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Scientific Research

DFT Cancer Energy Barrier and Spectral Studies of Aspirin, Paracetamol and Some Analogues

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ABSTRACT

Comparative DFT computations were studied between Paracetamol (PA) and its analogues such as p-nitroacetanilide (PA-NO_2), p-bromoacetanilide (PA-Br) and N-acetylanthranilic acid (NAA) which can be considered also as analogue of Aspirin (ASP). As well, Thio-Aspirin, Acetyl-Thio-Salicylic acid, (TASP) is another analogue of ASP. From DFT studies, it has been concluded that PA and its analogues have the predominant trans-conformers with respect to directions of the carbonyl group in the acetyl moiety and the amino-hydrogen atom but the predominant conformer of NAA molecule is the cis-form. Phenacetin (PH) molecule which has ethoxy group in the Para-position instead of the hydroxyl group in the Para-position in PA molecule is another analogue of PA. The electron transfer energy between the drugs and the nucleic acid bases can be illustrated as cancer energy barrier. The cancer energy barriers were calculated from the DFT parameters for all the studied molecules showing the carcinogenic effect. The metabolized product N-acetylimidoquinone, m-PA, is produced in the liver from PA and PH. m-PA has higher electron affinity more than those of the nucleic acid bases indicating to the strong electronic withdrawing power from the nucleus in the human being liver cell, hence m-PA is responsible for the carcinogenic behavior of the liver cell since it has low energy barrier with guanine, 0.3 eV. Therefore the electron transfer between m-PA and guanine takes place spontaneously in the liver. From CI calculations it has been concluded that the singlet transition energies for the trans and cis conformers of PA are the same. The comparative spectral studies have been scanned for some analogues in the visible and UV regions using solvents of different polarities. The complex between PA and Zn^{2+} was studied by DFT method.

KEYWORDS

B3LYP; CI; Paracetamol; Aspirin; Electron Transfer; Conformers; UV Spectra

1. Introduction

Paracetamol (acetaminophen) is worldwide used as analgesic and antipyretic drug [1] and there is a review by Vial *et al*. [2] including 93 references discussing the clinical side effects of paracetamol in terms of the following system processes: allergic and skin; hematol; renal diseases; lactation of pregnant; carcinogenesis. Bioavailability effect of ethyl alcohol on paracetamol was studied by Wojcicki *et al*. [3] in healthy men. Goto *et al*. studied the charge transfer ability values for various pyridines and pyrimidines by CNDO/2 [4].

Charge transfer complex formation between nucleic acid bases and isoproterenol was confirmed using UV absorption measurement by Taha *et al*. [5]. Tautomeric structures of uracil and its effect on the electrochemical corrosion behavior of mild steel in acidic medium were studied using CNDO calculations by Makhlouf *et al*. [6]. The hydrogen bonding in drug-receptor interactions has been studied by Ghafourian *et al*. [7]. Sever hepatotoxicity and nephrotoxicity due to the accumulation of toxic metabolites of paracetamol were studied by Moffat [8]. The charge transfer complex formation between adenine, cytosine, thymine and uracil with catechol in acidic medium was studied by Al-Obeidi *et al*. [9]. Lahiri [10] studied the charge transfer complex formation between

oxytetracycline and tetracycline with purines, pyrimidines and amino acids. The charge transfer complex formation between 4,4'-dimethoxydiquinone with uracil has been studied via CNDO calculations by El-Shahawy *et al*. [11]. Paracetamol toxicity is manifested primarily in the liver. Treatment with N-acetyl-cysteine (NAC), if started within 10 h from ingestion, can prevent hepatic damage in most cases [12].

The therapy of rheumatism started since thousands of years ago with the use of decoctions or extracts of herbs or plants such as willow bark or leaves, most of which turned out to contain salicylates. Following the advent of synthetic salicylate, Felix Hoffman, working at the Bayer Company in Germany, made the acetylated form of salicylic acid in 1897. This drug was named "Aspirin" and became the most widely used medicine of all time. In 1971, Vane discovered the mechanism by which Aspirin exerts its anti-inflammatory, analgesic and antipyretic actions. He proved that Aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) inhibit the activity of the enzyme now called cyclooxygenase (COX) which leads to the formation of prostaglandins (PGs) that cause inflammation, swelling, pain and fever. However, by inhibiting this key enzyme in PG synthesis, the Aspirin-like drugs also prevented the production of physiologically important PGs which protect the stomach mucosa from damage by HCl. This conclusion provided a unifying explanation for the therapeutic actions and shared side effects of the aspirin-like drugs. Twenty years later, with the discovery of a second COX gene, it became clear that there are two iso-forms of the COX enzyme. The constitutive iso-form, COX-1, supports the beneficial homeostatic functions, whereas the inducible iso-form, COX-2, becomes unregulated by inflammatory mediators and its products cause many of the symptoms of inflammatory diseases such as rheumatoid and osteoarthritis [13].

2. Experimental Work

2.1. Materials

Paracetamol (Chem. Pharm. Works, Dupnitsa) was recrystallized from water to show a melting point of 168˚. N-acetylanthranilic acid (NAA) CAS NO. (89-52-1) (2-acetamidobenzoic acid) ($C_9H_9NO_3$) of M.F 179.1, shows a melting point of 184˚C - 187˚C; acetylthiosalicylic acid (TASP) CAS. No. (55819-78-8) has melting point at 260˚C - 262˚C, Aspirin (ASP) CAS No. (50-78-2) (acetylsalicylic acid or 2-acetoxybenzoic acid) has melting point at 140˚C - 142˚C.

All organic solvents used, such as ethanol, methanol, isopropanol, chloroform, carbon tetrachloride, and diethylether were extra pure Prolabo and Merk grades.

2.2. Instrumentation

The UV-visible spectra of some of the studied compounds had been scanned by UV-2101 PC UV-vis scanning spectrophotometer Shimadzu.

The temperature effect on the PA spectrum has been scanned by Perkin Elmer Lambda 35 UV/V is spectrophotometer USA.

3. Method of Calculations

3.1. Computational Studies

Computational studies on the isolated molecules in the gas phase were performed by the aid of GAUSSIAN 03 package. Minimum energy structures have been achieved using B3LYP/6-31**G basis set. Calculations were performed on the minimum energy structures using the closed shell Hartree-Fock, Becke's three parameters density functional theory, **DFT**, [14] in combination with the Lee, Yang and Parr correlation functional B3LYP [15] with basis set 6-31**G. The differentiation between the conformers' cis and trans was based on the total energy difference which have been calculated via SCF using RHF for these types of molecules and UHF for the molecular ions (cations and anions).

With respect to DFT calculations, it has been carried out as B3LYP/6-31**G and the energy of the density function theory can be represented as follows [16,17]:

$$E|\rho| = \frac{-\hbar^2}{2m_e}\sum_{i=1}^{n}\int \psi_i^*(r)_1 \nabla^2 \psi_i(r_1)\,dr_1 - \sum_{i=1}^{n}\int \frac{z_r e^2}{4\pi\varepsilon_o r_{11}}\rho(r_1)\,dr_1 + \frac{1}{2}\int \frac{\rho(r_1)\rho(r_2)e^2}{4\pi\varepsilon_0 r_{12}}dr_1 dr_2 + E_{xc}|\rho|$$

where ρ is the electron density.

$$\rho = \sum_{i=1}^{n}\left|\psi_{i(r)}\right|^2 = \sum_{i}^{n} C_{i(r)}^2$$

where C_i is the eigenvectors and

$$\hat{H}_i = \frac{-\hbar^2}{2m_e}\nabla_i^2 - \sum_{i}^{n}\frac{z_1 e^2}{4\pi\varepsilon_0 r_{12}} + \int \frac{\rho(r_2)e^2}{4\pi\varepsilon_0 r_{12}} + V_{xc}(r_1)$$

where $\hat{H}_i$ is the Hamiltonian of the energy.

3.2. Electron Transfer Studies

The electron transfer energy in the CT-complex between the donor and the acceptor (cation and anion) was calculated according to the following equation [18].

$$E_{CT} = I_D - E_A - \left(C^+ + C^-\right) \quad (1)$$

where I_D is the ionization potential of the donor and E_A is

the electron affinity of the acceptor. C^+ is the columbic potential energy of the donor as a cation, and C^- is the columbic potential energy of the acceptor as an anion. The columbic potential energy can be calculated, according to the following equation [18].

$$C = 14.398 \sum_{i}^{N} \sum_{j \neq i}^{N} \frac{Z_i Z_j}{r_{ij}} \text{ eV} \quad (2)$$

where Z_i and Z_j are the charge densities and r_{ij} is the distance between two atoms in the molecule of N atoms. The ET-band position in nm can be obtained by dividing 1240.824 by the electron transfer energy in electron volts.

3.3. Spectroscopic Parameters

The Einstein transition probability coefficients of emission, A_{if}, and absorption, B_{if}, between two initial (i) and final (f) electronic states are given as follows [19]:

$$A_{if} = \frac{64\pi^4 \tilde{\nu}^3}{3h} G_f D_{if}^2 \quad (1)$$

$$B_{if} = \frac{8\pi^3 e^2}{3h^2 C} G_f D_{if}^2 \quad (2)$$

where h is the Planck's constant, e is the electron charge, c the light velocity, 3×10^{10} cm s^{-1}, ν the wave number of radiation in cm^{-1}, G_f the degeneracy of the final state, D_{if} is the dipole strength and τ is the life time of the excited state.

Substituting the numerical values and assuming the singlet degeneracy for the excited state, then:

$$A_{if} = 7.24 \times 10^{10} \tilde{\nu}^3 D_{if}^2 \quad (3)$$

$$B_{if} = 14.50 \times 10^{24} D_{if}^2 \quad (4)$$

The oscillator strength, f_{ij}, is the measure of the intensity.

$$f = \frac{8\pi^2 m_e C}{3h} G_f \tilde{\nu} D_{if}^2 = 1.085 \times 10^{11} G_f \tilde{\nu} D_{if}^2 \quad (5)$$

Also the oscillator strength can be related to the absolute intensity as follows:

$$f = 0.102 \left(\frac{mC^2}{N\pi e^2} \right) \int \varepsilon \, d\tilde{\nu} = 4.315 \times 10^{-9} \int \varepsilon \, d\tilde{\nu} \quad (6)$$

where m is the electron mass, N the Avogadro's number, and ε is the molar extinction coefficient. If a molecule is in an excited state then, in the absence of an external electromagnetic field, on the average, after a time τ it will emit a photon.

$$\tau = \frac{1}{A_{if}} \quad (7)$$

Generally D_{if} can be calculated numerically as follows:

$$D_{if}^2 = 4.23671 \times 10^{-20} \times \frac{c\hbar}{\nu} \varepsilon_{\max.} \quad (8)$$

where $\hbar$ is the half width of the absorption band in cm^{-1}. Hence, the oscillator strength can be calculated directly as follows:

$$f_{ij} = 4.6 \times 10^{-9} \varepsilon_{\max} \times \hbar \quad (9)$$

3.4. Configuration Interaction Studies

The configuration interaction [19] between the ground configuration Eigenfunction Φ_0 with the excited singlet configuration Eigenfunctions containing the transitions between the upper seven HOMO's, ψ_i and the lowest seven LUMO's, ψ_i for each molecule under study via ZINDO program to give the transition energies between the ground state, $\Psi_0 = \Phi_0$, and other three singlet excited states, Ψ_{ex1}, Ψ_{ex2} and Ψ_{ex3} which are the linear combination of the configuration Eigenfunctions, $\psi_i \psi_j$ containing the transitions between the upper seven HOMO's and the lowest seven LUMO's.

4. Result and Discussion

4.1. Conformational Studies

PA is metabolized primarily in the liver [20-21], into toxic and non-toxic products. Three metabolic pathways are notable, **Figure 1**. The hepatic enzyme system metabolizes Paracetamol, forming the toxic product as NAPQI (*N*-Acetyl-*P*-benzo-Quinone Imine) or N-acetylimido-quinone which has symbol (m-PA) **Figure 2** for simplicity. All three pathways yield final products that are inactive, non-toxic, and eventually excreted by the kidneys. The intermediate product m-PA is also produced via the metabolism of PH, **Figure 2**, in the liver, **Figure 1**. This means that m-PA is primarily responsible for the toxic effects of PA and PH.

Then it is interesting to use quantum mechanical DFT theory to study the situation of the toxicity of this product, m-PA, with respect to other derivatives of acetanilide such as para-nitroacetanilide (PA-NO_2) and para-bromoacetanilide (PA-Br) which have good structural resemblance with PA and PH. Also it is necessary to compare the study of PA with its analogues from the conformers' point of view. The cis-conformer is the structure in which the amino hydrogen atom and the carbonyl group are in the same side. The trans-conformer is the structure in which the amino hydrogen atom and the carbonyl group are in opposite sides, **Figure 3**. N-acetylanthranilic acid (NAA) molecule has structural resemblance with PA and ASP, **Figure 4**.

The existence of conformers cis and trans, **Figure 3**, is probable due to the small energy difference between them in the following molecules: PA, PH, PA-NO2,

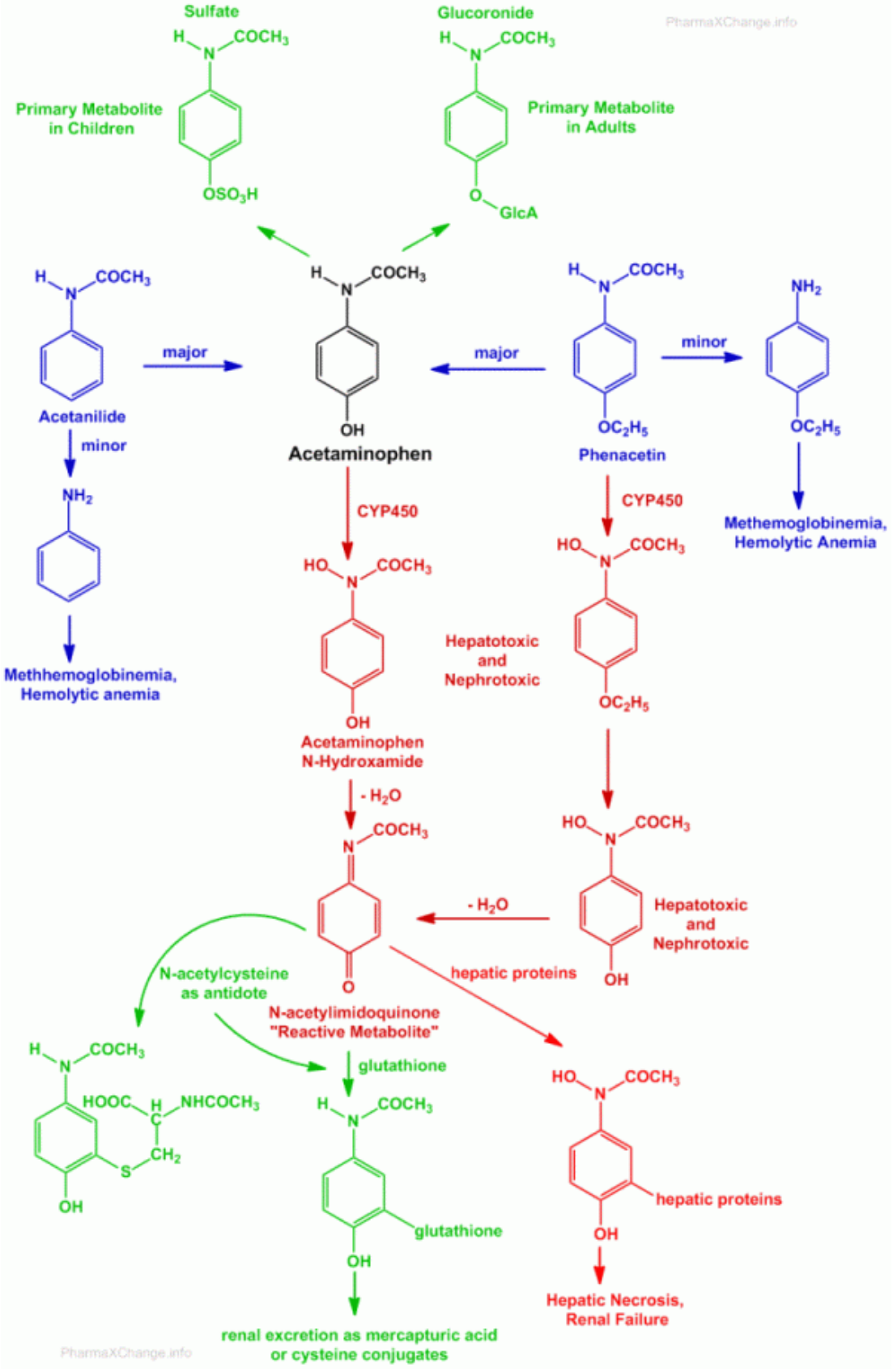


Figure 1. **Scheme of metabolism of PA and PH to form m-PA.**

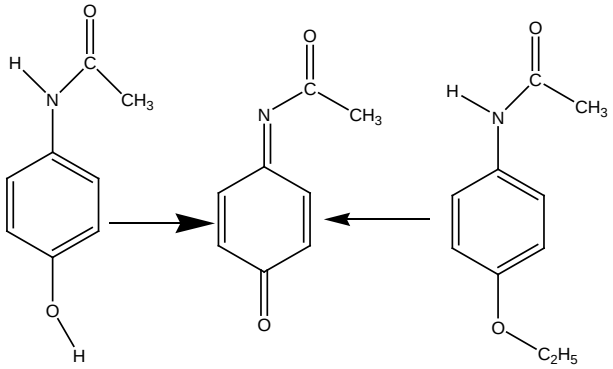


Figure 2. **Metabolized product, m-PA from PA, and PH.**

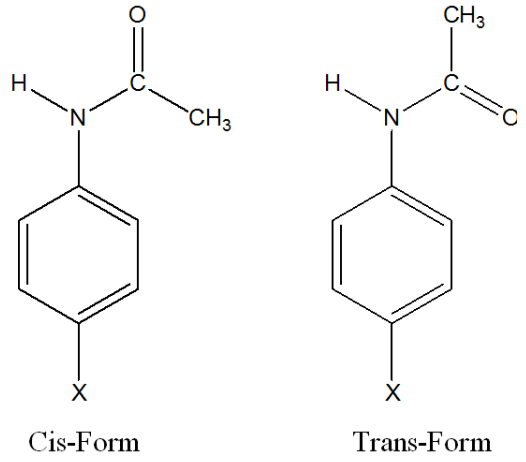


Figure 3. **The Conformers of X=OH, OEt, NO_2 and Br.**

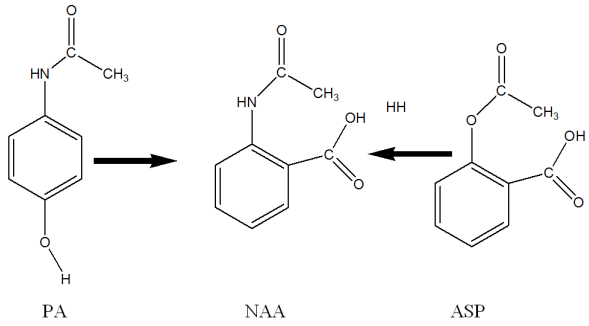


Figure 4. **Structural resemblance between NAA with PA and ASP.**

PA-Br and NAA. The ratio of the existence of the two conformers depends on the energy difference between them and the temperature, 27˚C, according to Boltzmann equation [19].

From the previous **Table 1**, it is clear that the trans-conformer has the lower energy in PA and PA analogues in contrary to NAA molecules which have the predominant cis-conformer of lower energy. The energy difference between the two conformers is a fraction of electron volt therefore their abundance is probable. The trans-conformer of NAA molecules is in small fraction due to the relative large energy difference with respect to the lower energy cis-form which is the predominant conformer in the NAA molecule at 27˚C, **Table 1**.

Table 1. B3LYP/6-31**G Energy difference between the conformers at 27°.

Compound	ΔE eV	N/N_0	N
PA cis/trans	0.16055	2.00404×10^{-3}	1.207037×10^{21}
PH cis/trans	0.27211	2.67×10^{-5}	106135×10^{19}
PA-NO_2 cis/tr	0.34531	1.5738×10^{-6}	9.4792×10^{17}
PA-Br cis/trans	0.18232	8.6309×10^{-4}	5.19839×10^{20}
NAA trans/cis	0.76355	1.47335×10^{-13}	2.3603×10^{10}

ΔE is the energy difference between the two conformers. N/N_0 is the ratio between the two conformers. N is the number of the conformer molecules of the higher energy in one mole.

4.2. Electron Transfer Studies

These studies concerned with the electron transfer energy of these molecules with nucleic acid bases, **Figure 5** to conclude the carcinogenic character of the studied molecules via the electron transfer values. The electron transfer energy depends mainly on the ionization potential of the donor, the electron affinity of the acceptor and the potential energies of the donor (cation) and the acceptor (anion). The ionization potential and the electron affinity were calculated via DFT method using the option B3LYP/6-31**G for the minimum energy structures of these compounds. Also the charge transfer energy depends not only on the ionization potential and electron affinity but also on the columbic potential energies of the cation (donor) and the anion (acceptor) using the Cartesian coordinates of the standard orientation and the Mulliken charge densities of the molecular ions using the data coming from the DFT method using Gaussian 03 program.

The acceptor and the donor can be defined by the relative values of the ionization potential energy and electron affinity of the two interacted molecules. The molecule having higher electron affinity and high ionization potential acts as acceptor to form an anion in the et-complex. The molecule having lower electron affinity and lower ionization potential acts as donor to form a cation in the et-complex.

Since the electron affinities of PA, PH, **Figure 2**, and PA-Br are lower than those of nucleic acid bases therefore they act as donor to produce charge transfer complex in which these molecules are cations and the nucleic acid bases are anions. But m-PA, **Figure 2**, PA-NO_2, NAA, **Figure 6**, ASP and TASP, **Figure 7**, have electron affinities larger than those of the nucleic acid bases, therefore they act as acceptor to be in the anionic-form in the et-complex with the cationic nucleic acid bases in the human being nucleus to render the cell behaves abnormally *i.e.* carcinogenic.

From the electron transfer energies **Tables 2-5** it can be concluded that the m-PA of quinoide structure has the lowest energy transfer, 0.382 eV, with guanine indicating to the easiest transfer of an electron to m-PA to render the nucleus is carcinogenic *i.e.* ionic., **Table 6**.

The electron transfer energy can be illustrated as cancer energy barrier whenever it has large value this means the safety of the drug from the carcinogenic effect. For example PA-Br, **Table 6**, has electron transfer energies with the nucleic acid bases among 4.0 and 5.012 eV. This means the strong safety of this drug from the carcinogenic effect. On the other hand, from the previous **Table 6**, it has been shown that the cancer energy barrier of M-PA with guanine is very small *i.e.* 0.382 eV therefore the contact of M-PA with the nucleus in the human being cell in the liver produces spontaneous electron transfer from Guanine to M-PA to produce ionic nucleus; hence the cell behaves abnormally which is known as cancer. Therefore, PA drug itself is safe only in the case of presence of glutathione preventing the formation of the quinoide structure as in M-PA, **Figure 1**. Glutathione, a tripeptide, γ-L-glutamyl-L-cysteinylglycine, was isolated from yeast, muscles, and liver tissue and is widely distributed in nature. So long as Phenacetin (PH) produces the quinoide structure, M-PA, as the same situation of PA in the liver, hence it is harmful as PA drug. Finally, it can be concluded that the probability of the carcinogenic effect is proportional inversely with the value of the electron transfer energy.

From other point of view, regarding n-acetylanthranilic acid (NAA), **Figure 6**, it has structural resemblance with Aspirin and Paracetamol, **Figure 4**, and it has considerable cancer energy barrier between 2.071 and 4.544 eV which is not far from the cancer energy barrier of ASP. This means that NAA, **Figure 6**, as a drug is safer from the carcinogenic effect and it can be advisable to use this compound as an alternative drug instead of ASP, **Figure 7**, and PA, **Figure 2**.

In June 2009, an FDA [22] advisory committee recommended that new restrictions should be placed on Paracetamol usage in the United States to protect people from the potential toxic effects. The maximum dosageto be consumed at any given time would be decreased from 1000 mg to 650 mg, while combinations of Paracetamol and narcotic analgesics would be prohibited. Committee members were particularly concerned by the fact that the present maximum dosages of Paracetamol had been shown to produce alterations in hepatic function. The FDA has not implemented their recommendations as of October 2010.

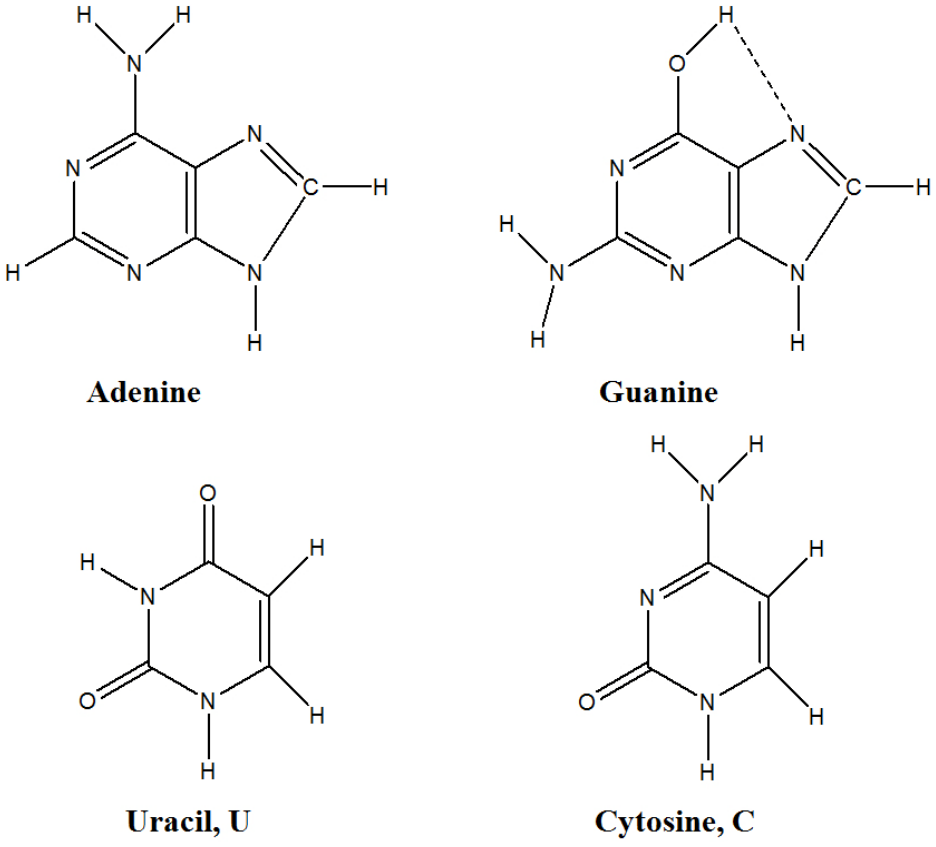


Figure 5. Nucleic acid bases (N.A.B.).

Table 2. Electron transfer energies of the studied compounds with adenine.

Compound	I_p eV of donor	E_a eV of acceptor	C eV $C = C^- + C^+$	E_{et} eV
PA cis	6.1634	1.2672	0.285692	4.61051
PA trans	5.8374	1.2672	0.149310	4.42089
PH cis	5.8105	1.2672	1.755315	3.48399
PH trans	5.7106	1.2672	0.088662	4.35474
M-PA	6.4061	4.2400	0.325528	1.8406
PA-No_2 cis	6.4061	2.9200	0.472047	3.0141
PA-NO_2 trans	6.4061	2.7630	0.330156	3.3129
PA-Br cis	6.5052	1.2672	0.225956	5.012044
PA-Br trans	6.2668	1.2672	0.404115	4.59549
NAA cis	6.4061	2.1146	0.491959	3.79954
NAA trans	6.4061	2.2656	0.664803	3.475697
ASP	6.4061	1.9173	0.491308	3.997492
TASP	6.4061	2.3979	0.460636	3.547564

N.B. I_p for adenine is equal to 6.4061 eV when it is donor. E_a for adenine is equal to 1.2672 eV when it is acceptor. C is the columbic energy of the anion and cation. E_{et} is the electron transfer energy.

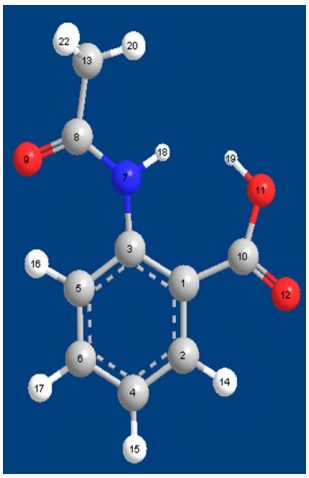
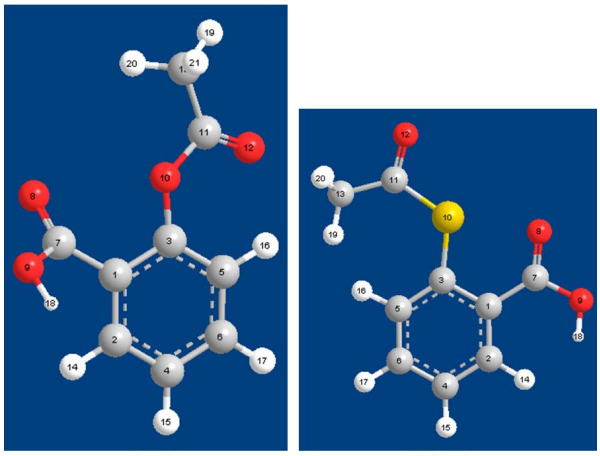


Figure 6. Minimum energy structure of trans-NAA.



ASP TASP

Figure 7. Minimum energy structures of ASP and TASP.

Table 3. The Electron transfer energies of the studied compounds with guanine.

Compound	I_p eV of donor	E_a eV of acceptor	C eV $C = C^- + C^+$	E_{et} eV
PA cis	6.1634	1.2828	0.86550	0.40151
PA trans	5.8374	1.2828	0.72931	3.82529
PH cis	5.8105	1.2828	0.75534	3.77236
PH trans	5.7106	1.2828	0.75555	3.67225
M-PA	6.1879	4.2400	1.56174	0.3816
PA-No_2 cis	6.1879	2.9200	1.71268	1.55522
PA-NO_2 trans	6.1879	2.7630	1.57079	1.85411
PA-Br cis	6.5052	1.2828	0.80576	4.41664
PA-Br trans	6.2668	1.2828	0.98392	4.00008
NAA cis	6.1879	2.1146	1.73259	2.34071
NAA trans	6.1879	2.2656	1.90543	2.01687
ASP	6.1879	1.9173	1.73194	2.53866
TASP	6.1879	2.3979	1.70127	2.08873

N.B. Ionization potential of guanine is 6.1879 eV when it acts as donor. Electron affinity of guanine is 1.2828 eV when it acts as acceptor.

Table 4. Electron transfer energies of the studied compounds with Cytosine.

Compound	I_p eV of donor	E_a eV of acceptor	C eV $C = C^- + C^+$	E_{et} eV
PA cis	6.1634	1.4768	0.79375	3.89285
PA trans	5.8374	1.4768	0.65737	3.70323
PH cis	5.8105	1.4768	0.68359	3.65011
PH trans	5.7106	1.4768	0.68382	3.54998
m-PA	6.5819	4.2400	1.23836	1.10354
PA-No_2 cis	6.5819	2.9200	1.38930	2.27260
PA-NO_2 trans	6.5819	2.7630	1.24741	2.57149
PA-Br cis	6.5052	1.4768	0.73402	4.29438
PA-Br trans	6.2668	1.4768	0.91218	4.05598
NAA cis	6.5819	2.1146	1.40921	3.05809
NAA trans	6.5819	2.2656	1.58205	2.73425
ASP	6.5819	1.9173	1.40856	3.25604
TASP	6.5819	2.3979	1.37789	2.80611

N.B. Ionization potential of cytosine is 6.5819 eV when it acts as donor. Electron affinity of cytosine is 1.4768 eV when it acts as acceptor.

4.3. Spectral Studies

The UV spectra of PA have been scanned in solvents of different polarities such as ethanol, methanol, isopropanol, carbon tetrachloride and distilled water. It has been noticed that the life-time τ of the excitation has its maximum value in case of $CC1_4$ solvent, 8.93 ns. The electronic transition energies in PA 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 7. The Einstein transition probabilities, A_{if} and B_{if}, have their maximum values in the case of isopropanol as a solvent, 7.37×10^8 s^{-1} and 2.28×10^9 sg^{-1} respectively as

Table 5. Electron transfer energies of the studied compounds with Uracil.

Compound	I_p eV of donor	E_a eV of acceptor	C eV $C = C^- + C^+$	E_{et} eV
PA cis	6.1634	1.8626	0.19885	4.10195
PA trans	5.8374	1.8626	0.06183	3.91297
PH cis	5.8105	1.8626	0.08869	3.85921
PH trans	5.7106	1.8626	0.17828	3.66972
m-PA	7.3316	4.2400	0.50251	2.58909
PA-No_2 cis	7.3316	2.9200	0.65345	3.75815
PA-NO_2 trans	7.3316	2.7630	0.51155	4.42949
PA-Br cis	6.5052	1.8626	0.13911	4.50349
PA-Br trans	6.2668	1.8626	0.31727	4.08693
NAA cis	7.3316	2.1146	0.67336	4.54364
NAA trans	7.3316	2.2656	0.84582	4.22018
ASP	7.3316	1.9173	0.67271	4.74159
TASP	7.3316	2.3979	0.64203	4.29167

N.B. Ionization potential of uracil is 7.3316 eV when it acts as donor. Electron affinity of uracil is 1.8626 eV when it acts as acceptor.

Table 6. The Cancer energy barrier, E_{et} of the studied compounds with N.A.B.

N.A.B	m-pa E_{et} eV	naa.ci E_{et} eV	naa.tr E_{et} eV	Pa.Br ci. E_{et} ev	Pa.Br tr. E_{et} ev	ASP E_{et} eV	TASP E_{et} eV
Adenine	1.811	3.80	3.476	5.012	4.596	3.998	3.548
Guanine	0.382	2.341	2.017	4.417	4.000	2.539	2.089
Cytosine	1.104	3.058	2.734	4.294	4.056	4.742	4.292
Uracil	2.589	4.544	4.220	4.503	4.087	4.742	4.292

well as the dipole strength D_{if} has its maximum value in the same solvent, 1.57×10^{-16}, **Table 7**.

From DFT calculations of PA molecules, **Table 8**, it has been found that the cis form and the transform have small energy difference, **Table 1**, 0.16055 eV, at 27˚C. Normally the presence of conformers of a compound produces duplicity at the top of the absorption band [23] suffering from relative intensity change by the heat effect. But the electronic absorption spectrum of PA in ethyl alcohol as a solvent at 249 nm, **Figure 8** doesn't show the duplicity and the relative intensity change by the heat effect, in spite of the presence of these conformers by DFT calculations, **Table 1**. The absence of the duplicity of the relative intensity change is coming from the coincidence of the same electronic transitions for the two conformers as shown in **Tables 9(a)** and **(b)** of the CI-calculations. It has been noticed that the calculated transition energies for both the cis and trans-conformers lie at 261 nm as it has been found in the spectrum of PA in CCl4 as a solvent, **Table 7**.

The complex of PA_2-Zn has been prepared by El-Shahawy *et al.* [24] since 2007. The complex had been performed bychelation of zinc ion as ethanolic solution

Table 7. The Einstein transition probabilities (A_{if} & B_{if}), dipole strength (D_{if}), oscillator strength (f_{if}) and life-time 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}	τ ns
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

ns is nanosecond.

Table 8. DFT(B3LYP/6-31G) parameters of the studied compounds.**

Compound	TE au	I_p ev	E_a ev
PA-cis	−515.3532	6.1634	0.9162
PA-trans	−515.3591	5.8374	0.6640
PH-cis	−593.95 au	5.8105	0.9265
PH-trans	−593.96 au	5.7106	0.5712
M-PA	−514.08867	7.3112	4.2400
PA-NO_2 cis	−644.57486	7.9408	2.9200
PA-NO_2 trans	−644.58755	7.1588	2.7630
PA-Br cis	−3011.1612	6.5052	1.2327
PA-Br trans	−3011.1679	6.2668	1.0536
NAA-cis	−628.67038	6.8347	2.1146
NAA-trans	−628.64232	7.0309	2.2656
ASP	−648.50274	7.3865	1.9173
TASP	−971.41183	6.8910	2.3979
ADENINE	−467.17488	6.4061	1.2672
GUANINE	−542.37704	6.1879	1.2828
CYTOSINE	−394.82291	6.5819	1.4768
URACIL	−414.70313	7.3316	1.8626

TE is the total energy in au unit. I_p is the ionization energy in eV unit. E_a is the electron affinity in eV unit.

of zinc acetate dihydrate with PA to form PA_2-Zn complex by refluxing the ethanolic solution of them. The DFT calculations were done via B3LYP/6-311*G [25], to get its ionization potential and electron affinity for the minimum energy structure of PA_2Zn, **Figure 9**.

From DFT calculations, it has been found that the chelation of Zn ion with cis-PA in their complex decreases the ionization potential from 6.1634 to 5.63249 eV and increases the electron affinity from 0.9162 to 1.39785 eV. Also, it can be noticed that the complex of PA drug is better than PA itself because there isn't amino hydrogen atom preventing the formation of the quinoide structure which has high carcinogenic effect as in the metabolized PA in the liver.

The UV spectra of ASP have been scanned in different solvents of different polarities such as ethanol, methanol,

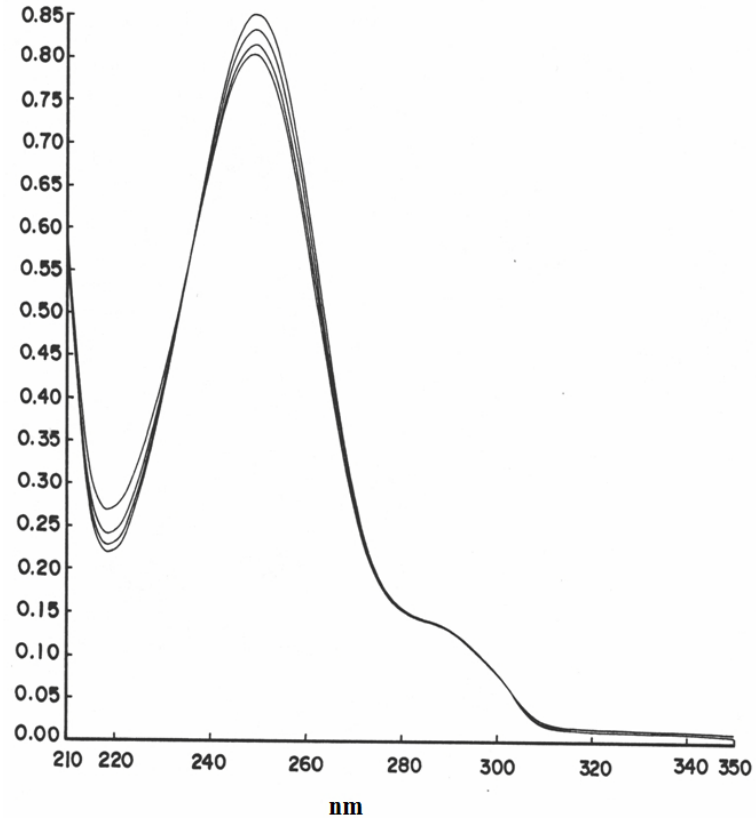


Figure 8. The heat effect on the electronic spectrum of PA molecule in EtOH. (a) at (45˚C), (b) at (35˚C), (c) at (25˚C), (d) at (15˚C).

Table 9. (a) Singlet Excited Transition States of cis-PA; (b) Singlet Excited Transition States of trans-PA.

(a)

Ex. State	Paraceta mol (cis)	ΔE ev	ΔE nm	f	ΔE exp. nm
Ψ_{exc1}	$-0.34628\Psi_{27}\Psi_{30} + 0.59941\Psi_{27}\Psi_{32}$	3.7078	334.4	0.0014	
Ψ_{exc2}	$-0.30680\Psi_{28}\Psi_{30} - 0.11867\Psi_{28}\Psi_{32}$ $+0.26327\Psi_{29}\Psi_{30} + 0.59007\Psi_{29}\Psi_{31}$	4.2834	289 .5	0.0546	
Ψ_{exc3}	$0.18011\Psi_{28}\Psi_{31} + 0.62677\Psi_{29}\Psi_{30} - 0.17615\Psi_{29}\Psi_{31}$	4.6722	265.4	0.3420	261

(b)

Ex. state	Paracetamol (trans)	ΔE ev	ΔE nm	f	ΔE exp. nm
Ψ_{exc1}	$0.54758\Psi_{27}\Psi_{30} + 0.4221\Psi_{27}\Psi_{32}$	3.5667	347.6	0.0004	
Ψ_{exc2}	$-0.26644\Psi_{28}\Psi_{30} + 0.21011\ \Psi_{28}\Psi_{32}$ $-0.11058\Psi_{29}\Psi_{30} + 0.60556\Psi_{29}\Psi_{31}$	4.2745	290.1	0.0558	
Ψ_{exc3}	$0.15788\ \Psi_{28}\ \Psi_{31} + 0.64183\Psi_{29}\ \Psi_{30} + 0.10783\ \Psi_{29}\ \Psi_{31} - 0.15680\Psi_{29}\ \Psi_{32}$	4.5535	272.3	0.3250	261

Where ΔE , is the transition energy between the ground state, Ψ_0 and the excited states Ψ_{exc} .

isopropanol, chloroform, diethyl ether and distilled water, **Figure 10**. It has been noticed that the life time τ of the excitation has its maximum value in case of diethyl ether solvent, 237 ns. The electronic transition energies in ASP UV spectra have been red shifted with decreasing the solvent polarity from 275 nm in H_2O solvent to 277 nm in $CHCl_3$ solvent, **Table 10**. The Einstein transition probabilities, A_{if} (Spontaneous transition probability) has its maximum value in case of $CHCl_3$ solvent 9.54×10^6 s^{-1}, in contrary the induced transition probability (B_{if}) and the dipole strength (D_{if}) which have the maximum values in the same solvent, 1.52×10^8 sg^{-1} and 10.50×10^{-18}

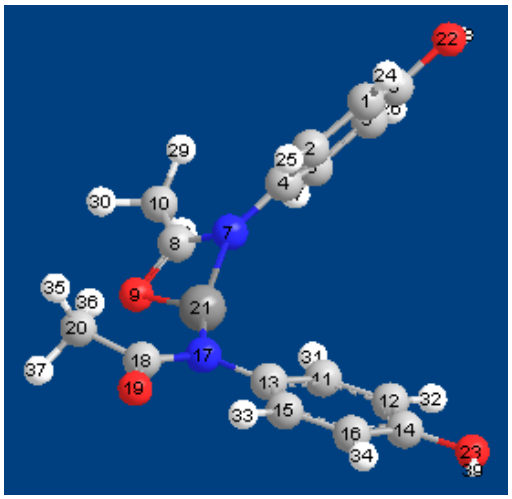


Figure 9. Minimum energy structure of PA_2-Zn complex.

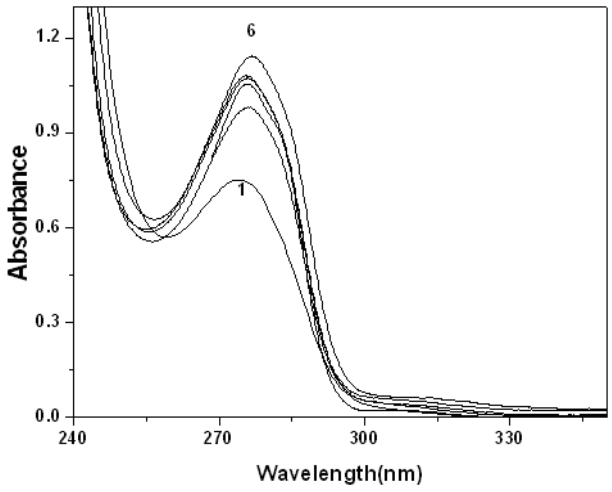


Figure 10. Electronic spectra of ASP (8.6×10^{-4} Mℓ^{-1}) in pure solvents 1—H_2O, 2—MeOH, 3—Diethyl ether, 4—EtOH, 5—Isopropanol and 6—$CHCl_3$.

ℓM^{-1}, respectively, Table 10.

The UV spectra of TASP (thio-aspirin) have been scanned in different solvents of different polarities such as ethanol, methanol, isopropanol, chloroform, diethyl ether and distilled water, Figure 11. It has been noticed that the lifetime τ of the excitation has its maximum value in case of H_2O solvent, 55.8 ns. The electronic transition energies in ATS spectra have been red shifted with decreasing the solvent polarity from 302 nm in H_2O solvent to 313 nm in $CHCl_3$ solvent, Table 11. The spontaneous Einstein transition probabilities, A_{if} has its maximum value in case of diethyl ether as solvent 2.57×10^7 s^{-1} as well as the induced transition probability (B_{if}) and the dipole strength (D_{if}) which have their maximum values in the same solvent, 4.62×10^8 sg^{-1} and 3.19×10^{-17} ℓM^{-1}, respectively, Table 11.

The UV spectra of NAA have been scanned in different solvents of different polarities such as ethanol, methanol, isopropanol, chloroform, diethyl ether and dis tilled water, Figure 12. It has been noticed that the life time τ of the excitation has its maximum value in case of H_2O solvent, 78.2 ns. The electronic transition energies in ATS UV spectra have been red shifted with decreasing the solvent polarity from 295 nm in H_2O solvent to 309 nm in $CHCl_3$ solvent, Table 12. The Einstein spontaneous transition probabilities, A_{if} has the maximum value in case of diethyl ether as solvent 2.11×10^7 s^{-1}, as well as the induced transition probability (B_{if}) and the dipole strength (D_{if}) which have the maximum values in the same solvent, 3.77×10^8 sg^{-1} and 2.60×10^{-17} ℓM^{-1}, respectively, Table 12.

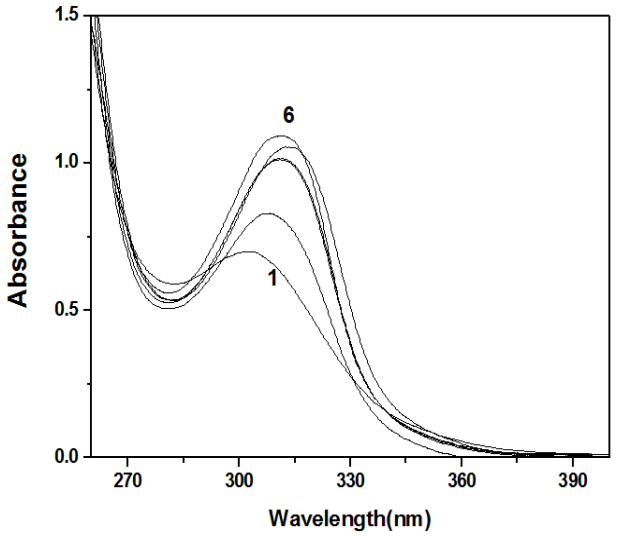


Figure 11. Electronic spectra of TASP (2.25×10^{-4} Mℓ^{-1}) in pure solvents 1—H_2O, 2—MeOH, 3—EtOH, 4—Isoprop, 5—$CHCl_3$ and 6—Dieth-yl ether.

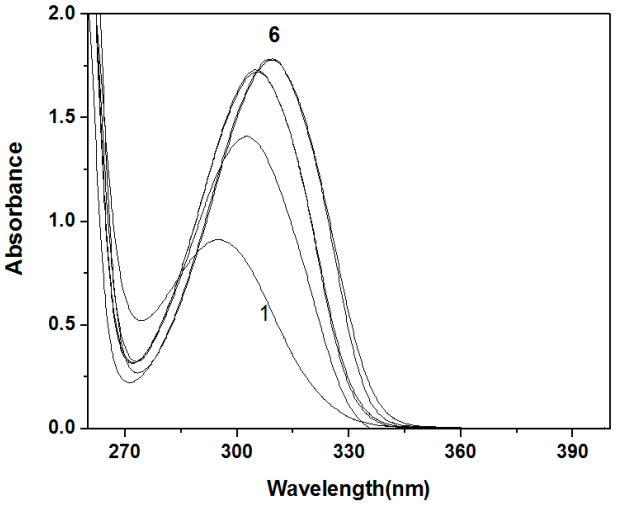


Figure 12. Electronic spectra of NAA (3.5×10^{-4} Mℓ^{-1}) in pure solvents 1—H_2O, 2—MeOH, 3—EtOH, 4—Isoprop, 5—$CHCl_3$ and 6—Deth-yl ether.

Table 10. The Einstein transition probabilities (A_{if}, B_{if}), dipole moment (D_{if}), oscillator strength (f_{if}), life time (τ) and extinction coefficient (ε) of the electronic transition bands of ASP in different solvents.

Solvent	λ_{max} nm	A_{max}	$\varepsilon_{max} \times 10^{-4}$ $LM^{-1}cm^{-1}$	$A_{if} \times 10^{-6}$ S^{-1}	$B_{if} \times 10^{-8}$ Sg^{-1}	f_{if} $LM^{-1}cm^{-1}$	$D_{if} \times 10^{18}$ LM^{-1}	τ ns
H_2O	275	0.751	0.8732	4.28	0.678	0.01850	4.68	234
MeOH	276	0.98	1.1395	4.78	0.761	0.0207	5.25	209
Isopropyl	275	1.08	1.2558	5.30	0.842	0.0229	5.81	189
EtOH	276	1.072	1.2465	5.65	0.900	0.0244	6.21	177
$CHCl_3$	277	1.142	1.3279	9.54	1.52	0.0412	10.50	105
Diethyl ether	276	1.054	1.2255	4.22	0.671	0.0182	4.63	237

Table 11. The Einstein transition probabilities (A_{if}, B_{if}), dipole moment (D_{if}), oscillator strength (f_{if}), life time (τ) and extinction coefficient (ε) of the electronic transition bands of TASP in different solvents.

Solvent	λ_{max} nm	A_{max}	$\varepsilon_{max} \times 10^{-4}$ $M^{-1}cm^{-1}$	$A_{if} \times 10^{-7}$ S^{-1}	$B_{if} \times 10^{-8}$ Sg^{-1}	f_{if} LM^{-1} cm^{-1}	$D_{if} \times 10^{17}$ LM^{-1}	τ ns
H_2O	302	0.700	0.3111	1.79	3.12	0.0077	2.15	55.8
MeOH	308	0.830	0.3688	1.98	3.52	0.0085	2.43	50.5
Isopropyl	310	1.016	0.4515	2.39	4.28	0.0103	2.95	41.9
EtOH	311	1.012	0.4497	2.52	4.52	0.0109	3.11	39.8
$CHCl_3$	313	1.056	0.4693	2.56	4.61	0.0110	3.18	39.1
Diethyl ether	312	1.094	0.4862	2.57	4.62	0.0111	3.19	38.9

Table 12. The Einstein transition probabilities (A_{if}, B_{if}), dipole moment (D_{if}), oscillator strength (f_{if}), life time (τ) and extinction coefficient (ε) of the electronic transition bands of NAA in different solvents.

Solvent	λ_{max} nm	A_{max}	$\varepsilon_{max} \times 10^{-4}$ $LM^{-1}cm^{-1}$	$A_{if} \times 10^{-7}$ S^{-1}	$B_{if} \times 10^{-8}$ Sg^{-1}	f_{if} $LM^{-1}cm^{-1}$	$D_{if} \times 10^{17}$ LM^{-1}	τ ns
H_2O	295	0.913	0.2608	1.28	2.18	0.0552	1.50	78.2
MeOH	302	1.412	0.4034	1.65	2.87	0.0711	1.98	60
Isoprpyl	305	1.734	0.4954	1.97	3.46	0.0851	2.39	50.8
EtOH	305	1.723	0.4922	1.99	3.51	0.0860	2.42	50.3
$CHCl_3$	309	1.779	0.5082	2.06	3.68	0.0890	2.54	48.5
Diethyl ether	309	1.785	0.5100	2.11	3.77	0.0912	2.60	47.4

5. Conclusions

1) Paracetamol complexes are safer than PA itself.
2) It is advisable to use PA-Br as a drug instead of PA.
3) NAA compound can be used as an alternative drug instead of PA and ASP.

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