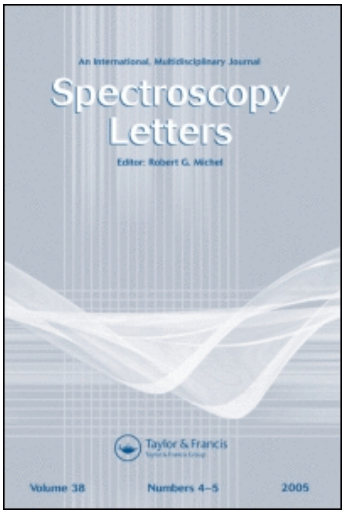

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Anwar S. El-Shahawy[a]; Abu-Bakr M. El-Nady[a]; Seddique M. Ahmed[a]; Nager Kh. Sayed[a]
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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Some CNDO Calculations and Structural Spectroscopic Studies of Paracetamol Complexes

Anwar S. El-Shahawy, Abu-Bakr M. El-Nady, Seddique M. Ahmed, and Nager Kh. Sayed
Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

Abstract: Through complete neglect of differential overlap (CNDO) calculations of the electronic energy among different possible structures of paracetamol (PA) molecule, it has been concluded that its structure has C_s point group symmetry of the *cis*-form in which the methyl group has a restricted free rotation around its bond with the carbon atom of the amide group. The electronic spectra of PA compound were studied in different polar and nonpolar solvents. The temperature effect on the electronic spectra confirms the presence of one conformer only. The hydrogen bonding and the orientation energies of the polar solvents were determined from the studies of mixed solvents. Complexes of PA with metal ions M(II) (Cu^{++}, Zn^{++}, or Fe^{++}) of ratio 2:1, respectively, were prepared, and their structure has been confirmed by elemental analysis, atomic absorption spectra, IR spectra, and ^{1}H-NMR spectra. It has been concluded that the structure of the complexes has C_{2h} point group symmetry in which two PA molecules are chelated to any one of the metal ions Cu^{++}, Zn^{++}, and Fe^{++}.

Keywords: CNDO, H-NMR, IR, Paracetamol, UV

INTRODUCTION

Paracetamol (pA) is an analgesic antipyretic drug with no anti-inflammatory effects and is widely used worldwide.[1] A review by Vial et al.[2] with 93 references discusses the clinical side effects of paracetamol in terms of the

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Address correspondence to Anwar S. El-Shahawy, Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt. E-mail: anwarshahawy@yahoo.com

following system processes: allergic and skin; hematol; renal; pregnancy and lactation; carcinogenesis. Decreasing bioavailability effect of EtOH on paracetamol was studied by Wojcicki et al. [3] in healthy men.

A continuous flow-based spectroscopic method for the determination of PA in pharmaceuticals has been reported by Criado et al.[4] to hydrolyze dilute samples containing PA. The important hydrogen bonding in drug–receptor interactions has been studied by Ghafourian et al.[5] to determine the partitioning of PA drug between phases, and the atomic charge on the most positive charged hydrogen atom in the molecule from the energy of the lowest unoccupied molecular orbit (LUMO) is the measure of hydrogen bond donor capacity using three semiempirical methods AM_1, PM_3, and MNDO, therefore the comparison of the modified neglect of differential overlap (MNDO) electrostatic derived atomic charges with the solvatochromic hydrogen bonding acidity has been correlated. The ultrasonic compaction studies that are capable of providing compaction pressure together with high power ultrasonic vibrations of 20 kHz to a powder or granular PA have been developed by Levina et al.[6] The simultaneous determination of some analgesic ingredients was described by Medenica et al.[7] using the spectrophotometer method. A simple spectrophotometer method based on the reaction of the hydrolyzed product of PA with $K_2Cr_2O_7$ to form a suitable violet-colored chromogen that can be quantitatively measured at 550 nm has been reported by Chowdary[8] using Bear's law in the concentration range 0–5.0 mg/mL. Paracetamol can be detected quantitatively by dissolving in analytical grade water.[9] The interference of degradiation products in the UV spectrophotometry of PA is the main obstruction in using this method in drug thermal stability by Correa et al.[10] A method of spectroscopic determination of paracetamol based on color reaction with 2-hydrazone-3-methylbenzothiazoline (MBTH) was worked out by Pospisilova et al.[11] A spectrophotometric method[12] is proposed for the determination of PA in pure form in tablets, and this method depends on the reactions of drug with ammonium molybdate in strongly acidic medium to produce molybdenum blue.

The preference of *cis*-amide structure in *N*-methylanilides both in crystal and solution was studied by Saito et al.[13] using *ab initio* molecular orbital calculations for acetanilide and *N*-methylacetanilide. The gas phase conformations of a series of isolated *N*-phenylamides have been determined by Manea et al.[14] from vibrationally resolved electronic spectra obtained by resonant two photon ionizations in supersonic jet expansion. Both the *cis* and *trans* isomers of formanilide were identified with the *cis* isomer in 6.5% abundance. The restricted rotation about the carbonyl–nitrogen bonds of acetanilide has been investigated by Moriyasu et al.[15] by means of high-performance liquid chromatography (HPLC). The hydrogen bonds in the structural distortion of the monoclinic and the orthorhombic polymorphs of PA induced by hydrostatic pressure were studied by Boldyreva et al.[16] who noticed two groups of phenomena including the anisotropic structural distortion of the same polymorph and the transition between the polymorphs induced by pressure.

The conversion of two polymorphic forms in range of temperature was studied by Beyer et al.[17] using the reflection limitation of x-ray crystallography and the dynamical motion of the methyl group. The structures of three bioactive molecules containing PA molecule were described by Wilson et al.[18] together with a brief account of the molecular geometry and hydrogen bonding. By using FTIR and Raman spectroscopic studies, Al-Zoubi et al.[19] suggested the identification of orthorhombic and monoclinic PA.

EXPERIMENTAL

The solvents were purified according to literature.[20–23] Paracetamol was purified by recrystallization from water or ethyl ether and its melting point has been detected to be 168°C. The materials that were used to prepare the complexes in addition to PA are $FeSO_4 \cdot 7H_2O$ (Adwic), $Cu(OCOCH_3)_2 \cdot H_2O$ (Al Nasr Pharmaceutical Chemical Company, Egypt), and $Zn(OCOCH_3)_2 \cdot 2H_2O$(BDH).

Preparation of complexes between PA and Cu^{++}, Zn^{++}, or Fe^{++} was done by refluxing PA with metal ion salt in ethanolic solution in ratio 2:1 ligand to metal ion (M^{++}) for about 6–8 hr. By cooling the reaction solution after filtration to 5°C, the complex is precipitated and then washed firstly by ethanol and secondly by diethyl ether. Table 1 contains the melting points of the prepared complexes.

Purification of the complexes studied was verified by TLC using 5 × 15 cm glass plate covered by a thin film of silica gel (60 mesh). The UV-visible spectra of the studied compounds had been scanned by a UV-2101 PC UV-Vis scanning spectrophotometer (Shimadzu, Japan). The temperature effect on the PA spectrum has been scanned by a Perkin Elmer Lambda 35 UV/Vis spectrophotometer. The atomic absorption spectra of the complexes were studied by using an atomic absorption spectrophotometer (Buck Scientific, Model 210 GVP, U.S.A.). The infrared spectra of the studied compounds were scanned by Shimadzu 470 Infrared spectrophotometer (Japan) using KBr wafer and thin film techniques. The elemental analyses of complexes were done by using Elementer Analysensyteme, GmbH, Donaustr-7, D-63452 (Hanau, Germany).

All melting points of the studied compounds were determined on the electric melting point operators (Gallen-kamp, Japan). ^{1}H-NMR spectra were recorded in deutrated dimethylsulfhoxide (DMSO) with a JNM-LA

Table 1. Melting points of the complexes

Complex	Melting point (°C)
PA–Cu^{++}	130
PA–Zn^{++}	153
PA–Fe^{++}	155

400 a MHz FT-NMR spectrometer (Japan). All chemical shifts (δ) are given in ppm versus tetra-methylsilane (TMS).

Method of Calculations

The electronic energies have been calculated by CNDO calculations using the following equation:[24]

$$\varepsilon = 2\sum_{i}^{n} H_{ii} + \sum_{i}^{n} J_{ii} + \sum_{i}^{n}\sum_{j(\neq i)}^{n} (zJ_{ij} - K_{ij})$$

where H_{ii} is the expectation value of the one-electron core Hamiltonian corresponding to the molecular orbital, and J_{ij} is the coulomb integral and mathematically can be expressed as follows:

$$J_{ij} = \int \Psi_i^*(1)\ \Psi_j^*(2)\frac{1}{r_{12}}\Psi_i(1)\ \Psi_j(2)\ d\tau_1 d\tau_2$$

and K_{ij} is the exchange integral and can be expressed mathematically as follows:

$$K_{ij} = \int \Psi_i^*(1)\ \Psi_j^*(2)\frac{1}{r_{12}}\Psi_j(1)\ \Psi_i(2)\ d\tau_1 d\tau_2$$

It is useful to define a set of one electron orbital energies,

$$\varepsilon_i = H_{ii} + \sum_{j}^{n} (2J_{ij} - K_{ij})$$

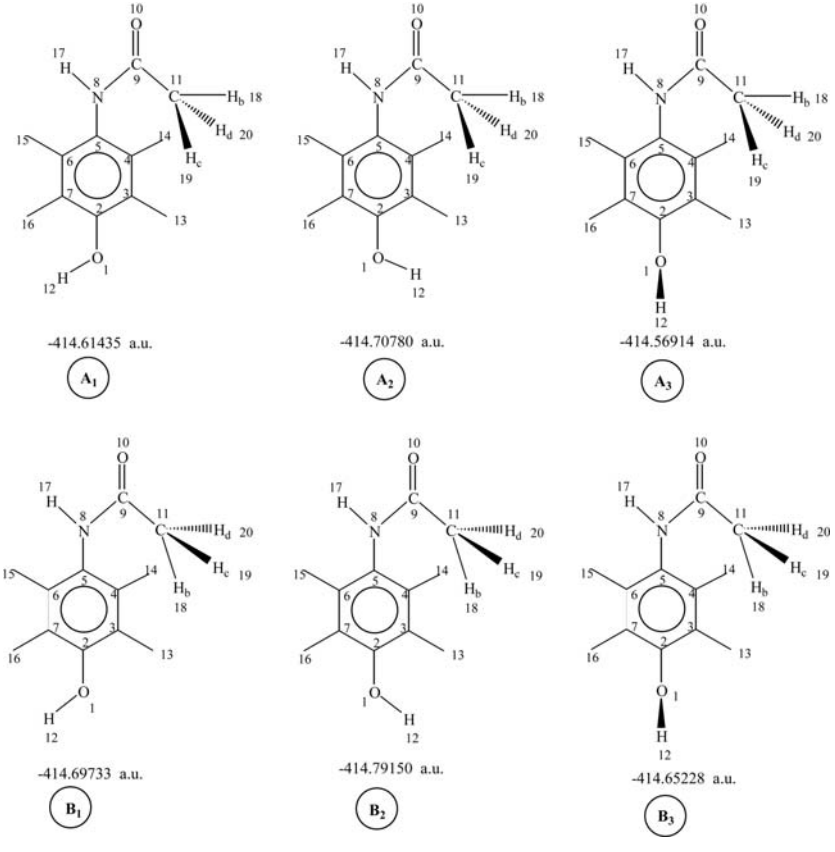
and this is essentially the energy of an electron in the molecular orbital Ψ_i interacting with the core and the other $2n - 1$ electrons. Assuming that there is no recognition of the other $2n - 1$ electrons on ionization, ε_i may be the ionization potential of an electron in Ψ_i.

RESULTS AND DISCUSSION

From CNDO calculations of PA molecules, it has been found that the B_2 structure of the *cis* form has the lowest electronic energy -414.7915 au among different possible structures, especially with the *trans* forms (Scheme 1), the restricted rotation of the methyl group by $\pm 90^\circ$ around its bond with the carbon atom of the carbonyl group in the amide moiety in PA molecule does not affect strongly the electronic energy of PA molecule in B_2' structure -414.7425 au, (Scheme 2), which is not far from the value of the electronic energy of B_2 structure. Therefore, the most abundant B_2 structure has a dynamic stability with a restricted free rotation of the methyl group. The electronic energy difference between the *cis* structure of B_2 and the others, especially the *trans* form, does not permit the presence of

conformers between the *cis* and *trans* forms, and this has been confirmed by the heat effect on the electronic spectrum of PA in ethyl alcohol as a solvent at 249 nm (Fig. 1). It has been noticed that the variation of the temperature of PA sample during the UV scanning does not affect the relative intensity of PA spectrum except very slight changes at $\lambda_{max} = 249$ nm in ethanol due to the contraction of the ethanolic solution at lower temperatures, which increases slightly the concentration hence the absorbance at the same wavelength. The restricted rotation of the methyl group in the amide moiety in PA molecule of B_2 structure does not affect strongly the calculated dipole moment, ionization potential, and electron affinity (Table 2).

Generally, the charge densities of PA atoms in B_2 structure are not affected drastically by the restricted free rotation of the methyl group in B_2' structure (Table 3). The negative charges are concentrated mainly on the



Scheme 1. The electronic energies of different possible structures of paracetamol molecule.

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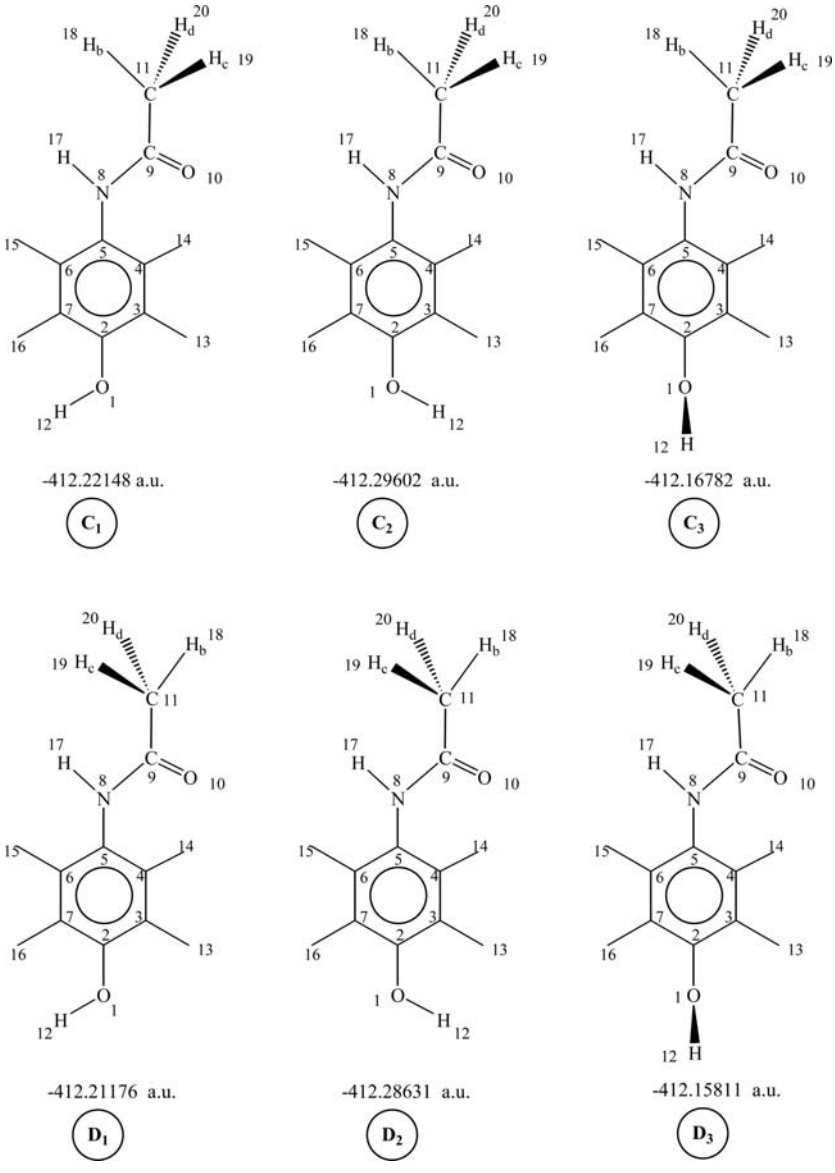
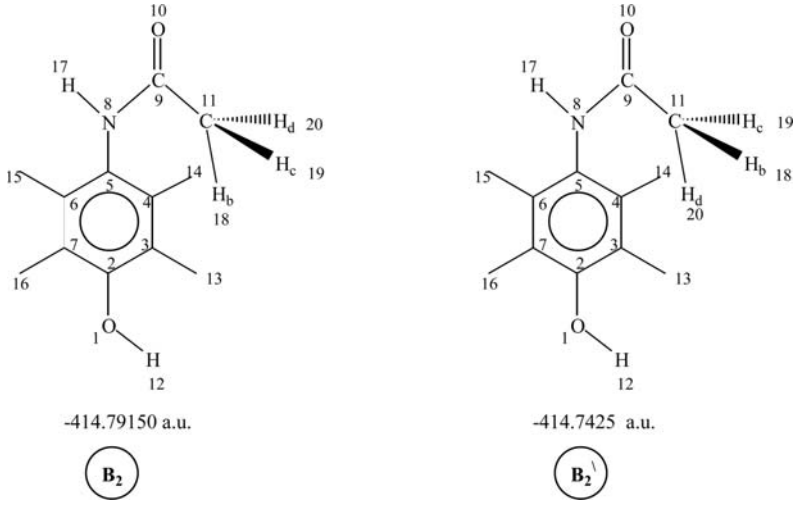


Scheme 1. Continued.

oxygen atoms in PA molecule especially on the carbonyl oxygen atom (-0.3427) compared with the negative charge of the oxygen atom of the hydroxyl group in the para position (-0.2506). It can be noticed also that the hydrogen atom attached to the nitrogen atom in the amide moiety has a remarkable positive charge $+0.1201$ in B_2 structure, which is not far from



Scheme 2. B_2 structure of the restricted rotation ± 90 in $B_2^{\backslash}$ structure.

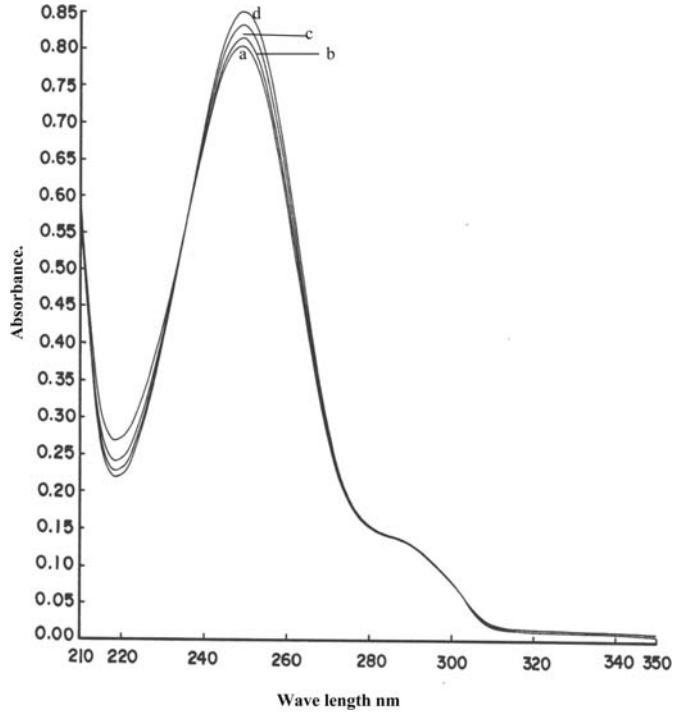


Figure 1. The heat effect on the electronic spectrum of PA molecule in EtOH: (a) at 45°C, (b) at 35°C, (c) at 25°C, and (d) at 15°C.

Table 2. CNDO calculated parameters of PA molecule

Calculated parameters	B_2 structure	B_2' structure
dipole moment	2.3518 D	2.3349 D
Ionization potential	0.3947 au	0.3952 au
Electron affinity	−0.1335 au	−0.1313 au

the positive charge value of the hydrogen atom of the hydroxyl group in the para-position of the PA molecule, +0.1403.

The UV spectra of PA have been scanned in solvents of different polarity such as ethanol, methanol, isopropanol, carbon tetrachloride, and distilled water. It has been noticed that the lifetime τ of the excitation has its maximum value in case of $CC1_4$ solvent, 8.93×10^{-9} s. The electronic transition energies in PA electronic spectra have been blue-shifted with increasing the solvent polarity from 261 nm in $CC1_4$ solvent to 243 nm in H_2O solvent (Table 4).

The Einstein transition probabilities, A_{if} and B_{if}, have their maximum values in the case of isopropanol as a solvent, $7.37 \times 10^8\,s^{-1}$ and $2.28 \times 10^9\,sg^{-1}$, respectively, and the dipole strength D_{if} has its maximum value in the same solvent, 1.57×10^{-16} (Table 4).

Table 3. CNDO charge densities of PA molecule

No. of atom	Atom	Charge densities of B_2 structure	Charge densities of B_2' structure
1	O (OH)	−0.2506	−0.2500
2	C benz.	+0.1567	+0.1569
3	C benz.	−0.0314	−0.0338
4	C benz.	−0.0989	−0.0776
5	C benz.	+0.1256	+0.1250
6	C benz.	−0.0326	−0.0321
7	C benz.	−0.0263	−0.0265
8	N(NH)	−0.2198	−0.2181
9	C (C=O)	+0.3721	+0.3661
10	O (C=O)	−0.3427	−0.3345
11	C (M_e)	−0.0978	−0.0859
12	H (OH)	+0.1403	+0.1409
13	H benz.	−0.0027	+0.0000
14	H benz.	+0.0691	+0.0554
15	H benz.	+0.0017	+0.0026
16	H benz.	+0.0091	+0.0099
17	H (NH)	+0.1201	+0.1193
18	H_b (M_e)	+0.0374	+0.0401
19	H_c (M_e)	+0.0353	+0.0186
20	H_d (M_e)	+0.0353	+0.0237

Table 4. The Einstein transition probabilities (A_{if} and B_{if}), dipole strength (D_{if}), oscillator strength (F_{if}), and lifetime τ of the electronic transition bands of PA in different solvents

Solvent	λ_{max} (nm)	$A_{if} \times 10^{-8}\ s^{-1}$	$B_{if} \times 10^{-9}\ sg^{-1}$	$D_{if} \times 10^{16}$	F_{if}	$\tau \times 10^{9}$ s
Isopropanol	249	7.3699	2.2787	1.5716	0.685	1.3569
Ethanol	249	4.9119	1.5187	1.0474	0.457	2.0359
Methanol	248	4.7479	1.4504	1.0003	0.438	2.1062
CCl_4	261	1.1199	0.3988	0.2750	0.114	8.9296
Water	243	1.9083	0.5484	0.3782	0.169	5.2403

The mixed solvents studies have been tabulated in Table 5, in which the commutative data of PA in different mixed solvents are given below.

The maximum wavelength λ_{max} of PA UV-spectra have been blue-shifted with increasing the mole fraction of the polar solvent in the mixed solvents with respect to the other of lower polarity (e.g., from 261 nm in the case of 100% CCl_4 to 249 nm in case of 100% isopropanol for example). On plotting the excitation energy ΔE in kJ mol^{-1}, against the mole fraction of isopropanol with respect to CCl_4 solvent, a broken line with three segments is obtained.

The first segment indicates the orientation energy, which is equal to 5.2 kJ mol^{-1} for the isopropanol molecules toward PA molecule in the ground and excited states. The second segment corresponds to the molecular complex formation between isopropanol molecules with PA molecule, which is the hydrogen bonding energy between them. The hydrogen bonding energy in this case is equal to 16.8 kJ mol^{-1}. The third segment represents the steady state of energy attained after complex formation of the isopropanol-PA complex. In case of $EtOH/CCl_4$ mixed solvents, the orientation energy of EtOH molecules toward PA molecule is equal to 7.2 kJ mol^{-1}, the hydrogen bonding energy between ethanol molecules and PA molecule is equal to 14.8 kJ mol^{-1}. Scoping on the case of $H_2O/EtOH$ mixed solvents, the orientation energy of H_2O molecules around PA molecule is equal 9.9 kJ mol^{-1}. Extending our scoping to the case of $EtOH/H_2O$ mixed solvents, the orientation energy of EtOH molecules toward PA molecule is equal to 4.0 kJ mol^{-1}, and the hydrogen bonding energy between EtOH molecules and PA molecule equals 7.9 kJ mol^{-1}. The free energy ΔG of formation of EtOH/PA complex in case of $EtOH/H_2O$ mixed solvents equals 5.02 kJ mol^{-1} but it has a higher value in case of $H_2O/EtOH$ mixed solvents, 7.59 kJ mol^{-1}. A support of hydrogen bond formation between PA and solvent molecules may be obtained by determining the stability constant of the complex formed, K_f. The method used for determination of stability constant K_f of solvent–PA complex depends on the fact that absorbance variation when adding the different proportions of the proton donor is the

Table 5. Commutative data of PA in mixed solvents

Mixed solvents	Orientation energy (kJ mol^{-1})	H-bonding energy (kJ mol^{-1})	n = 2	K_f	$-\Delta G$ (kJ mol^{-1})
$EtOH/CCl_4$	7.2	14.8	1.55	7.114	4.856
$MeOH/CCl_4$	8.8	15.0	1.66	13.960	6.524
Isoprop./CCl_4	5.2	16.8	1.77	6.18	4.508
$H_2O/EtOH$	1.8	9.9	2.11	21.48	7.591
$EtOH/H_2O$	4.0	7.9	2.22	7.59	5.016

K_f, formation constant; ΔG, free energy.

measure of formation tendency of the solute–solvent complex. The stability constant of the solute–solvent complex has its maximum value in case of H_2O/EtOH mixed solvents and is equal to 21.48 kJ mol^{-1}, and the maximum free energy ΔG of formation of H_2O/PA complex has the maximum value 7.59 kJ mol^{-1}. Generally, the number of solvent molecules oriented toward PA molecule to be molecular complex does not exceed 2 molecules from the solvent.

Table 6. The IR spectrum assignments of paracetamol

Wave number (cm^{-1})	Intensity	Assignment
3300	s	ν (N–H) and ν (O–H)
3200 (sh)	m	
3150 (broad)	vs	ν C–H
1640	vs*	ν C═O
1600	s	8a (benzene ring)
1560	vs	8b (benzene ring)
1540 (sh)	s*	δ (CNH) in the amide group
1500	vs	19a (benzene ring)
1440 (broad)	vs	19b asymm. Deformation of Me and ν (CH_3–CO)
1370	s	Symm. Deformation of Me group
1320	s	14 overlapped with ν φ-N
1300 (sh)	m	15
1260	vs*	δ (CNH) in the amide group
1240	vs	ν φ–OH
1220	vs	7a
1180 (sh)	m	9a
1160	m*	δ (N–H)
1100	m	13
1065 (sh)	w	18b
1022 (sh)	m	18a
1005	m	CH_3 rock
960	m	5
920 (sh)	w	17b
840	s*	δ C═O
800	s	1
790 (sh)	s	12
720	s	Out of plane wagging of NH (amide group)
705	s	4
650 (sh)	m	6b
620	m*	δ φ–OH
600	m	δ C–CH_3
500	s	16b

φ, benzene ring; ν, stretching; δ, in-plane-bending; vs, very strong; s, strong; m, medium; and w, weak.

The IR spectrum of PA has been assigned according to the texts[25,26] as shown in, Table 6 as follows. The CNH vibration in which N and H atoms move in opposite direction of carbon atom in the amide moiety appears as a shoulder at 1540 cm^{-1}, the CNH vibration in which N and H atoms move in the same direction of the carbon atom in the amide group appears at 1260 cm^{-1}, and the NH rock in the plane appears at 1160 cm^{-1}. The out-of-plane wagging of NH of the amide moiety appears at 720 cm^{-1}.

The stretching vibration of the carbonyl group appears at 1640 cm^{-1} and the in-plane-bending vibration of the carbonyl group appears at 840 cm^{-1}. The stretching vibration of the hydroxyl group (ν Benz-OH) with respect to the phenyl moiety appears at 1240 cm^{-1}, and the appearance of the in-plane-bending vibration of the hydroxyl group with respect to the benzene moiety (δ Benz-OH) at 620 cm^{-1}.

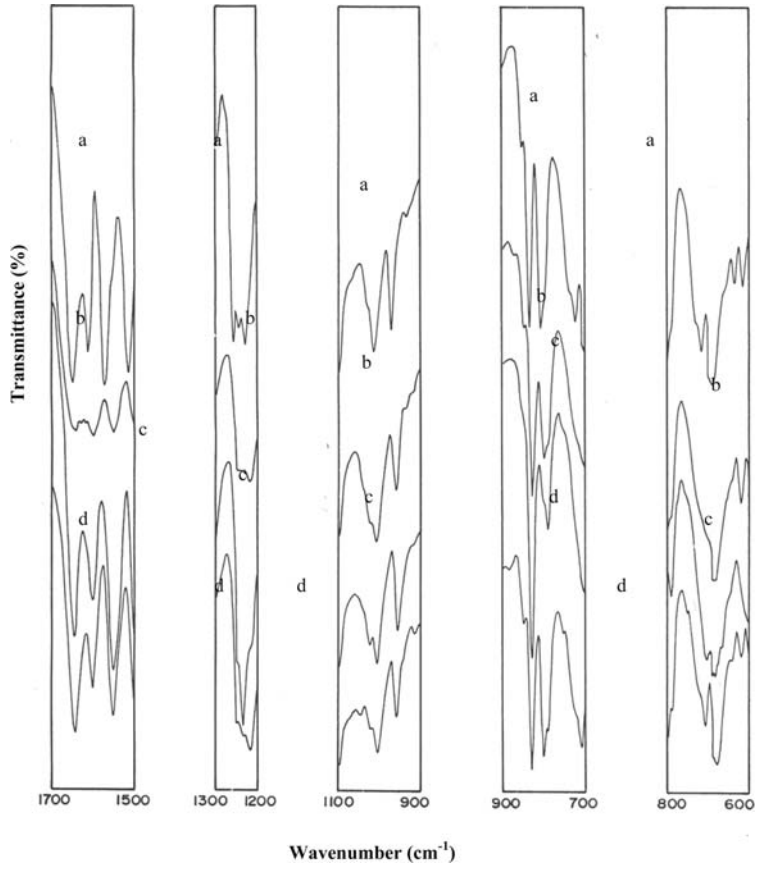


Figure 2. Comparative IR spectra among (a) paracetamol with (b) $(PA)_2-Cu^{++}$, (c) $(PA)_2-Zn^{++}$ and (d) $(PA)_2-Fe^{++}$.

Table 7. The atomic absorption data of the complexes

Complex	% Theoretical	% Experimental
$(PA)_2-Cu^{++}$	17.47	17.41
$(PA)_2-Zn^{++}$	16.11	15.98
$(PA)_2-Fe^{++}$	11.54	11.46

From the comparative studies of ir spectra of paracetamol and the complexes (Fig. 2), the changes of the relative intensities of their IR-bands of the complexes after chelating of PA with the metal ions M^{++} (Cu^{++}, Zn^{++}, or Fe^{++}) indicates the change of the C_s point group of PA molecule to another point group in the complex molecule.

Dealing with the atomic absorption spectra (Table 7), it has been found that the theoretical percentage of the metal ions (e.g., Cu^{++}) is nearly coincident with the experimental percentage (17.47 and 17.41, respectively). Generally, the theoretical percentage of metal ion M^{++} in the atomic absorption spectra has a good coincidence with the experimental metal ion percentage in accordance with the ratio 2:1 PA to M^{++} in the complex.

From the nitrogen elemental analyses, (Table 8), the theoretical percentages of nitrogen element have good coincidence with the experimental percentages of nitrogen element in the complex confirming the ratio 2:1 PA to M^{++} in the complex.

From the atomic absorption spectra data and from the elemental analyses of nitrogen element of the complexes, it can be concluded that the complex molecule has been formed by the chelation of two molecules of PA with a metal ion M^{++}.

From the comparative IR spectra of PA and complexes (Fig. 2), we notice a slight blue shift of the stretching vibration band of the carbonyl group at $1640\,cm^{-1}$ in PA IR spectrum to $1650\,cm^{-1}$ in the complexes spectra, a slight red shift of the in-plane-bending vibration band of the carbonyl group of the PA spectrum at $840\,cm^{-1}$ to $830\,cm^{-1}$ in the complexes spectra, and the disappearance of the in-plane-bending vibration bands of CNH at the positions $1540\,cm^{-1}$ and $1260\,cm^{-1}$ in the IR spectra of the complexes, in addition to the disappearance or the intensity change of the out-of-plane

Table 8. The nitrogen elemental analyses of the complexes

Complex	% Theoretical	% Exprimental
$(PA)_2-Cu^{++}$	7.33	6.7
$(PA)_2-Zn^{++}$	7.0	7.25
$(PA)_2-Fe^{++}$	5.8	6.05

wagging vibration band of NH in the amide moiety at 720 cm^{-1} in the complexes spectra. The appearance of the stretching vibration and the in-plane-bending vibration bands of the hydroxyl group with respect to the phenyl moiety at positions 1240 cm^{-1} and 620 cm^{-1}, respectively, excludes

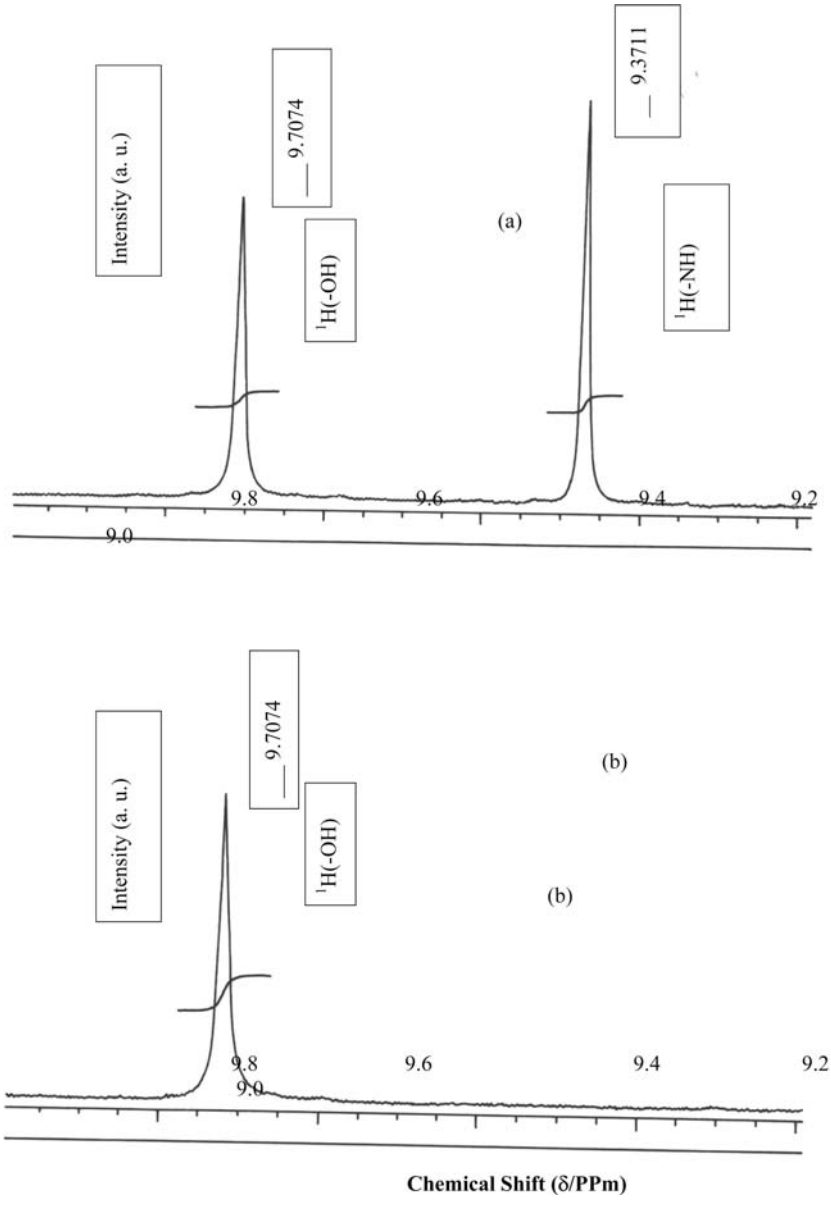
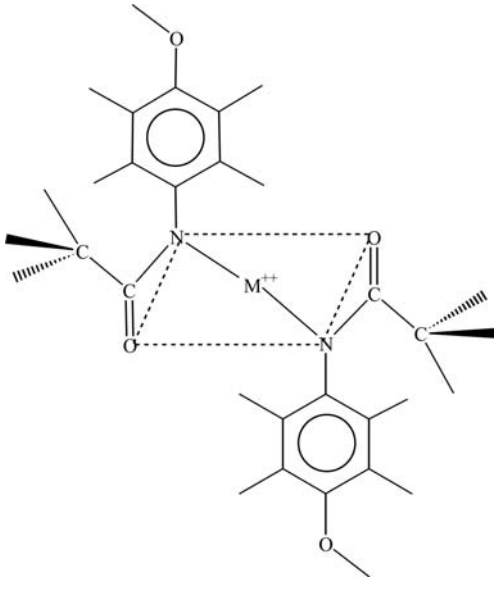


Figure 3. ^{1}H-NMR spectra of (a) paracetamol (PA) and (b) PA–Zn(II).

the contribution of the hydroxyl oxygen atom to be chelated with the metal ion M^{++}, and the appearance of the stretching band of the hydroxyl group between oxygen and hydrogen atom at position $3300\,cm^{-1}$ verifies the assumption of exclusion of the hydroxyl oxygen atom to be chelated with the metal ion in the complex.

Also from the CNDO charge densities point of view (Table 3), it has been found that the carbonyl oxygen atom has a more negative change -0.3427 than the negative charge of the hydroxyl oxygen atom -0.2506 in the B_2 structure of the *cis*-form. Dealing with the hydrogen atoms attached with the amide nitrogen atom and the hydroxyl group at the para-position in PA molecule, they have positive charges with slight difference (Table 3), and hence the hydrogen atom of positive charge -0.1201 of the amide group is ionizable. Because the PA molecule in the *cis*-form of B_2 structure has the more negative carbonyl oxygen atom and the ionizable hydrogen atom of NH moiety in the amide group, therefore this molecule introduces good circumstance to form the complex with metal ions in ratio 2:1 PA to M^{++} in the amide moiety.

The ^{1}H-NMR spectrum of paracetamol (Fig. 3a) has the signals $\delta = 9.27$ and 9.72 ppm, which are due to the protons of the amide group, and the hydroxyl group, respectively. The disappearance of signal $\delta = 9.27$ ppm of the amide hydrogen atom in the ^{1}H-NMR spectrum of the complex of PA with Zn(II) as an example, Fig. 3b, confirms the consumption of the amide hydrogen atom in the complexation between PA and metal ion (M^{++}), and



Scheme 3. The possible structure of $(PA)_2$–M^{++} complex.

the N–H bond in the paracetamol molecule has been replaced by N–M^{++} bond in the complex. The persistence of the signal of the proton of the hydroxyl group in the ^{1}H-NMR spectrum of the complex (Fig. 3b), confirms that the hydroxyl group does not contribute in the complexation between PA and Zn(II) or more generally with M(II), therefore the hydroxyl group is still free in the complex of PA with the metal ion M^{++}.

Therefore, the complexation between two molecules of PA with a metal ion M^{++} has been formed by the chelation of the metal ion with the more negative carbonyl oxygen atoms and the amide nitrogen atoms consuming the amide hydrogen atom to form the complex $(PA)_2$–M(II) including the nitrogen–metal bond, and the complex structure has C_{2h} point group symmetry as shown in Scheme 3, but the paracetamol molecule has the C_s point group symmetry in which the amide group is in the *cis* form.

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