

Original Article

AVERTING CANCER EFFECT OF PARACETAMOL AND PHENACETIN BY N-ACETYLCYSTEINE

ANWAR EL-SHAHAWY, NAGWA ABO EL-MAALI AND HASSAN H. EL-HAWARY

Chemistry Department-Faculty of Science Assiut University,71516 Egypt.  
Email: anwarshahawy@yahoo.com

Received: 24 Mar 2014 Revised and Accepted: 27 Apr 2014

ABSTRACT

Comparative DFT computations were studied for Paracetamol (PA) and its analogue Phenacetin (PH). From DFT studies, it has been concluded that PA and PH have the predominant trans conformers with respect to the carbonyl group in the acetyl group and the amino-hydrogen atom. Extension to our comparative studies, the electron affinities of cis-PA and cis PH are nearly the same in contrary, the electron affinity of trans-PA is higher than that of trans-PH. The electronic transition energies between the ground state and singlet excited states for the two conformers have been studied by TD-DFT method. The metabolized product of PA or PH in the liver of the human being is N-acetylimidoquinone (m-PA). The electron affinity of metabolized Paracetamol (m-PA) is sufficient to interact with the nucleic acid bases in the liver. So long as the metabolized PA is produced in the liver and the electron transfer energy between m-PA and nucleic acid bases gives very small energy value especially with guanine, i.e. 0.382 eV, from the nucleus of the cell in the liver producing a spontaneous electron transfer from the nucleus to m-PA inducing cationic nucleus leading to the carcinogenic behavior of the cell in the liver. The presence of glutathione or N-Acetylcystine (NAC) in the liver prevents the formation of m-PA via proton transfer avoiding the carcinogenic effect of PA and PH. Therefore PA and PH can be used as safe drugs after mixing with the pharmacological dose of N-Acetylcystine.

**Keywords:** DFT, TD-DFT, Paracetamol, Phenacetin, N-Acetylcystine, Electron Transfer, Conformers, UV Spectra.

INTRODUCTION

Paracetamol instead of Phenacetin is world wide use as analgesic and antipyretic drug [1] not as anti-inflammatory and the literature including 93 references reported the clinical side effects of Paracetamol in terms of the following system processes: allergic and skin; hematol; renal diseases; lactation of pregnant; carcinogenesis[2]. Availability effect of ethyl alcohol with PA was studied by Wojcicki et al.[3] in healthy man. Goto et al had studied the charge transfer ability values for some pyridines and pyrimidines by CNDO/2 [4]. CT-complex formation between nucleic acid bases and isoproterenol was studied using UV spectrophotometer measurement by Taha et al. [5]. Tautomeric uracil structures and its electrochemical corrosion behavior of mild steel in acidic medium have been studied using CNDO calculations by Makhlof and El-Shahawy [6]. The hydrogen bonding interaction studies in drug-receptor has been performed by Ghafourian et al.[7]. Sever hepatotoxicity and nephrotoxicity as a reason of the accumulation of toxic metabolites of Paracetamol have been studied by Moffat [8]. The CT-complex formation between cytosine, thymine adenine, and uracil with catechol in acidic medium was studied by Al-Obeidiet al.[9]. The charge transfer complex formation between oxytetracycline and tetracycline with purines, pyrimidines and amino acids has been studied by Lahiri [10].

El-Shahawy et al. studied the CT- complex formation between 4,4'-dimethoxydiquinone with uracil via CNDO calculations[11]. Paracetamol toxicity is manifested primarily in the liver. Hepatic damage from PA can be treated with N-acetyl-cysteine (NAC), if started within 10 h from ingestion, [12]. The therapy of rheumatism has been known since many years ago with the use of extracts of plants such as willow bark or leaves, most of which contain salicylates.

Following Bayer Company in Germany, made the acetylsalicylate form salicylic acid in 1897. This drug was named "Aspirin" and became the most world wide use medicine of all time. In 1971, Vane found out the mechanism by which aspirin performs its anti-inflammatory, analgesic and antipyretic effects. He proved that aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) prevent the activity of the enzyme now called cyclooxygenase (COX) which produces 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 save the stomach mucosa from

damage by HCl. This conclusion provided an explanation for the therapeutic actions and accompanied side effects of the aspirin-like drugs. Twenty years later, with the discovery of a second COX gene, it was clear that there are two forms of the COX enzyme. The constitutive form, COX-1 which supports the beneficial homeostatic functions, whereas the second inducible form, COX-2, is unregulated by inflammatory mediators and its products lead to many of the symptoms of inflammatory diseases such as rheumatoid and osteoarthritis [13]

Experimental work

Materials

Paracetamol (Chem. Pharm. Works, Dupnitsa) was re-crystallized from water to show a melting point of 168°. The ethyl alcohol solvent was extra pure Prolabo and Merk grades.

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.

Method of calculations

Computational studies

Computational studies on the isolated gaseous molecules were studied 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 performed as B3LYP/6-31\*\*G and the energy of the density function theory can be represented as follows [16, 17]:

$$E|\rho\rangle = \frac{-\hbar^2}{2m_e} \sum_{i=1}^n \int \psi_i^*(r_1) \nabla^2 \psi_i(r_1) dr_1 - \sum_{i=1}^n \int \frac{z_i e^2}{4\pi\epsilon_0 r_{1i}} \rho(r_1) dr_1 + \frac{1}{2} \int \frac{\rho(r_1)\rho(r_2)e^2}{4\pi\epsilon_0 r_{12}} dr_1 dr_2 + E_{xc}|\rho\rangle$$

where  $\rho$  is the electron density.

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

where  $C_i$  is the eigenvectors and

$$\hat{H}_i = \frac{-\hbar^2}{2m_e} \nabla_i^2 - \sum_i \frac{z_i e^2}{4\pi\epsilon_0 r_{1i}} + \int \frac{\rho(r_2)e^2}{4\pi\epsilon_0 r_{12}} + V_{xc}(r_1)$$

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

### 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].

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

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

$$C = 14.4 \sum_{i=1}^N \sum_{j \neq i}^N \frac{Z_i Z_j}{r_{ij}} \quad \text{eV} \quad (2)$$

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.

## RESULT AND DISCUSSION

### Conformational studies

Also it is necessary to compare the conformers of PA with its analogue PH. 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, fig.1.

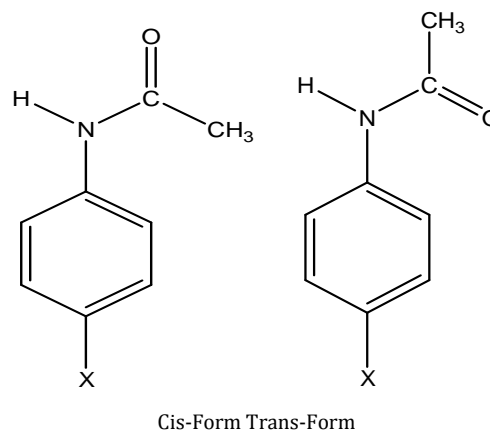


Fig.1: The Conformers of X= OH or OEt

The existence of cis and trans-conformers, fig.1, is probable due to the small energy difference between them in Paracetamol and Phenacetin. 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].

Table 1: DFT (B3LYP/6-31\*\*G) parameters of the studied compounds.

compound	TE au	I <sub>p</sub> eV	E <sub>a</sub> eV
PA-cis	-515.3532	6.1634	0.9162
PA-trans	-515.3591	5.8374	0.6640
PH-cis	-593.9488	5.8105	0.9265
PH-trans	-593.9606	5.7106	0.5712
M-PA	-514.0887	7.3112	4.2400
N-Acetylcystine	-799.2027	7.2159	1.8585
Glutathione	-1404.793	6.9944	0.0559
ADENINE	-467.1749	6.4061	1.2672
GUANINE	-542.3770	6.1879	1.2828
CYTOSINE	-394.8229	6.5819	1.4768
URACIL	-414.7031	7.3316	1.8626

TE is the total energy in au unit, I<sub>p</sub> is the ionization energy in eV unit, E<sub>a</sub> is the electron affinity in eV unit

Table 2: B3LYP/6-31\*\*G Energy difference between the conformers at 27 °.

Compound	$\Delta E$ eV	N/N <sub>0</sub>	N
PA cis/trans	0.16055	2.00404x10 <sup>-3</sup>	1.207037x10 <sup>21</sup>
PH cis/trans	0.27211	2.67x10 <sup>-5</sup>	106135x10 <sup>19</sup>

$\Delta E$  is the energy difference between the two conformers., N/N<sub>0</sub> is the ratio between the two conformers., N is the number of the cis-conformer molecules of the higher energy in one mole.

From the previous table 2, it is clear that the trans-conformer has the lower energy in PA as the situation in PH molecules. The energy difference between the two conformers is a fraction of electron volt therefore their abundance is probable in the normal temperature especially the trans-forms.

Regarding the existence of the two conformers in the room temperature in solutions [20], it is possible to change the temperature of the uv-spectra of PA solution in ethyl alcohol, fig. 2, to find out duplicity in the uv-band and the relative intensity change of this duplicity at different temperatures. In reality, there isn't

duplicity at the top of the uv-band of PA and hence there isn't any change in the relative intensity indicating to the absence of the conformers. The TD-DFT calculations have been studied for the both cis and trans- conformers, to find out the electronic transitions between the ground state to the singlet excited states as follows in the following tables 3 and 4.

From the previous tables 3 and 4, it is clear that the allowed transition energies for cis and trans conformers lie at 254 nm and 267 nm respectively which are very near to each other, then the expected duplicity is not exist via the temperature effect at 248 nm in the uv spectrum in ethyl alcohol [21] as shown in the following fig. 2. The experimental  $\lambda_{\max}$  of Paracetamol lies at 261 nm in chloroform [21] over a broad band including the  $\lambda_{\max}$  at position 254 nm of the cis-conformer.

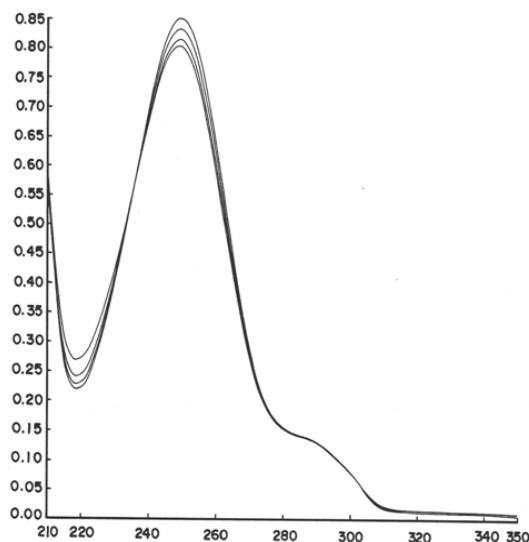


Fig. 2: The heat effect on the electronic spectrum of PA molecule in EtOH . (a) at (45 c°), (b) at (35 c°), (c) at (25 c°), (d) at (15 c°).

Table 3: Electronic transition energies between the ground state and the singlet excited states of trans-Paracetamol.

Excited State 1: Singlet-A 4.5698 eV 271.31 nm f=0.0001
40 -> 42 0.69844
Excited State 2: Singlet-A 4.6453 eV 266.90 nm f=0.0428
38 -> 41 0.23477
38 -> 46 -0.11219
40 -> 41 0.18160
40 -> 43 0.61001
Excited State 3: Singlet-A 4.7303 eV 262.11 nm f=0.0001
40 -> 44 0.70111

### Electron transfer studies

PA and PH are metabolized primarily in the liver [22-24], into toxic and non-toxic products figs.3,4 and 9. Three metabolic pathways are notable, figs. 4 and 9. The hepatic enzyme system metabolizes Paracetamol, forming the toxic product as N-acetylimidoquinone which has the symbol (m-PA) for simplicity, fig. 4. 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 in the liver, Figs 3 and 4. 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

(B3LYP/6-31\*\*G) calculations to study the interaction between this product, m-PA, and the nucleic acid bases in the nucleus in the liver cell.

Table 4: Electronic transition energies between the ground state and the singlet excited states of cis-Paracetamol

Excited State 1: Singlet-A 4.5836 eV 270.49 nm
f=0.0442
38 -> 42 0.21497
40 -> 41 0.63233
40 -> 42 -0.13652
Excited State 2: Singlet-A 4.7849 eV 259.11 nm
f=0.0033
40 -> 42 0.18779
40 -> 43 0.66942
Excited State 3: Singlet-A 4.8894 eV 253.58 nm
f=0.1126
39 -> 41 -0.18640
39 -> 42 -0.40338
39 -> 45 0.10294
39 -> 46 -0.19266
40 -> 42 0.38604
40 -> 43 -0.162221

f is the oscillator strength.

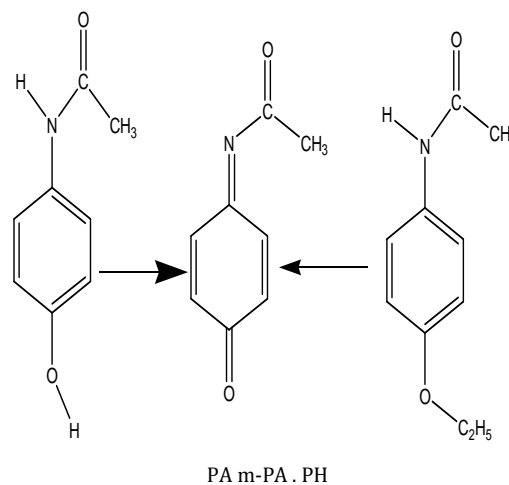
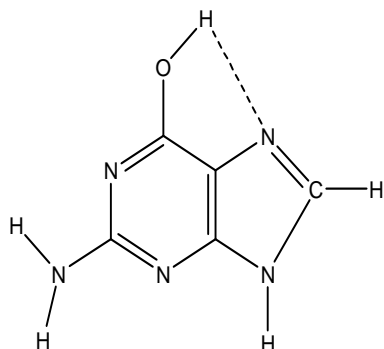
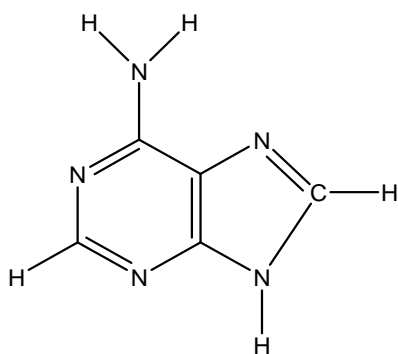
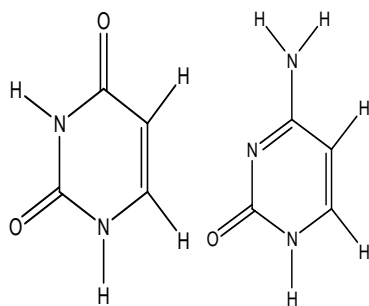


Fig. 3: Metabolized product, m-PA from PA, or PH.

These studies concerned with the electron transfer energy of the metabolized product, m-PA with the nucleic acid bases (NAB), Fig. 5, in the liver to acquire the liver cell the carcinogenic nature via the electron transfer between them. The electron transfer energy depends mainly on the ionization potential of the donor, the electron affinity of the acceptor and the coulombic potential energies of the cation of the donor and the anion of the acceptor. The ionization potential and the electron affinity were calculated via DFT/B3LYP-6-31\*\*G method for these molecules and their ions. Also the coulombic potential energies of the cation (donor) and the anion (acceptor) were calculated using the Cartesian coordinates of the optimized molecular ions and the Mulliken charge densities of the molecular ions using the output data coming out from the DFT method using the equation 2 in the 3.2-electron transfer section.



Adenine Guanine



Uracil, U Cytosine

Fig. 5: Nucleic Acid Bases (NAB).

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

Since the electron affinities of PA and PH are lower than those of nucleic acid bases, table 1, therefore they act as donor to produce charge transfer complex in which these molecules are cationic and the nucleic acid bases are anionic. In contrary, the metabolized product, m-PA, has much higher electron affinity than those of the nucleic acid bases, table 1, therefore m-PA is anionic and the nucleic acid bases are cationic in the ct-complex. After calculation of the columbic potential energies of PA, PH and m-PA with the nucleic acid bases using equation 2 in the 3.2-electron transfer section, the total columbic potential energies with the nucleic acid bases have been obtained in the following table 5. Using the ionization potential energies, the electron affinities of the studied molecules from table 1 and the columbic potential energies from the previous table 5, to calculate the electron transfer energies which can be illustrated as cancer energy barrier. When it has small value it means the electron transfer being easy to produce the carcinogenic effect. In contrary the high value of the cancer energy barrier indicates to the

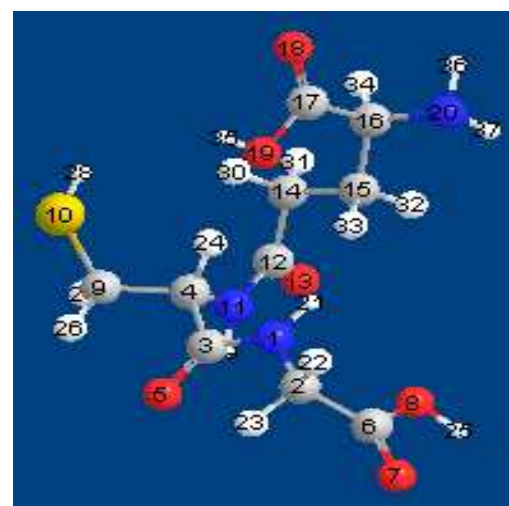
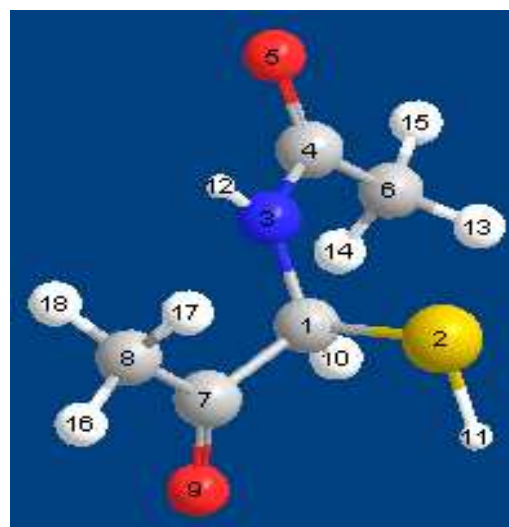
arduousness of the electron transfer to render the drug being safe from the cancer effect. The values of the cancer energy barriers  $E_{et}$  of the studied compounds have been obtained in the following table 6.

#### Eet is the electron transfer energy

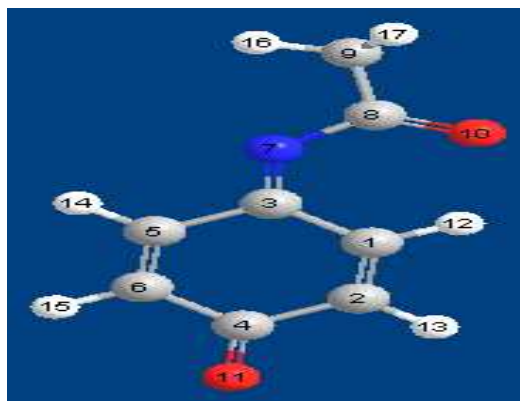
From the values of cancer energy barrier, table 6, it can be concluded that the metabolized Paracetamol (m-PA) has the lowest electron transfer energy, 0.382 ev, with guanine leading to the easiest electron from the nucleus rendering the cell being carcinogenic. This means the spontaneous electron transfer from guanine to m-PA in case of the contact between m-PA and the nucleus in the liver.

Although the PA and PH are carcinogenic in one path way of metabolism in the liver due to the formation of m-PA by the hepatic enzymes, the existence of glutathione or N-Acetylcystine (NAC) prevents the formation of m-PA avoiding the electron transfer from the nucleus protecting the cell from the carcinogenic behavior.

The mechanism of the interaction between NAC and m-PA can be studied via DFT calculations to reveal the mechanism of the interaction between them. From the charge densities of these molecules table 7, it can be noticed that the oxygen atom at position 11, fig. 6, in the m-PA molecule has the highest negative charge and the hydrogen atom at position 12 in NAC has the highest positive charge therefore the proton transfer from amino hydrogen atom of NAC to the oxygen atom at position 11 in m-PA molecule rendering them being free radicals fig. 8 and table 8. The same situation will be carried out between H at position 22 in GSH and O at position 11 in m-PA molecule.



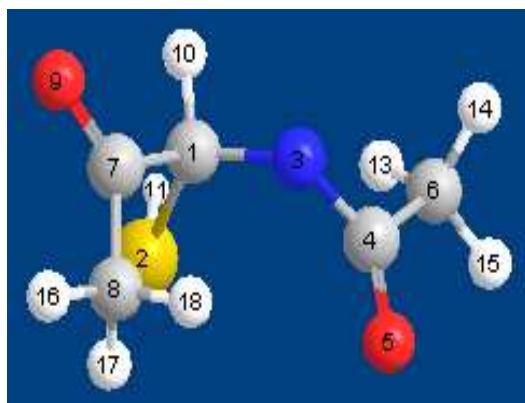
N-Acetylcystine (NAC) Glutathione (GSH)



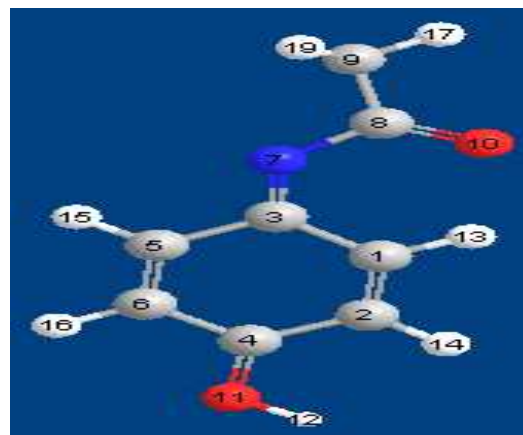
m-PA

Fig. 6: The optimized structures of NAC, GSH and m-PA.

From table 8, fig. 7, it clear that the high negative carbon atom at position 1 in the free radical of N-Acetylcystine will be attached to the higher positive charged carbon atom at position 2 in the benzene ring of the free radical of m-PA. The N-Acetylcystine will be attached at position 2 in the ring since the hydrogen atom attached with



carbon atom at position 14 has less positive charge therefore there is a competitive attraction between H 14 in the ring of m-PA and the highly negative C1 in NAC. Hence C1 in NAC will be attached with the ring of m-PA at position 2. The positive hydrogen atom at position 7 will be attracted with the negative nitrogen atom at position 7 producing amino-hydrogen at this position and the quinoid structure of m-PA will disappear producing another molecule preventing the formation of the quinoid structure as in m-PA which is responsible for the cancer effect.



N-Acetylcystine (NAC) Free Radical m-PA Free Radical

Fig. 7: The minimum energy structures of the free radicals of NAC and m-PA.

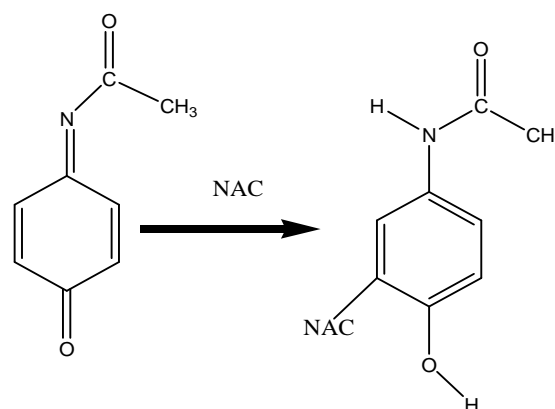


Fig. 8: The interaction between m-PA and NAC.

In June 2009, an FDA advisory committee recommended that new restrictions should be placed on Paracetamol usage in the United States to help protect people from the potential toxic effects. The maximum dosage to 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

Table 5: The columbic potential energies (C= C<sup>+</sup> + C<sup>-</sup>) of PA, PH and m-PA with the nucleic acid bases in eV.

Compound	C, eV adenine	C eV guanine	C eV, cytosine	C eV, uracil
PA cis	0.2857	0.8655	0.7938	0.1989
PA trans	0.1493	0.7293	0.6574	0.0618
PH cis	1.7553	0.7553	0.6836	0.0887
PH trans	0.0887	0.7556	0.6838	0.1782
m-PA	0.3255	1.5617	1.2384	0.5025

Table 6: The Cancer energy barrier of the studied compounds with (NAB)

N.A.B	m-pa Eet eV	Ph.ci Eet eV.	Ph.tr Eet eV	Pa cis Eet eV	Pa.tr Eet eV
Adenine	1.811	3.484	4.355	4.611	4.421
Guanine	0.382	3.772	3.672	4.015	3.825
Cytosine	1.104	3.650	3.550	3.893	3.703
Uracil	2.589	3.859	3.670	4.102	3.975

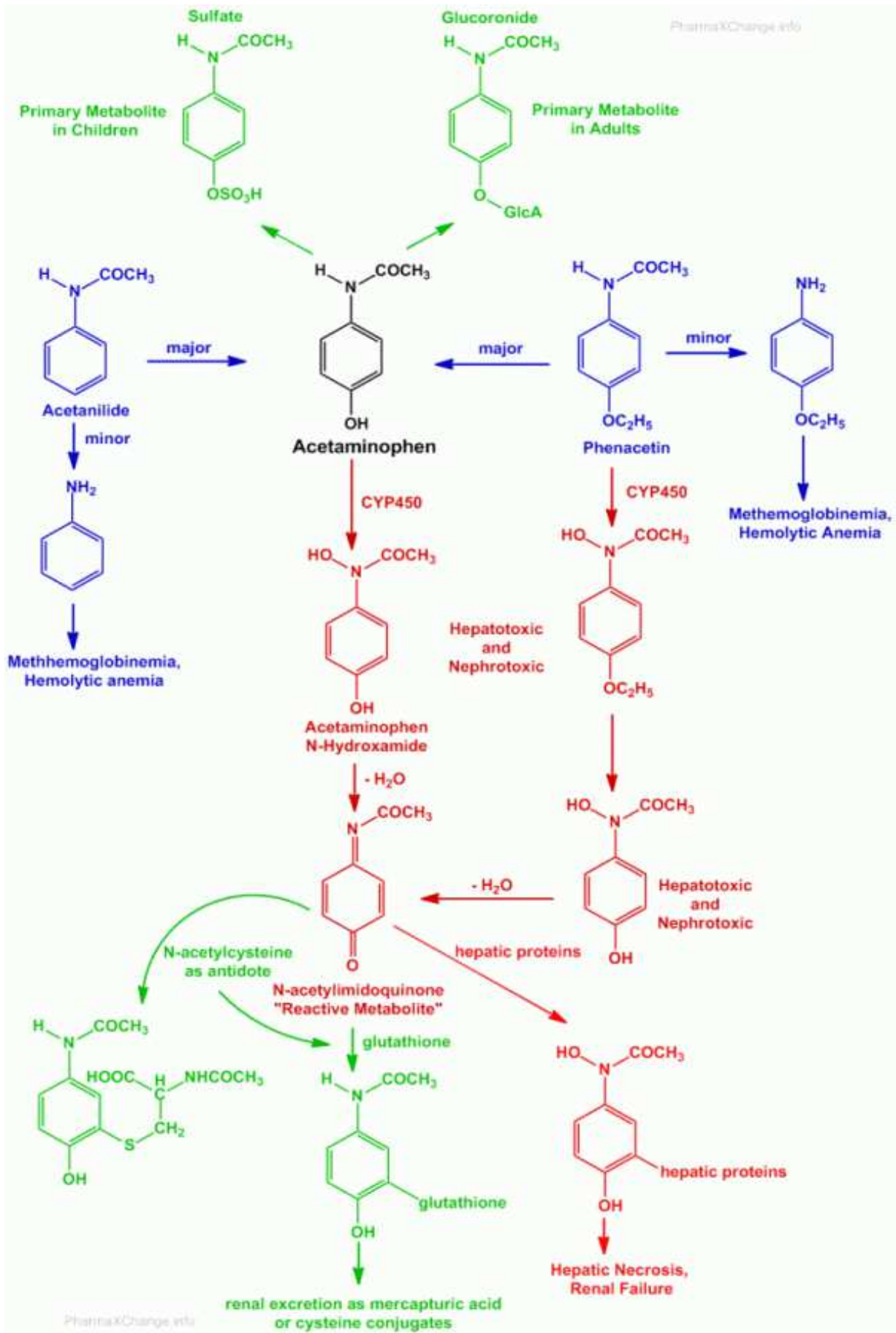


Fig. 4: Scheme of metabolism of PA and PH to form m-PA.

Table 7: DFT/B3LYP-6-31G\*\* Charge densities

S. No.	GSH	NAC	m-PA
1	N -0.057143	C -1.003289	C 0.285352
2	C -0.615967	S 0.397550	C 0.492989
3	C -0.196757	N -0.206871	C -0.84676
4	C -0.373881	C 0.540236	C -0.45967
5	O -0.456866	O -0.465326	C -0.24005
6	C 0.355514	C -0.746486	C 0.182835
7	O -0.402651	C 0.338204	N -0.10934
8	O -0.482321	C -0.820600	C 0.652457
9	C -1.163754	O -0.388053	C -0.919709
10	S 0.383267	H 0.335015	O -0.413230
11	N -0.190125	H 0.068367	O -0.451106
12	C -0.140436	H 0.462384	H 0.316077
13	O -0.421302	H 0.244840	H 0.260896
14	C -0.121432	H 0.248682	H 0.280168
15	C -0.454235	H 0.254663	H 0.257812
16	C -0.605286	H 0.242716	H 0.225737
17	C 0.360928	H 0.236793	H 0.242777
18	O -0.380013	H 0.261176	H 0.242759
19	O -0.435481		
20	N -0.421719		
21	H 0.614308		
22	H 0.279929		
23	H 0.306883		
24	H 0.183612		
25	H 0.496271		
26	H 0.351963		
27	H 0.287111		
28	H 0.030564		
29	H 0.477789		
30	H 0.371327		
31	H 0.262664		
32	H 0.255370		
33	H 0.367222		
34	H 0.231998		
35	H 0.517138		
36	H 0.409611		
37	H 0.37590		

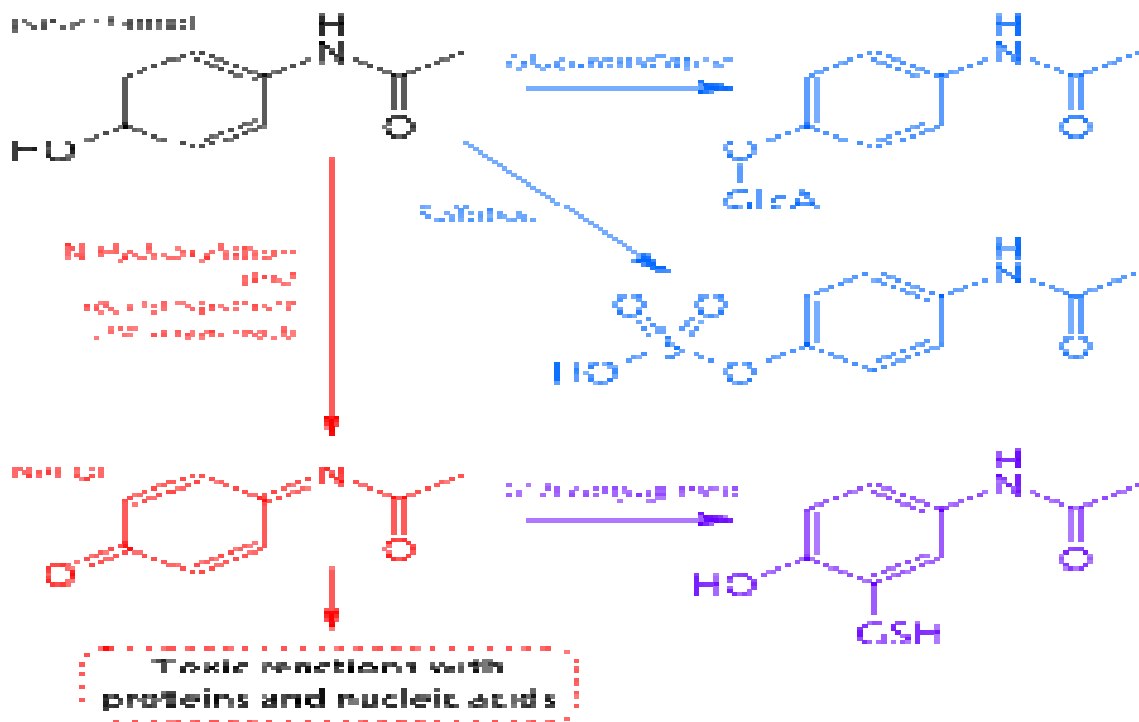


Fig. 9: The three pathways of Paracetamol in the liver.

Table 8: The Charge densities of the free radicals of NAC and m-PA.

No. of atom	NAC free radical	m-PA free radical
1	C -1.006906	C 0.349037
2	S 0.430132	C 0.384714
3	N 0.239680	C -0.906151
4	C 0.100551	C -0.002261
5	O -0.363729	C -0.271942
6	C -0.598040	C -0.298343
7	C 0.340232	N -0.160492
8	C -0.670558	C 0.689206
9	O -0.372600	C -0.914644
10	H 0.375061	O -0.448519
11	H 0.071781	O -0.581359
12	H 0.220141	H 0.293696
13	H 0.253135	H 0.211427
14	H 0.242265	H 0.259567
15	H 0.237844	H 0.244277
16	H 0.211060	H 0.217471
17	H 0.289948	H 0.238823
18		H 0.238836
19		H 0.456656

## CONCLUSION

Paracetamol and Phenacetin as drugs are safe from the cancer effect in presence of pharmacological dose from N-Acetylcystine.

## ACKNOWLEDGEMENT

This work has been supported by the Egyptian Ministry of Higher Education, Management of Supporting Excellence, Competitive Excellence Project of Higher Education Institutions, (project: CEP1-043-ASSU), Grant 2014.

## REFERENCES

- de Paramo, B. J.; Gancedo, S.Q.; Cuevas, M.; Camo, I. P.; Martin, J. A.; Cosmes, E. L. Paracetamol (acetaminophen) hypersensitivity. *Ann. Allergy Asthma Immunol.* 2000, 85, 508-511.
- Vial, T.; Bergeret, A.; Delattre, D.; Descotes, J. Side effect of Paracetamol. *Lyon Pharm.* 1988, 39(3), 187-189.
- Wojcicki, J.; Zdzislaw, B.; Barbara, G.S.; Jozsef, K.; Pol, K. K. The of single dose of ethanol on pharmacokinetics of Paracetamol. *J. Pharmacol. Pharm.* 1978, 30(6), 749-753.
- Goto Y., Niiya T., Honjo N., Sakamoto T., Yoshizawa H., Yamanaka H and Kubot T, Molecular Orbital Study of the Reactivity of Active Alkyl Groups of Pyridine and Pyrimidine Derivatives, *Jpn. Chem. Pharm. Bull.*, 30, 1982, 1126.
- Taha H. M., Al-Obeidi F. A. and Borazan H. N., UV Studies of Nucleic Acid Base Complexation with Isoproterenol in Different Solvents, *J. Pharm. Sci.*, 68 (5), 1979, 631.
- Makhlouf M Th, El-Shahawy A. S. and El-Shatory S. A., CNDO Study of the Tautomeric Structure of Uracil and its Effect on the Electrochemical Corrosion Behavior of Mild Steel in Acid Media, *Mat. Chem. Phys.* 43(2), 1996, 153.
- Ghafourian, T.; Dearden, J. C., The use of atomic charges and orbital energies as hydrogen-bonding-donor parameters for QSAR studies comparison of MNDO. AM1, PM3 methods. *J. Pharm. Pharmacol.* 2000, 52 (6), 603-610.
- A, C. Moffat, *Clarks Isolation and Identification of Drugs*. second ed. The pharmaceutical press, London, 1986.
- Al-Obeidi F. A. and Borazan H. N., Interaction of Nucleic Acid Bases with Catechol: UV studies, *J. Pharm. Sci.*, 65 (6), 1976, 892.
- Lahiri J. and Basu R., Estimation of Electron Affinities of Tetracycline and Oxytetracycline, *Indian J. Chem.* 21B(3), 1982, 260.
- Anwar S El-Shahawy and Ahmed S. Hammam, CNDO/SCF Molecular Orbital Structural Studies and Charge Transfer Complex Formation Between 4,4'-Dimethoxydiquinone and Uracil. *Bull. Chem. Soc. Ethiop.* 2004, 18(2), 193-204.
- K. Eran and K. Gideon, "Management of Paracetamol Overdose: Current Controversies", *Drug Saf.*, 24 (7), 503 (2001).
- J.R. Vane, R.M., "The mechanism of action of aspirin", *Botting The William Harvey Research Institute, St. artholomew's and the Royal London School of Medicine, Charterhouse Square, London EC1M 6BQ, UK Thrombosis Research*, 110 (2003), p. 255-258 (2003).
- A.D. Becke, *J. Chem. Phys.*, 98 (1993), p. 5648.
- B.A. Miehlich, H.S. Savin and H. Preuss., *Chem. Phys. Lett.*, 157(1989), p. 200.
- P.Hohenberg, W. Kohn, *Phys. Rev.*, 136, B864 (1964).
- W. Kohn, L. Sham, *J. Phys. Rev.*, 140, A1133 (1965).
- Anwar S El-Shahawy, Seddique M Ahmed, Nager Kh Sayed, *IJPAC*, 1(4) (2006), p.577-587.
- Anwar El-Shahawy, *J. Mol. Stru.*, 987(1-3) (2011), p. 232-240.
- A.S. El-Shahawy, M.M. Girgis and M.T. Ismail, *Specrochimica Acta* 43A(11) (1987), p. 1371-1375.
- A.S. El-Shahawy, S.M. Ahmed, N.Kh. Sayed. *Spectrochim. Acta., Part A*, 66 (2007), p. 143-152.
- Borne, R. F. Non-steroidal Anti-inflammatory Agents. In: *Foye's Principles of Medicinal Chemistry 6th Edition*; Williams D. A.; Lemke T. L., Lippincott Williams & Wilkins Philadelphia, 2007; p751-793.
- Prescott, L. F. *Paracetamol (Acetaminophen): A Critical Bibliographic Review* CRC Press, 1996
- Wikipedia Free encyclopedia (Paracetamol\_ metabolism. svg).