O]H_2O{\cdot}H_3PO_4$	27–291	122.5	17.2	16.18	Loss of H_2O, CH_3N, and C_2H_4 and molecules
	241–682	403	13.02	12.36	Loss of CH_3OH and $2H_2O$ molecules and formation of [Fe(rem L)] H_3PO_4 as residue
$[FeL(OH)_2H_2O]H_3PO_4$	25–604	134	26	25.75	Loss of CH_3N, C_2H_4, C_2H_2, C_2O, and CH_3O molecules and formation of [Fe(rem L)]·H_3PO_4 as residue.
$[CoLOH)H_3PO_4$	65–605	146	27.74	29.02	Loss of CH_3N, $2C_2H_4$, C_2H_3 and CH_3O molecules and formation of [CO(rem L)]·H_3PO_4 as residue
$[CoL(NO_2)2H_2O]H_2O{\cdot}H_3PO_4$	54–604	166	29.2	29.14	Loss of CH_3N, CH_3O, $2NO_2$ and H_2O molecules and formation of [Co(rem L)]·H_3PO_4 as residue.
$[NiL(OH)]H_3PO_4$	22–601	150	28.11	28.83	Loss of CH_3N, CH_3O, $2C_2H_4$ and OH^- and formation of [Ni(rem.L)]·H_3PO_4 as residue
$[CuL(OH)]H_3PO_4$	36–230	129	9.67	9.79	Loss of $CH_3O{\cdot}CH_3$ molecule
	234–495	316	8.83	8.21	Loss of C_2H_4N molecule
	497–865	720	3.57	3.36	Loss of OH^- and formation [Cu (rem L)]·H_3PO_4 as residue
$[ZnLOH]3H_2O{\cdot}H_3PO_4$	39–159	88	8.62	8.68	Loss of Loss of OH^- molecule
	160–660	296	9.56	9.30	Loss of $3H_2O$ molecules and formation of [Zn(rem L) OH]·H_3PO_4 as residue

The loss of these fragments and their sequences from the drug molecule in skeleton of the complexes changes from one metal to the other. It depends upon the metal cation size and its charge per unit volume. It also depends on the charge redistribution on atoms of the complex skeleton occur during complex formation. Finally it is related to the effect of metal cation charge on the electron density of coordination centers. Consequently, this leading to the change of the mode of fragmentation of ligand molecule during heating of the complex. This behavior is greatly different from that occur in thermal treatment of the pure drug. Mass spectra show the remainder parts of the complexes after each fragmentation step, which are identified as molecular ions. In MS the Fe(II)–Cod. shows molecular ions of $m/z = 522$ (RI = 17.39%) corresponding to the complex $[M]^+$, followed by, molecular ion of $m/z = 437$ of corresponding to the remainder complex after loss of H_2O, CH_3N and CH_3O of Σ mass = 85 in a similar way to the TA losses. This means that the thermal decomposition pathways are in congers with the proposed mass spectral pathways of Fe(II)–Cod. complex. In case of Fe(III)–Cod. complex, it shows a molecular ion of $m/z = 452$ (RI = 13.13%) followed by a molecular ion of $m/z = 370$ (RI = 2.7 %) as a result of the losses of CH_3N, C_2H_4, CO_2 and CH_3O of $\sum$ mass = 82. This means that some differences are present between TA and MS data of Fe(III)–Cod. complex. The mass spectra of Co(II)–Cod. complex show molecular ion of $m/z = 465$ (RI = 3.37%) of the complex itself, followed by molecular ion of $m/z = 322$ (RI = 5.47%) as a result of loss CH_3N, $2C_2H_4$, C_2H_3 and CH_3O of $\sum$ mass = 143. This means that mass confirm TA drug mass losses of Co(II)–Cod. complex. Co(III)–Cod. complex (MW = 582) MS show a molecular ion of $m/z = 412$ (RI = 23.0%) as result of loss of CH_3N, CH_3O, $2NO_2$ and H_2O of $\sum$ mass = 170. The loss of CH_3N and CH_3O is more or less similar to the parts loosed from the drug by TA. Ni(II)–Cod. complex MS show a molecular ion of $m/z = 473$ of RI = 1.0% of the complex itself. It give another molecular ion of $m/z = 337$ of RI = 6.31%, which may account for the loss of CH_3N, CH_3O, $2C_2H_4$ and OH molecules of $\sum$ mass = 134. This means that most of mass fragments coming from drug in the moiety of this complex are similar to those obtained by TA fragmentation of the pure drug. The MS of Cu(II)–Cod. complex show three molecular ions in three steps like its thermal fragmentation behavior. The first molecular ion appear at $m/z = 476$ of RI = 8.42%, which is related to the complex itself. The second molecular ion appear at $m/z = 430$ (RI = 7.89) as a result of CH_3OCH_3 loss of mass = 46. It followed by molecular ion of $m/z = 388$ (RI = 11.05%) as a result of loss of C_2H_4N of mass = 42 and finally it gives a molecular ion of $m/z = 370$ of RI = 4.21 as a result of the loss of OH group in the form of H_2O. The MS of Zn(II)–Cod. show the molecular ion of the complex itself at $m/z = 535.5$ (RI = 12.56%) which loosed CH_3OCH_3 to give a molecular ion of $m/z = 490$ (RI = 12.27%). Finally it gives a molecular ion of $m/z = 436$ (RI = 13%) as a result of loss of $3H_2O$ one of them may reasonably account for the loss of OH of the legend and the other two as water of coordination. Therefore, we may assign this behavior to Zn(II) cation as one live at the end of 3d series and of $3d^{10}$ electronic configuration, i.e. non-transitional ion. The detailed discussion of thermal and mass fragmentation of these complexes show that most of fragments coming from the legend in moiety of complexes are more or less similar to those obtained by mass and thermal fragmentation of pure drug. Sometimes it is different depending upon the nature of the metal itself in the complex species and/or due to the presence of other constituents in the complex moiety more than the drug like nitrite in Co(III) complex and water molecules or OH used of completing the coordination number of the metal cation. The main difference is that in mass spectra the OH^- corresponds to water molecule in TA. In most complexes some loosed water molecules are coming from the loss of water of crystallization and/or coordinated water. The water molecules loosed from drug itself are coming from OH group and proton from aromatic skeleton of the drug.

References

[1] J.M. Gulland, R. Robinson, M. Mem. Lit. Phil. Soc. 69 (1925) 75.
[2] M. Gates, G. Tschudi, J. Am. Chem. Soc. 78 (1956) 1390.
[3] D. Ginsburg, The Opium Alkaloids, Interscience Publishers Inc., New York, 1962.
[4] M. Mackay, D. Crowfoot-Hodgkin, J. Chem. Soc. 3261 (1955) 1.
[5] J.M. Lindsey, W.H. Barnes, Acta Crystallogr. 8 (1955) 227.
[6] G. Kartha, F.R. Almed, W.H. Barnes, Acta Crystallogr. 15 (1962) 326.
[7] H. Engelhardt, T. Koenig, Chromatographia 28 (1989) 341.
[8] T. Turcant, A.C. Premel, A. Cailleux, P. Allain, Clin. Chem. 37 (1991) 1210.
[9] H.J. Fang, H.J. Duan, T.H. Zhou, Yaoxue Xuebad 24 (1989) 759.
[10] F. Sayin, S. Kir, A. Temizer, FABAD Farm. Bilimler DERG. 21 (1996) 155.
[11] I.E. Cone, W.C. Goradetzky, Y.S. Yeh, D.W. Darwin, J. Chromatogr. 230 (1982) 57.
[12] M. Junack, A. Eicke, W. Sichtermann, S.A. Bennighoveny, Ser. Chem. Phys. 25 (1983) 177.
[13] D.M.S. Wheeler, T.H. Kinstle, K.L. Rinehart, J. Am. Chem. Soc. 89 (1967) 4494.
[14] L.J. Hayanes, G.E.M. Husband, K.L. Tuart, J. Chem. Soc. (c) 951 (1968) 1.
[15] H. Audier, M. Feitzon, D. Ginburg, A. Madelbaum, T. Rubl, Tetrahedron Lett. 13 (1965) 1.
[16] H. Nakabi, Y. Hirata, A. Tatematsu, A. Tada, Y.K. Sawan, Tetrahedron Lett. 29 (1981) 1.
[17] B.S. Larsen, C.N. McEwen (Eds.), Mass Spectrometry of Biological-Materials, Maecel-Dekker, New York, 1998.
[18] K. Levsen, Fundametal Aspects of Organic Mass Sopectrometry, Verlag, Chemie, Weinheim, New York, 1978.
[19] S. Bourecier, E. Hoppilliiard, Eur. J. Mass Spectrom. 9 (2003) 351.
[20] M.A. Fahmey, M.A. Zayed, Y.H. Keshok, Thermochem. Acta 366 (2001) 183.
[21] M.A. Fahmey, M.A. Zayed, J. Therm. Anal. Calorimet. 67 (2002) 163.
[22] M.A. Zayed, M.F. El-shahat, S.M. Abdullah, Spectrochem. Acta, Part A 61 (2005) 1955.
[23] M.A. Zayed, S.M. Abadallah, Spectrochem. Acta, Part A 60 (2004) 2215.
[24] A. Somogi, A. Gomory, K. Vekey, A. Tamas, J. Org. Mass Spectrom. 26 (1991) 936.

[25] J.I.P. Stewart, J. Comp. Chem. 10 (1989) 209.
[26] J.I.P. Stewart, Fuujitsu Limited, Tokyo, Japan, EF Routine (Eigen Vector Following), 1999.
[27] J. Baker, J. Comp. Chem. 7 (1986) 385.
[28] G.B. Waller, Biochemical Applications of Mass Spectrometry, Wiley/Interscience, New York, 1972.
[29] M.A. Fahmey, M.A. Zayed, H.G. El-Shobaky, Therm. Anal. Calorimet., 2005, in press.
[30] M.A. Zayed, M.A. Fahmey, M.F. Hawash, Egypt. J. Chem., 2005, in press.
[31] M.A. Zayed, M.A. Fahmey, M.F. Hawash, Spectrochem. Acta, Part A 61 (2005) 799.
[32] (a) M.A. Zayed, S.M. Abdallah, Spectrochem. Acta, Part A 61 (2005) 2231;
(b) G.G. Mohamed, M.A. Zayed, F.A. Nour El-Dien, R.G. El-Nahas, Spectrochem. Acta, Part A 60 (2004) 1775.