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NMR Shielding and S-NICS Investigation for Imipenem,Penicillin G, Ticarcillin, Ampicillin and Clavulanic Acid in Viewpoint of Bio-Nanotechnology

MARYAM DERAKHSHANDEH and MAJID MONAJJEMI*

Department ofChemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran.
*Corresponding author E-mail: m_monajjemi@srbiau.ac.ir

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ABSTRACT

Ampicillin, Clavulanic acid, Imipenem, Penicillin G and Ticarcillin properties for the drug delivery in viewpoint of NMR shielding and S-NICS investigation have been studied.Phenoxy-acetic acid for Penicillin V or Penicillin and its alteration Penicillin G are used for large scale production. Various Penicillins and the other cells-wall inhibitor are mainly specific against Gram(+) bacteria due to highest percentage of peptidoglycan" in the cells-wall of those organisms. Ampicillin which is belongs to the penicillin groups of beta lactam-antibiotics is capable to penetrate Gram(+) and some Gram(-) bacteria. Imipenem or Primaxine is an intravenous-β-lactamantibiotic discovered by William Leanza, Kenneth Wildonger and Burton Christensen from Merck scientists in 1980. It was the first part of the carbapenem kinds of antibiotics. Based on our previous works[82] we have design and simulated a drug delivery system of those antibiotics. In this study, we have discussed a statistical approach via computing of nucleus-independent chemical shifts (S-NICS) in view point of probes motions in a sphere of de-shielding and shielding spaces of antibiotic rings. In the related work[82], it has been exhibited that S-NICS method is a suitable method for evaluting the aromaticity in the non-benzene rings such as those antibiotics which are important compounds for organic chemical synthesize and reactions.

Keyword: Ampicillin, Clavulanic acid, Imipenem, Penicillin G, Ticarcillin, NMR and S-NICS

INTRODUCTION

Antibiotics are molecules that stop or kill the growth of, microorganisms, including both bacteria and fungus. Antibiotic that block the growth of bacteria is called bacteriostatic" andantibiotic that kill bacteria is called "bactericidal.

Antibioticis specific chemical substance produced (or derived) by living organisms that are capableof inhibiting the life processes of other organisms[1-10.]

A test, resulting in the classification of bacteria, has developed by "Hans Christian Gram"

(a Danish microbiologist)including gram(+) bacteria and gram(-) bacteria.

Currently there are several classifications of antibiotics which can be summarized as various groups such as (1)-Benzyl-penicillins which are including Penicillin G, benzyl-penicillin sodium, procaine benzyl-penicillin, benzathine penicillin (2)- anti-staphylococcal penicillins(3)-Phenoxy-penicillins including Penicillin V and PropicillinOxacillin, Dicloxacillin and Flucloxacillin (4)-Quinolones including Group(I):Norfloxacin Group(II): Enoxacin, Norfloxacin, Ciprofloxacin, Group(III):Levofloxacin, Group(IV):Moxifloxacin(5)-ß-Lactam/ß-lactamase inhibitor includingAmpicillin[1-5], Amoxicillin[3-5], Mezlocillin[2-4], Piperacillin, Ampicillin/ sulbactam[3-6], Amoxicillin / clavulanate, Piperacillin/ tazobactam and Sulbactam in free combinations[4-7] (6)-Cephalosporinsincluding Cefotaxime[4-7], Ceftriaxone, Ceftazidime, Cefepime, Cefixime[3-7], Cefpodoxime proxetil[4-8], Ceftibuten (oral) (7)-Azol derivatives including Miconazole, Ketoconazole, Fluconazole, Itraconazole, Voriconazole, Posaconazole(8)-Macrolides including Erythromycin, Spiramycin, Roxithromycin[5-9], Clarithromycin, Azithromycin (9)-Echinocandins including Caspofungin, Anidulafungin, Micafungin(10)-Aminoglycosides including Streptomycin, Gentamicin, Tobramycin, Netilmicin, Amikacin[1-10]

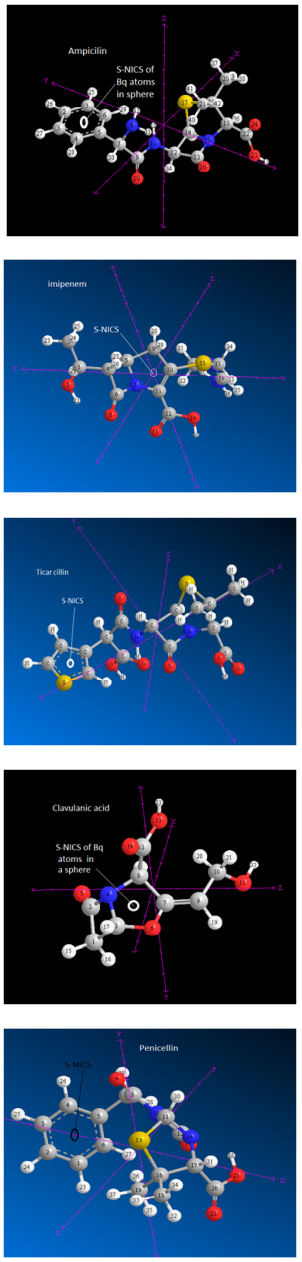

Fig.1: Ampicillin, Clavulanic acid, imipenem, Penicillin G and Ticarcillin structures

Antibiotics are special chemical substances isolated or produced from by living organisms that are able for inhibiting the life activities of other organisms. The first antibiotics were derivedfrom micro-organisms" but currently some are obtained through higher plants and animals. Over 3,000 antibiotics have been synthesized and classified butonly a few dozen are used as medicine.

As an example penicillins which has been discovered by Alexander Fleming in 1928, is a kind of antibiotic that has been used inthe treatment towards bacteria invasion. Fleming whoworks at St. Mary's Hospital London[6-10], left for his holidays therefor left the culture of the microbe near the window of his lab thenafter he came back, he found an unusual phenomenon of theculture (of microbe) that he had left[1-10].

In the past years (decades), pharmaceutical antibiotic was recognized and sensitized as emerging soil pollutants[11-13]. Compounds such assulfonamides and tetra-cyclins reach agricultural land mostly viainfecteddung from medicated chattels used as muck. Pharmaceutical antibiotics[5-11] are a large group that comprise mostly ionize and polar able compounds. Hence, their soil adsorption behavior swerved from hydrophobic organic pollutants. furthermore to hydrophobic" interaction, antibiotic

may sorb to soils through van der Waals forces, hydrogen bonding,ion or cation exchange and bridging, finally surface complexes[1-10].

However, sorption can be overcome by investigating either separated natural soil constituents such as "humic" acid or polymers from well-defined "phenolic" compounds, representing specific site and functionality of "humic" substances that can serve as a model to elucidate mode of binding. "Phenolic" compoundis a major building block of "humic" polymer and was found to polymerize to humus-like substance[5-10].

Penicillin attaches such as penicillin binding protein and interfere with the last step of bacterial cell-wall synthesis which is trans-peptidation or cross linkage by inhibition of transpeptidase and production of autolysin leads to bactericidal action. The mechanism of action for various antibiotics is different. In view point of bacterial spectrum several points are important such as in effective against organism devoid of peptidoglycan can such as mycobacteria,effective against active organism which synthesizes peptidoglycan cell wall,fungi, viruses and protozoa. Gram positive organisms have cell wall easily traversed by penicillins and therefore theyare susceptible to penicillins, several Gram negative organisms have "porin" permit transmembrane entry of penicillin and so they are susceptible organisms. Staphylococci developed resistance to natural Dicloxacillin,penicillin Gand Methicillin which are

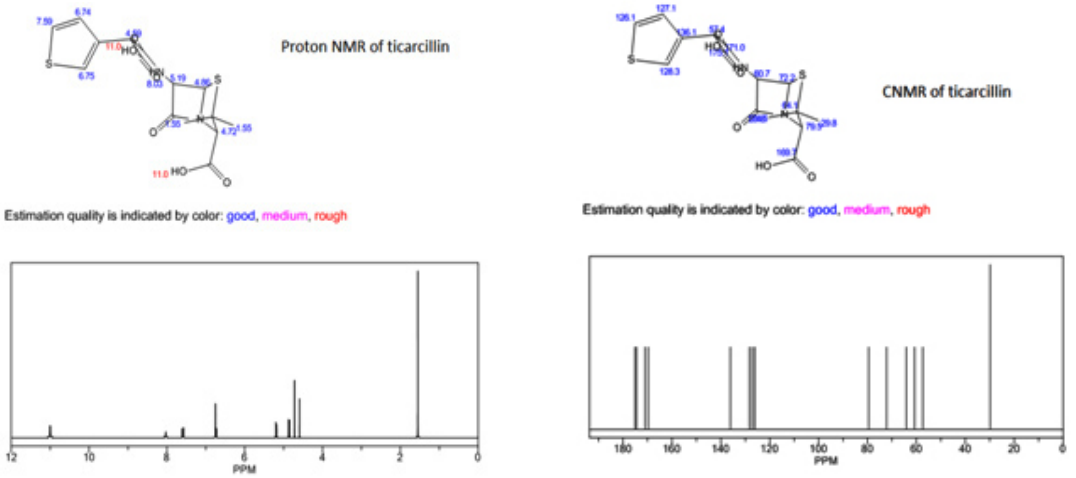

Fig. 2: Proton & Carbon NMR of Ticarcillin

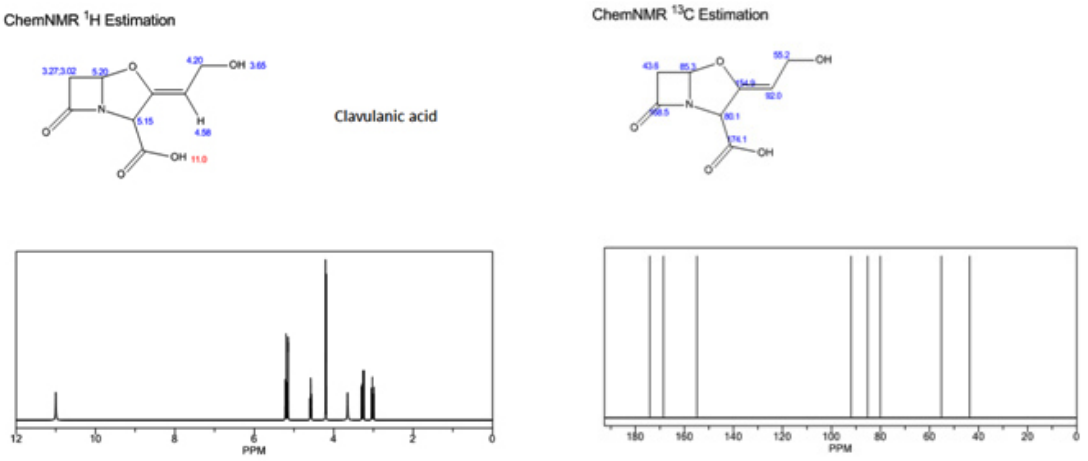

Fig. 3: Proton & Carbon NMR of Clavuanic acid

penicillinase resistance preparations are effective against staphylococci.Combination of penicillins and aminoglycosides has synergistic effect while in view point of absorption; most of them are poorly absorbed after oral administration except amoxicillin and ampicillin. Penicillinase resistant preparation should be given one hour before meals because their absorptionsare delayed by presence of food[10-20].

Van der Waals forcesand multiple weak H-bonds between zeolites and antibiotics are responsible for the ir-reversible extraction from water of all the examined drugs. Lastly, the most stable tautomer form of each antibiotics adsorbed into the zeolites were identified.

As an instant and important antibiotic it can be mentioned the sulfonamidewhich is commonly used drug in primary care practice. Reaction to Sulfonamide Antibiotic (SA) is relatively common as compared to other antimicrobials[20-30] .

The hypersensitivities reaction, consisting of fever and non-urticarial rash, usually developseven up to fourteen days after the medication initiation. The term “sulfa” refers to a derivative of an antimicrobial agent, “sulfanilamide”.

Penicillin was the first antibiotic discovered from naturalproducts (Penicillium). It is a “beta-lactam-antibiotic” that is a part of the amino-penicillin” family and is hastily equivalent to successor,amoxicillin in its spectrum and level of activity which is produced by Penicilliumchrysogenum[10-12]. Phenylacetic acid for PenicillinG or phenoxyacetic” acid for PenicillinVis used for the larger scale production. Otherpenicillins are produced semi-synthetically”. Penicillinis primarilyspecific against Gram(+) bacteria because of its higher percentage of peptidoglycan in the cell wall ofthat organism.

Ampicillin belongs to the penicillin group of β-lactamantibiotics, ampicillinsare able to penetrate

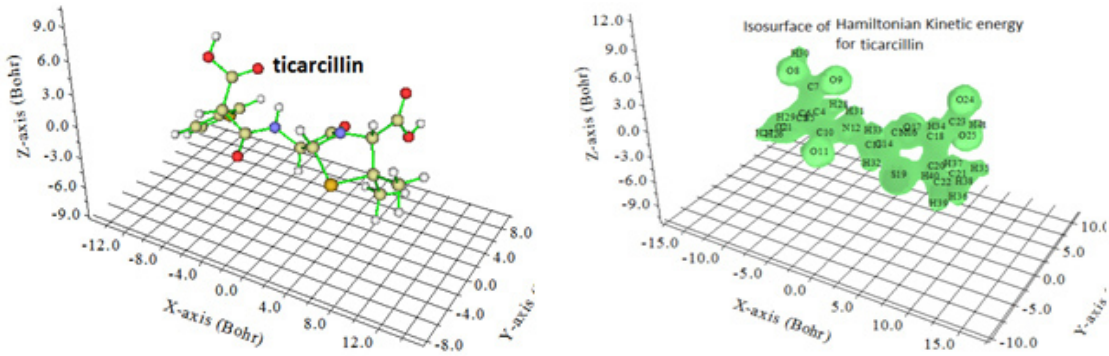

Fig. 4: the optimized oriental and iso-surface Hamiltonian kinetic energy for Ticarcillin Versus Z, Y and X-axis

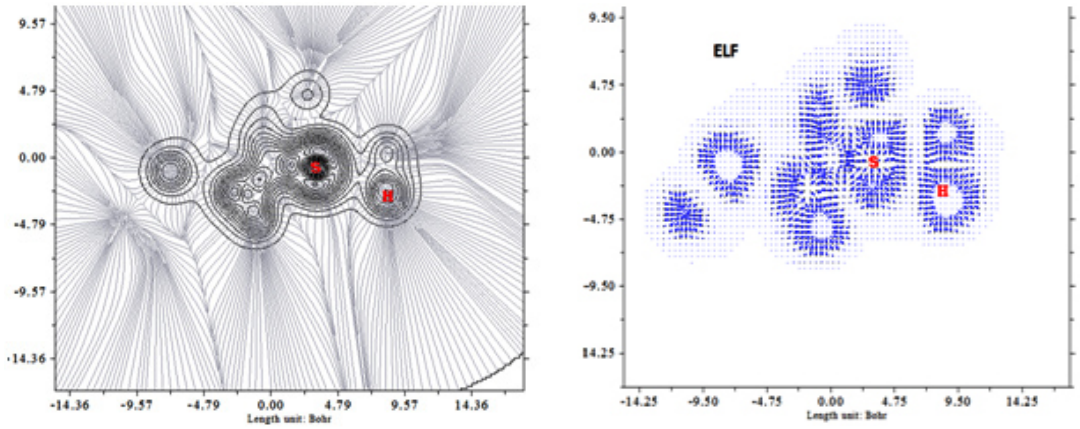

Fig. 5: Gradient map of LOL and ELF for Imipenem in gas phase

Gram(+) and some Gram(-) bacteria. Ampicillinsare semi synthetic penicillins with an extera amino-chain synthesized into the penicillin molecules.

Imipenem is intravenous β-lactamantibiotics discovered which is the first member of the carba-penem" classes of antibiotic. Carba-penems are highly resistant to the β-lactamase enzymes produced by many multiple drug resistant Grams(-) bacteria, thus play a key role in the treatment of infection not readily treated with other antibiotics[20-30].

Based on previous works we have modeled and simulated drug delivery systems of those antibiotics[30-88] .In this work we have exhibited the especial properties of Ampicillin, Clavulanic acid, Imipenem, Penicillin G and Ticarcillin in view point of NMR shielding and S-NICS methods for delivering in cell body via QM/MM and Abinitio methods.

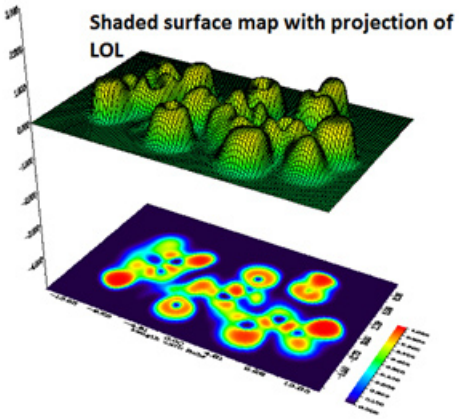

Fig. 6: Shaded surface map of LOL for ticarcillin in water

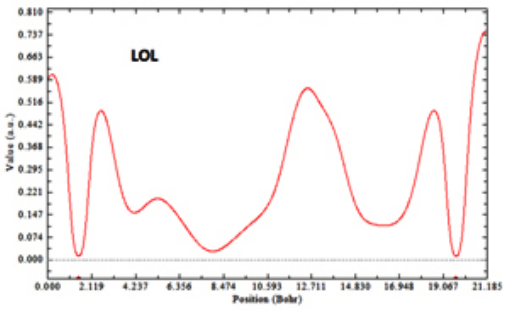

Fig. 7: The LOL curves of ticarcillin in water

Theoretical back ground

NMR Shielding and S-NICS method

There are not theoreticallyor mathematically reports for the statistical approaches in NMR shielding and nucleus-independent-chemical-shift (S-NICS), Since the asymmetry(η)and skew(K) parameters have fluctuated in a short distances and in contrast are alternative in long distances.

In the item of axially-symmetric tensor, the $\sigma_{22}$is the same value of σ11 or σ_{33},and then skew is K=±1. Through changing the asymmetry between 0≤η≤+1 skewis changed between -1≤K≤+1 , and the parameter "K" is zero when $\sigma_{22} = \sigma_{iso}$.

We have investigated a statistical method via computing of nucleus-independent-chemical-shift (S-NICS) in view point of probes motionsin a sphere of de-shielding and shielding spaces of hereto rings in some antibiotics.The reduced anisotropy defined as: [(1): Anisotropy (Δσ) with relation of $\Delta\sigma 3/2\ \zeta$ including shielding asymmetry(η) is defined as: $\eta = (\sigma_{yy}-\sigma_{xx}/\zeta)$ (2) and $\Delta\sigma = \sigma_{zz}-1/2(\sigma_{xx}-\sigma_{yy})$ ...(3).

In severalitems of the axially symmetric tensor, $(\sigma_{yy}-\sigma_{xx})$ is zero and hence $\eta = 0$. However, the asymmetry (η) parameter indicates that how much of the line deviates from an axially- symmetric-tensor, therefore, $(0 \le \eta \le +1)$.

The tensor of shielding is interpreted as the sum of an anti-symmetric with the symmetric, and terms (scalar), which are ranks{2- 0 t} tensorswhich defined as: $\Omega = \Omega^{(0)} + \Omega^{(1)} + \Omega^{(2)}$ ...(4).

The total chemical-shielding-tensors{r}are non-symmetric tensors that can be decomposed into 3 independent tensors as:(1) a traceless symmetric component, (2) an isotropic component, and (3) The traceless component (anti-symmetric). In a spherical representation of tensor, Haeberlenhas pointed a fundamental level tensoris better represented in the spherical presentation, so a general second-order property of "σ" may be written as $\sigma = \sigma^{iso(o)} + \sigma^{anti(1)} + \sigma^{sym(2)}$ ...(5), where the number in brackets indicates to tensor ranks. Spherical tensoris involved in considering the effects of tensor quantities in the density matrix , so using of thoserepresentations are inevitable for such study. It is notable that:

$\sigma_0^{t\sigma o(2)} = {}^2\sqrt{3/2}\ \zeta$ ...(6) And $\sigma_{+2}^{sym(2)} = 1/2\ \zeta$ ...(7)

The component of the shielding tensors have symmetric tensor elements with $r_{ij} = r_{ji}$. These tensorsare responsible for a relaxation (CSA) most often illustrated in the literature and can be diagonalizedthroughthe rotation onto the shielding tensorsof the principal coordinate system.

With a statistical calculation it has beenexhibited that a time independent average of (Ω*) can be remodeledfor all above sum of anti-symmetric, asymmetric,and the scalar term, which are rank tensors equal 1, 2 and zero respectively. These methodsare based on of a probe with random motions in the de-shielding and shielding spaces of the aromatic rings and anti-aromatic molecules. The magneticsmedia of spin are seldom isotropic. Therefore, are represented through of span tensor: $(\Omega) = \sigma_{33} - \sigma_{11}$ ...(8) and $k = 3(\sigma_{\iota\sigma o} - \sigma_{22}/\Omega)$ ...(9). In the notation of Herzfeld-Berger, tensors have explained with3 parameters, which they are a combination of the major components in this standard notation. These are including, (Ω), which indicates of a maximum width, ($\Omega \geq 0$), and (**κ**) tensors which are a magnitude of this value.

The accurate formulation of (Ω), including the factor of $(1-\sigma_{ref})$ have been described by

Table1: Charge (ESP), isotropy, anisotropy, span and aromaticity of Ampicillin in gas phase and solvent

	Ampicillin gas phase						Ampicillin in water					
Atom	**Charge**	**σ iso**	**σ aniso**	**η**	**Δδ**	**Ω**	**atom**	**charge**	**σ iso**	**σ aniso**	**η**	**δΔδ**	**Ω**
17S	0.413	28.6	14.67	0.76	-16.65	-11.1	17S	0.415	28.4	14.8	0.77	-16.7	-11.17
10O	0.12	27.8	9.051	0.66	9.05	6.034	10O	0.14	29.9	7.5	0.7	-8.82	-5.8
16O	-0.36	144.6	28.2	6.9	23.9	-17.3	16O	0.104	29.7	7.9	0.85	-8.54	-5.6
23O	-0.46	166.9	24.6	8.9	29.9	-13.3	23O	-0.24	110.6	40.4	0.36	-59	-39.3
24O	-0.5	294	72.4	8.45	52.9	-31.3	24O	-0.46	167.2	24.3	0.6	24.3	16.2
1 C	-0.53	249	64.4	2.61	-18.7	-79.1	1 C	0.242	66.18	99.5	0.51	99.56	66.37
2 C	-0.242	157.5	11.48	11.6	36.27	-9.15	2 C	0.004	121.9	34.9	0.18	34.9	23.2
3 C	0.13	29.4	6.03	0.52	6.03	4.02	3 C	-0.25	160.8	12	0.97	-12.13	-8.089
4 C	-0.283	152.1	26.84	9.63	30.85	-12.76	4 C	0.132	29.4	6.25	0.48	6.25	4.16
5 C	0.243	120.5	35.8	8.6	26.9	-15.387	5 C	0.242	120.2	36.1	0.28	36.13	24.09
6C	-0.678	248.3	47.2	8.6	59	-27.5	6C	-0.69	245.2	50.4	0.58	50.4	33.6
7C	-0.258	160.5	12.67	13	37.5	-8.33	7C	-0.52	244.2	98.4	0.54	-127.4	-84.9
8N	0.006	121.9	34.8	9.7	29.5	-13.6	8N	-0.284	152.2	26.4	0.43	26.4	17.6
11N	0.237	67.88	96.88	0.44	96.88	64.59	11N	-0.5	293.7	72.9	0.33	72.9	48.6
15 N	-0.09	148.4	25.1	8.98	29.9	-13.3	15 N	-0.09	148.8	24.9	0.58	24.9	16.6
16 C	0.322	65.43	93.16	0.25	93.16	62.11	16 C	-0.24	157.5	11.47	0.72	-13.3	-8.86
12 C	-0.45	168.5	22.9	8.6	29.7	-13.4	12 C	-0.45	168.4	22.7	0.78	22.7	15.1
13 C	-0.19	130.3	65.7	5.9	9.53	-26.9	13 C	-0.19	129.9	67.5	0.2	67.5	45
14 C	0.13	76.92	141.3	0.23	141.3	94.21	14 C	0.335	62.2	95.9	0.25	95.99	63.99
25 H	0.12	25.4	12.86	0.59	12.86	8.5	25 H	0.13	25.7	13.3	0.59	13.3	8.87
26 H	0.1	29.8	8.01	0.9	-8.4	-5.61	26 H	0.154	73.57	132.9	0.22	132.9	88.61
27 H	0.138	29.97	7.36	0.68	-8.72	-5.81	27 H	0.14	30.2	9.33	0.4	9.33	6.22
28 H	0.13	29.7	10.1	0.53	10.15	6.7	28 H	0.14	29.7	10.2	0.53	10.28	6.85
29 H	0.077	78.31	140.6	0.35	140.6	93.76	29 H	-0.328	89.87	107.9	0.77	107.93	71.95
30 H	0.14	30	7.1146	0.8	-7.88	-5.25	30 H	0.146	30	6.87	0.82	-7.52	-5.01
31 H	0.1803	73.56	153.2	0.49	153.23	102.1	31 H	0.187	74.61	151.7	0.47	151.7	101.1
32 H	0.134	28.3	9.349	0.59	9.34	6.23	32 H	0.134	28.3	9.29	0.58	9.29	6.19
33 H	-0.3116	85.4	114.26	0.83	114.26	76.17	33 H	0.13	27.8	9.17	0.65	9.17	6.11
34 H	0.14	30.2	9.46	0.4	9.46	6.31	34 H	0.074	75.88	144.3	0.34	144.3	96.22

$\Omega = (\sigma_{33} - \sigma_{11})\ (1-\sigma_{ref})$ ...(10).

Moreover the orientation of a-symmetry tensorsare given by (κ = 3a/ Ω)and the skew is $\boldsymbol{\kappa}$= 3($\sigma_{\iota so} - \sigma_{22}$ / Ω) ;(-1≤ κ≤+1) and dependentto the position of σ_{22} with consideration of σ_{iso}, the sign of $\boldsymbol{\kappa}$ is either negative or positive.

In the items of the axially symmetric tensors, σ_{22} equals either σ_{11} or σ_{33} and $\boldsymbol{\kappa}$= ±1 therefore***a*** = Ω/3, and then parameter "***a***" and "$\boldsymbol{\kappa}$" are equal to zero when $\sigma_{22} = \sigma_{iso}$and the parameter "$\mu$" used with the Herzfeld-Berger is dependent to the span of a tensor. $R_1^{dia,CSA} = 2/15\gamma_S^2 B_0^2[5\ \rho^2.\ \tau_{r,1} / 1+\omega_s^2\tau^2_{r,1} + \Delta\sigma^2(1 + \eta^2/3\ \tau_{r,2} / 1 + \omega_S^2\tau^2_{r,2})]$ ...(11) and ρ^2 is defined by: $\rho^2 = (\sigma_{XY} - \sigma_{YX} / 2)^2$ ...(12) $R_2^{dia,\ CSA} = 2/45\gamma_s^2\ B_0[15\ \rho^2.\ \tau_{r,1} /\ + \omega_S^2\tau^2_{r,1} + \Delta\sigma^2(1 + \eta^2/3)\ (4\tau_{r,2} + 3\tau_{r,2} / 1 + \omega_S^2\tau^2_{r,2})]$ ...(13)

Where $\tau_{r,1}$ and $\tau_{r,2}$ correspond to the correlation times for isotropic tumbling and small-step molecular rotation, respectively and in the case of axial symmetry or for isotropic $\tau_{r,1}=3\tau_{r,2}$.

Density and energy of electrons

The electron densities have been illustrated as $\rho(r) = \eta\ |\ \varphi_i(r)\ |\ \nu\ |^2 = \Sigma_i\ \eta_i\ |\Sigma_l C_{L,l}\chi_i(r)|^2$...(14)**.** Where is occupation number of orbital (*i),*is orbital wave function,is basis function and *C* is coefficient matrix, the element of i_{th} row j_{th} column corresponds to the expansion coefficient of orbital *j*respect to basis function *i*. Atomic unit for electron density can be explicitly written as e/Bhor^3. $\nabla\rho(r) = [(\partial\rho(r)/\ \partial(x))^2 + (\partial\rho(r)/\ \partial(y))^2 + (\partial\rho(r)/\ \partial())^2$ ...(15) $\nabla^2\rho(r) = \partial^2\rho(r) / \partial x^2 + \partial^2\rho(r) / \partial y^2 + \partial^2\rho(r) / \partial z^2$ ...(16).

The relationships between $\nabla^2\rho$ and valence shell electron pair repulsion have been built by Bader[90,91].The kinetic energies density are not uniquely defined, since the expected value of kinetic energies operator $<\varphi\ |\ -(1/2)\nabla^2|\ \varphi>$ ...(17) can be

Table2: Charge (ESP), isotropy, anisotropy, span and aromaticity of Clavulanic acid in gas phase and solvent media

Clavulanic acid in gas phase							Clavulanic acid in water						
atom	**charge**	**σiso**	**σaniso**	**η**	**Δδ**	**Ω**	**atom**	**charge**	**σiso**	**σaniso**	**η**	**Δδ**	**Ω**
N(4)	10.05	0.13	29.7	10	0.5	10.05	N(4)	0.004	121.9	34.8	0.2	-120.7	113.8
O(5)	0.13	29.9	7.29	0.6	-8.7	-5.8	O(5)	0.24	120.4	36.2	0.2	-123.2	115.4
O(6)	-0.2	157.6	11.6	0	-113.7	109.5	O(6)	-0.32	88.9	110.4	0.7	110.4	73.63
O(11)	-0.5	293.83	71.96	0.2	-247.9	231.8	O(11)	0.16	76.6	129.4	0.2	129.4	86.3
O(13)	-0.19	130.4	65.3	0.4	-140	126.6	O(13)	0.34	63.4	94.8	0.2	94.89	63.2
O(14)	0.005	121.8	35.1	0.2	-120.6	113.7	O(14)	0.183	74.96	151.8	0.4	151.8	101.2
C(1)	-0.4	167	24.5	0.1	-120.6	113.7	C(1)	-0.24	157.4	11.6	0	-113.5	109
C(2)	-0.25	160.5	12.4	0	-112.1	108.1	C(2)	0.24	66.7	98.4	0.4	98.4	65.6
C(3)	-0.44	141.1	29.9	0.1	-125.7	117.1	C(3)	-0.28	152.1	26.4	0.2	-118.8	112.5
C(7)	-0.45	168.3	22.9	0.1	-120.7	113.8	C(7)	0.07	76.4	144.4	0.3	144.4	96.3
C(8)	-0.67	248.3	46.93	0.1	-240.6	227	C(8)	-0.67	247.1	49.33	0.1	-241.2	-27.4
C(9)	0.32	65.27	93.7	0.2	93.78	62.5	C(9)	-0.52	242.1	87.2	0.1	-234	189.3
C(10)	0.23	67.9	97	0.4	97	64.6	C(10)	0.14	29.9	7.41	0.6	-8.7	-5.81
C(12)	0.13	78.2	139.2	0.2	139.2	92.8	C(12)	-0.5	293.6	72.8	0.2	-248.5	232.3
H(15)	-0.53	250.2	65.4	0	-219.2	179.4	H(15)	-0.25	160.6	12.2	0	-112.5	108.3
H(16)	0.24	120.5	36	0.2	-123.4	115.6	H(16)	-0.46	167.2	24.5	0.1	-120.3	113.5
H(17)	-0.09	148.6	25.2	0.1	-119	113.1	H(17)	-0.45	168.4	22.8	0.1	-120.4	113.6
H(18)	-0.28	152.07	26.29	0.2	-118.7	112.5	H(18)	-0.19	130.5	65.3	0.4	-140.1	126.7
H(19)	0.12	25.5	12.2	0.6	12.2	8.1	H(19)	-0.094	148.8	25.24	0.1	-119.6	113.1
H(20)	73.5	153	0.4	153	102	6.7	H(20)	0.13	25.8	12.4	0.6	12.48	8.3
H(21)	0.1	29.8	8	0.9	-8.4	5.3	H(21)	0.1	29.7	7.9	0.8	-8.4	-5.6
H(22)	0.14	30.2	9.4	0.4	9.45	6.3	H(22)	0.14	30.2	9.43	0.4	9.4	6.2

recuperated by integrating kinetic energies density from alternative definition and has been explained as: $k(r) = -1/2\Sigma_i \eta_i \varphi_i^*(r)\nabla^2\varphi_i(r)$ ...(18).

The Lagrangian kinetic energy density,"G(r)" is also known as positive definite kinetic energy density. $G(r) = 1/2\Sigma_i \eta_i |\nabla(\varphi_i)|^2 = 1/2\Sigma_i \eta_i \{[(\partial\varphi_i(\mathbf{r})/\partial(\mathbf{x})^2 + \partial\varphi_i(\mathbf{r})/\partial(\mathbf{y}) + \partial\varphi_i(\mathbf{r})/\partial(\mathbf{z})\}$ (19) $K(\mathbf{r})$ and $G(\mathbf{r})$ are directly related by Laplacian of electron density $1/4\ \nabla^2\rho(r) = G(r) - K(r)$ ...(20).

Becke and Edgecombe noted that spherically averaged like-spin conditional pair probability has direct correlation with the Fermi hole and then suggested electron localization function $(ELF)(r) = 1 / 1 + [D(r)/D_{0(r)}]^2$ ...(21) where $D(r)=1/2 \Sigma_i \eta_i |\nabla\varphi_i| - 1/8[|\nabla\rho_\alpha|^2/\rho_\alpha(r) + |\nabla\rho_\beta|^2/\rho_\beta(r)]$ ...(22) where $D_0(r) = 3/10\ (6\pi^2)^{2/3}[\rho_\alpha(r)^{5/3} + \rho_\beta(r)^{5/3}]$ ...(23) for close-shell system, since $\rho_\alpha(r) = \rho_\beta(r) = 1/2\rho$, D and D_0 terms can be simplified as $D(r) = 1/2\Sigma_i \eta_i |\nabla\varphi_i|^2 - 1/8[|\nabla\rho|^2/\rho(r)]$ ...(24) $D_0(r) = 3/10\ (3\pi^2)^{2/3}\rho(r)^{5/3}$ ...(25).

LOL or Localized orbital locator is another item for locating high localization regions likewise ELF, defined by Schmider and Becke[89-91]. $LOL(r) = \tau(r) / 1 + \tau(r)$ ...(26) ,where $(r) = D_0(r) / 1/2\Sigma_i \eta_i |\nabla\varphi_i|^2$ ...(27).

In all calculations the default gauges-including atomic orbital (GIAO) orbitals were used to obtain molecular magnetic susceptibilities, NMR shielding with Gaussian program.

Table3: Charge (ESP), isotropy, anisotropy, span and aromaticity of Clavulanic acid in gas phase and solvent media

Imipenem in gas phase							Imipenem in water						
atom	charge	σiso	σaniso	η	Δδ	Ω	atom	charge	σiso	σaniso	η	Δδ	Ω
P(15)	0.07	80.3	138.7	0.3	138	92.5	P(15)	0.24	120.1	36.12	0.2	123	115
O(2)	-0.09	148.6	25.3	0.5	125	16.9	O(2)	0.18	73.4	154.9	0.4	154	103
O(8)	-0.32	92.04	125.2	0.7	125	83.4	O(8)	-0.32	90.6	138.8	0.6	138	92.5
O(13)	0.07	79.2	131.9	0.4	131	87.9	O(13)	-0.2	152.1	26.1	0.3	126	17.4
O(14)	-0.01	78.9	128.3	0.3	128	85.5	O(14)	0.32	64.9	93.1	0.2	93.1	62
N(7)	0.29	64.25	90.55	0.2	90.5	60.3	N(7)	0.23	68.1	97	0.4	97	64.6
C(1)	-0.24	157.4	11.04	0.9	-62.8	-108	C(1)	-0.24	157.4	11.8	0	113	109
C(3)	-0.25	160.4	12.8	0.9	112	8.5	C(3)	-0.25	160.3	12.7	0	112	108
C(4)	0	121.6	34.4	0.1	134	22.9	C(4)	-0.6	248.6	46.9	0.1	240	226
C(5)	0.24	120.5	36.1	0.3	136	24	C(5)	0.07	76.9	143	0.3	143	95
C(6)	-0.6	247.1	47.3	0.6	247	31.5	C(6)	-0.4	168.2	23.2	0.8	123	15.5
C(9)	-0.5	252	81.2	0.4	231	54.1	C(9)	0.18	74.8	153.2	0.5	153	102
C(10)	-0.28	152.3	25.6	0.1	117	111	C(10)	-0.5	253.3	84.1	0.1	221	181
C(11)	0.006	121.9	35.2	0.2	120	113	C(11)	-0.5	293	74.2	0.2	249	232
C(12)	0.23	67.42	98.4	0.4	98.4	65.6	C(12)	-0.09	148.6	25.3	0.1	119	113
C(16)	-0.46	167	24.7	0.7	124	16.5	C(16)	-0.46	167.2	24.5	0.1	120	113
C(17)	0.44	81.03	33.3	0.8	33.3	22.2	C(17)	-0.45	168.4	22.9	0.1	120	-13
C(19)	-0.18	130.6	63.9	0.2	163	42.6	C(19)	-0.19	130.4	65.31	0.4	139	126
H(28)	0.12	27.8	9.01	0.6	9.01	6	H(28)	0.003	107.3	83.1	0.4	83.1	55.4
H(29)	0.12	26.1	11.1	0.6	11.1	7.4	H(29)	0.14	25.2	12.3	0.7	12.3	8.2
H(30)	0.1	29.7	7.9	0.9	-8.1	-5.4	H(30)	0.1	29.7	8.06	0.9	-8.3	-5.5
H(31)	0.14	30.1	9.4	0.4	9.46	6.31	H(31)	0.14	30.2	9.49	0.4	9.49	6.3
H(32)	0.13	29.7	10	0.5	10	6.6	H(32)	0.13	29.7	10	0.5	10	6.7
H(33)	0.13	29.9	7.24	0.6	-8.62	-5.75	H(33)	0.13	29.9	7.31	0.6	8.71	5.8
H(34)	0.14	29.9	7.18	0.8	-7.9	-5.31	H(34)	0.14	29.9	7.16	0.7	-8	-5.3
H(35)	0.41	28.6	14.4	0.7	-16.3	-10.9	H(35)	0.41	28.5	14.5	0.7	14.5	11
H(36)	0.13	28.3	9.5	0.6	9.5	6.33	H(36)	0.1	29.7	7.9	0.9	-8.1	-5.4

Computational details

Calculations were accomplished using Gaussian and GAMESS-US packages. The ONIOM methodcontainingthree levels from high (H), medium (M), and low (L)calculations have been accomplished in this study. The "advanced DFT" methods are used for high layer of the model and semi-empirical method of Pm6" including pseudo=lanl2 and Pm3MM" are used for the low and medium layers, respectively. There are various situations of non-covalent interaction in this system between hydrogen diffused. In this study, we have mainly focused on getting the optimized results for each item from "advanced DFT" methods including the "m06" and "m06-L". The "m062x", "m06-L", and "m06-HF" are a novel Meta hybrid DFT functional with a good correspondence in non-bonded calculations.

The charge calculation based on molecular-electrostatic-potential or MESP fitting are not well-suited for treating larger systems whereas some of the innermost atoms are located far away from the points at which the MESP is computed.The MESP charge was also calculated using the Merz-Kollman-Singh chelpG[92-96].

The representative atomic charges should be computed as expection values over several molecular positions. The electron densities have been calculated, values of orbital wave-functions, electron spin densities, electrostatic potentials from nuclear / atomic charges, electron localization functions (ELF), localized orbital locators, total electrostatic potentials (ESP) and the exchange-correlation densities, correlation hole and correlation factors, Average local ionization energiesusing Multifunctional Wave-function analyzer[89-91].

The contour line map has drawn via Multiwfnsoftware[89-91]. The relief map has used to present the height value at every point. The graphsare shown on interactive interface.Shaded surface mapand shaded surface map with projection are used in our representation of height value at each situation[89-91] .

RESULT and DISCUSSIONS

Three steps have been investigated in this study, first (1), set up a molecule with appropriate starting geometries andsecond (2) choose a calculation method and its associated choices. Third (3) choose the types of calculations with the relevant options. The Monte Carlo simulations always detect the so-called "important-phase-space" regions which are of low energyies.

In this work, difference in force field has illustrated by comparing the energies calculated by using force fields, Amber,MM+, and OPLS. Also, we have investigated polar solvent and the temperature effects on the stability of antibiotics to CFA (or CGA) in various solvents. The quantum mechanics (QM) calculations were carried out with the HyperChem 8.0 program. This study mainly focuses on the electron density Ampicillin, Clavulanic acid, Imipenem, Penicillin G and Ticarcillinin viewpoint of S-NICS method. The models and situation of molecular structures and binding interaction are shown in figs1- 7. As it is indicated in tables 1-3, the NMR parameters including isotropy, anisotropy, asymmetry, span and S-NICS value have been simulated.

The fermi hole is a six-dimension function and as a result, it is difficult to be studied visually. Based those equations, Becke and Edgecombe noted that the Fermi hole is a spherical average of the spin which is in good agreementwith our results in tables and Figs.

According to the equations 16- 22 the largest electron localization is located onatoms which are bonded to nanotubes wherethe electron motion is more likely to be confined within that region. If electrons are completely localized in those atoms, they can be distinguished from the ones outside. As shown the large density is close to the bonded atoms. The regions with large electron localization need to have large magnitudes of Fermi-hole integration which would leadthose atoms towards superparamagnetic.

CONCLUSION

Once a compound that fulfills all of these requirements has been identified, it will begin the process of drug development prior to clinical trials. Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization

of those hits to increase some properties. One or more of these steps may involve computer-aided drug design. A fascinating result of the theoretical analysis of antibiotics- S-NICS methods were the stable model for drug delivery.

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