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Study of Interaction between Tigecycline and Sulbactam

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Authors' contributions

This work was carried out in collaboration among all authors. Author HSS managed the literature searches designed the study, wrote the protocol and interpreted the data. Author FK anchored the field study, gathered the initial data and performed preliminary data analysis. Author FG produced the initial draft. All authors read and approved the final manuscript.

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ABSTRACT

Drug interactions can have desired, reduced or unwanted effects. The probability of interactions increases with the number of drugs taken. Side effects or therapeutic drug interactions can increase or decrease the effects of one or two drugs. Failure may result from clinically meaningful interactions. Clinicians rarely use foreseeable drug-drug interactions to produce the desired therapeutic effect. For example, when we consider two drugs each causing, peripheral neuropathy increases the likelihood of neuropathy occurrence. In this study geometry optimizations of tigecycline and sulbactam drugs and their combination have been carried out with the evaluation of B3LYP/6-311G (d, p), B3LYP/6-311G (2d, 2p) levels, and the reaction mechanism at semi empirical PM6, which was parameterized for biochemical systems and B3LYP/6-311G (d,p) levels. The main objective of the study is to understand the interaction ofsulbactam with tigecycline, to

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describe energetic condition of bond formation and electronic structure (orders of the broken and formed bonds). The reaction mechanisms of sulbactam with tigecycline have been studied as stepwise and concerted mechanisms using semi-empircal PM6 and B3LYP/6-311G (d,p) levels.

Keywords: Tigecycline; sulbactam; semi-empirical; PM6; B3LYP.

1. INTRODUCTION

Sulbactam, is the β-lactamase inhibitors in clinical use. Sulbactam sodium (SBT) named as 4-thia-1-azabicyclo [3.2.0] heptane 2-carboxylic acid, 3,3-dimethyl-7-oxo-4,4 dioxo sodium salt, and it is official in the British Pharmacopoeia [1].

Tigecycline representing a new class of antimicrobials known as glycylcyclinesis (4S,4aS,-5aR,12aS)-9-(2-tert butylaminoacetylamino)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,-6,11,12a-octahydronaphthacene-2-carboxamide [2] and it has more potent activity against a variety of tetracycline-resistant and multidrug-resistant Gram-positive and Gram-negative bacterial pathogens. Because of its microbiological, pharmacodynamic and pharmacokinetic properties, this antibiotic has been evaluated as monotherapy for serious infections in human clinical trials [3,4].

The effects of meropenem, imipenem, sulbactam, colistin, and tigecycline, alone or in combination, on biofilm-embedded were investigated due to difficulty in destruction of *Acinetobacter baumannii* biofilms [5] and reported that significant decreases in the maximum biofilm thickness were observed after exposure to meropenem and imipenem. Meropenem plus sulbactam significantly decreased the biomass and mean thickness and increased the roughness coefficient of biofilms, but sulbactam plus tigecycline only decreased the maximum and mean biofilm thickness compared to any of these agents used alone.

The clinical efficacy between salvage antimicrobial regimen consisting of tigecycline plus extended-infusion imipenem/cilastatin (TIC) and regimen of sulbactam plus imipenem/ cilastatin (SIC) for patients with ventilator-associated pneumonia and pneumonic bacteremia due to extensively drug-resistant (XDR) *Acinetobacter baumannii* (Ab) isolates were compared and determined the correlation of results of *in vitro* tigecycline imipenem synergy test with clinical efficacy [6].

Numerous studies have shown that combinations of tigecycline and sulbactam are promising treatment options for MDR A. baumannii. They tested ten clinical isolates of A. baumannii sensitive colistin and tigecycline synergistic effects of tigecyline and sulbactam and reported that Tigecycline MIC values decreased 2-4 fold with sulbactam and this combination resulted in synergy or partial synergy in 50% of the isolates [7].

In vitro study conducted on 25 XDR A. baumannii, it has been shown that sulbactam plus tigecycline provides synergy or additional effects at 84% of stains and no antagonism [8].

Quantum chemical calculations were used to analyze the formation of a peptide bond between phenylalanine and Ceftriaxone molecules [9]. The reaction mechanism of phenyl alanine with meropenem have been studied as stepwise mechanism by means of PM6-semi-empirical [10].

In this work, we present a density functional theoretical and semi-empirical studies on the mechanism of the reaction between the sulbactam, and tigecycline. The calculated reaction mechanism is presented and discussed in a general way.

2. MATERIALS AND METHODS

2.1Computational Details

All the reactants, products and transition states have been optimized again within the semi-empirical method-pm6 and density functional theory (DFT) framework, by using the B3LYP functional. This functional is based on Becke's three-parametrization adiabatic connection method (ACM) and consists of a combination of Slate [11] Hartree-Fock, [12] and Becke [13] exchange functionals, the Vosko, Wilk, and Nusair (VWN) local correlation functional, [14] and the Lee, Yang, and Parr [15] nonlocal correlation functional. The IRC have been computed automatically using intrinsic reaction coordinate (IRC), following algorithms. IRC was

proposed by Fukui in 1970 as a pathway of chemical reactions, 1, 2, the steepest descent path weighted predominantly on the potential energy surface (PES), starting from the transition (TS), ie the first rank saddle point. Starting from nonstationary structures, the mass - weighted steepest descent path is called meta - IRC.

The reaction mechanism between tigecycline and sulbactam were performed with the theoretical method of PM6 and B3LYP functional with full geometry optimization and E_{HOMO} and E_{LUMO} for tigecycline, sulbactam and tigecycline sulbactam were calculated with the B3LYP/6-311G (d, p) level and the B3LYP/6-311G (2d, 2p) level.

The calculations have been carried out with the GAUSSIAN 09 series of programs [16].

3. RESULTS AND DISCUSSION

The relative energies of the ground and transition states in the addition of tigecycline to sulbactam in gas media are presented in Fig. 1 that the reactant located on the left side in the diagram reaches the product on the right side via several intermediates and transition states. These profiles were obtained from the results of analysis of the PES by relaxed scanning over the reaction coordinate using the B3LYP/6311G (d,p) method.

Two transition states for stepwise mechanism are depicted as saddle points, and the energies required to go over each barrier (ΔG1, ΔG2) are called activation energies. One transition state for concerted mechanism is depicted as saddle point and activation energy is ΔG3.

The concerted and stepwise mechanisms for the bond formation are illustrated with the optimized structures of the reactants, the three transition states and one intermediate, and for products calculated with B3LYP/6-311G(d,p) level in Fig. 2.

In this reaction we considered the reaction between the HOMO of tigecycline and the LUMO of sulbactam. For both the B3LYP and PM6 success was achieved when the interaction of tigecycline N lone pair with the carbonyl centre of sulbactam was performed. When considering both the charge interaction and most likely the HOMO/LUMO interactions led to the conclusion that glycine react with sulbactam by nucleophilic attack of tigecycline nitrogen (N) lone pair on the carbonyl carbon C7 of sulbactam considered the reaction between the HOMO of tigecycline and the LUMO of sulbactam. HOMO, LUMO, electron density of the optimized structures of reactants, IN, transition states and products are shown in Fig. 3.

Electrostatic potential maps enable us to visualize the charge distributions of molecules and charge related properties of molecules. They also allow us to visualize the size and shape of molecules. Different colors represent the different values of the electrostatic potential at the surface. Potential increases in the ordered (most negative) < orange < yellow < green < blue (most positive). (MEP) surfaces are plotted over the optimized electronic structure of reactants, the three transition states and one intermediate, and for products calculated with B3LYP/6-311G(d,p) level in Fig. 3. MEP surface directly provides information about the electrophilic (electronegative charge region) and nucleophilic (most positive charge region) regions.

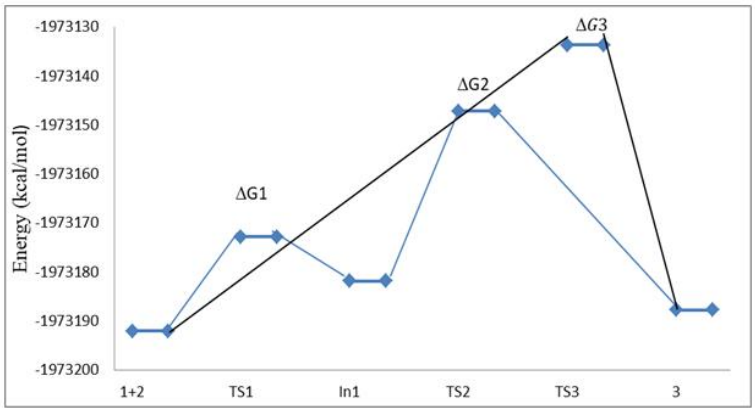

Fig. 1. Reaction energy diagram

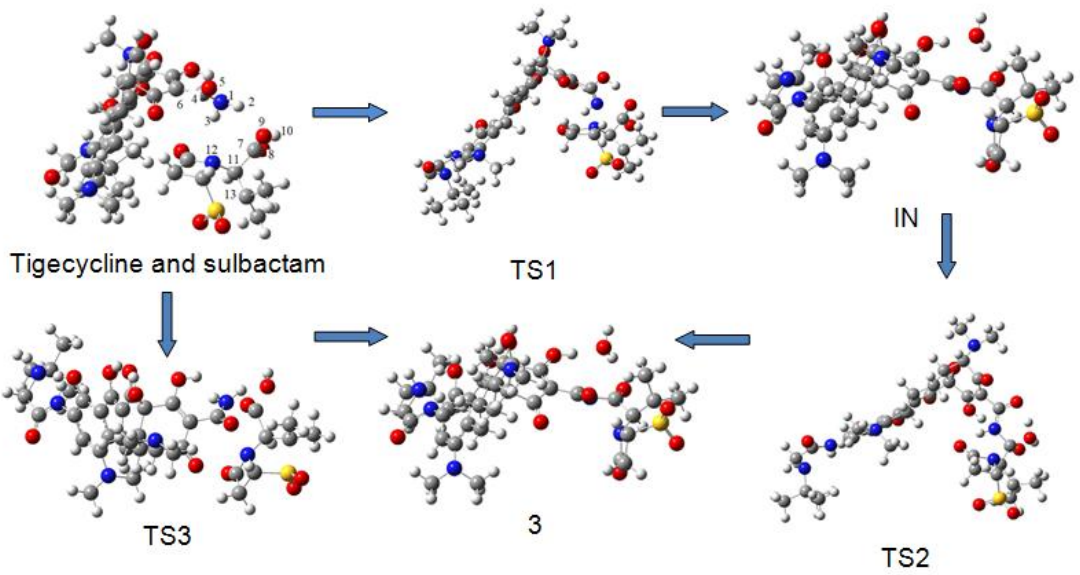

Fig. 2. Reaction mechanism between sulbactam and tigecycline

In general, two molecules which are either the two atoms that have highest and opposite charges or two atoms that have a highest electron densities in their highest occupied or lowest unoccupied atomic molecular orbital's interact each other.

In the first step nitrogen lone pair of one amino group belonging to tigecycline attacks the carbonyl carbon atom of the sulbactam, molecule leading to the formation of C-N bond which is the addition step. The second step is the elimination of water molecule.

For the stepwise process, an intermediate INT1 is separated from reactants by 19.21 kcal/mol barrier at transition state TS1 and from products by 34.64 kcal/mol at transition state TS2. For concerted process 3 is separated from reactants by 58.43 kcal/mol at transition state TS3. Vibration analysis was performed for the reactants, intermediates, transition states and final molecules. We found a negative imaginary frequency which is characteristic of an ordinary TS for transitional states (TS). Generally, an imaginary frequency for TS is the first order saddle. The imaginary frequencies for TS1 and TS2 in the stepwise process are -338 cm-1 and -1655 cm-1, and for concerted mechanism TS3 is -970 cm-1.

The reacting molecules tigecycline and sulbactam (1+2).being far from each other (N1- C7 = 3.000 Å) have a summary energy -1973192 kcal/mol with the calculation B3LYP/6-311G (d,p) level for both tigecycline and sulbactam.

From Table 1 it was found that the bonds between N-H is 1.01 Å and 1.03 Å for B3LYP and PM3 respectively and bond length for O=C is 1.20 Å and 1.21 Å, respectively while sulbactam and tigecycline were sufficiently far apart, the bonds between N-H in the course of reaction increase by 1.32 Å and 0.11 Å for B3LYP and PM3 respectively. While for O=C it increases by 0.03 Å and 0.19Å for B3LYP and PM3 respectively. All these are due to pulling of electron by the reacting atoms in the transition state (TS1). The N1-C7 bond between tigecycline and sulbactam is partially formed at the TS1. N1-C7 bond length with the calculation B3LYP in the course of reaction changes to 2.15 Å, 1.49 Å, 1.50 Å and 1.39 Å at TS1, IN, TS2 and 3, respectively.

The distance between the carbon and nitrogen involved in the formation of the new N–C single bonds in the synchronous TS1 and in IN is found to be 2.15 Å and 1.49 Å for B3LY/6-311G (d,p) and 3.32 Å and 1.50 Å for PM6 level. The distance between the carbon and nitrogen involved in the formation of the new N–C single bonds in TS3 is found to be 2.13 Å and 1.49 Å for B3LY/6-311G (d,p) and PM6 levels.

Now let's consider TS2. The C7-O9 distance of 1.65 Å and 1.62 Å for B3LY/6-311G (d,p) and

PM7 levels, respectively compared to the approximation value of 1.350 A for a single bond, does not suggest any significant bonding between those two atoms.

The Mulliken charges of atom C7 at 1+2, TS3 and 3 for calculations with B3LY/6-311G(d,p) are 0.38 ē, 0.0.38 ē, 0.41 ē, respectively; charges on atom N1 at 1+2, TS3 and 3 are -0.50 ē, -0.65 ē, -0.38 ē, and those of atoms O8 and O9 are -0.33 ē, -0.31 ē for 1+2, -0.23 ē, -.543 ē for TS3 and -0.38 ē, -0.50 ē for 3. Different orbitals overlapping cause changing of Mulliken charges.

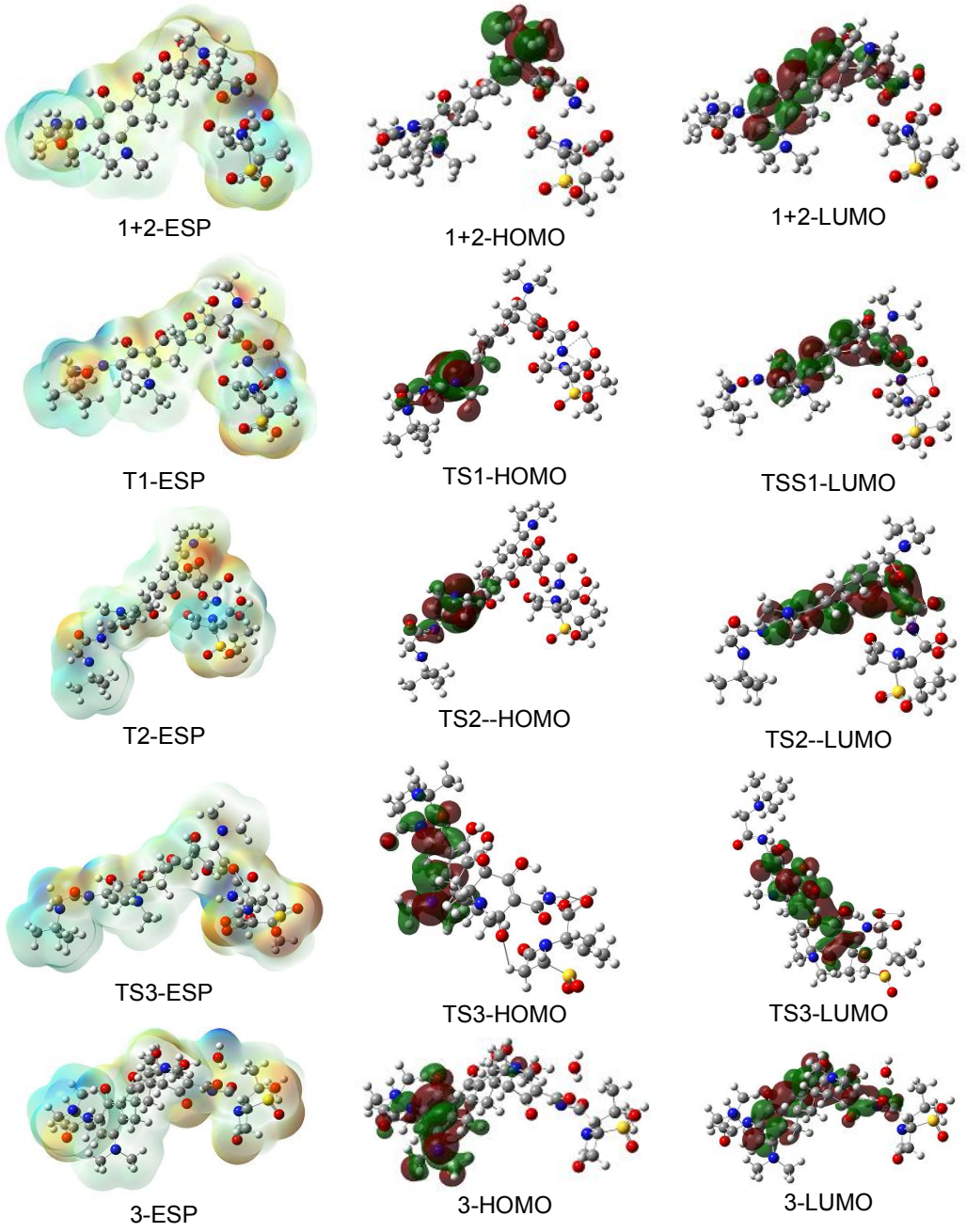

Fig. 3. ESP, HOMO, LUMO of reeactants, intermediate, transition states and products

Table 1. Bond lengths and mulliken charges of the reactants, the three transition states and one intermediate, and products

Atom	B3LYP/6-311g(d,p)						PM6					
numbers	1+1	TS1	IN	TS2	TS3	3	1+1	TS1	IN	TS2	TS3	3
Bond lengths (Å)												
N_1-C_4	1.40	1.29	1.39	1.37	1.38	1.41	1.41	1.35	1.42	1.41	1.44	1.42
C_4-C_6	1.50	1.47	1.49	1.49	1.50	1.49	1.48	1.44	1.47	1.48	1.47	1.47
C_4-O_5	1.21	1.32	1.23	1.24	1.21	1.21	1.22	1.31	1.23	1.23	1.24	1.22
N_1-H_2	1.01	2.33	2.33	2.32	1.04	3.73	1.03	1.14	2.54	2.55	1.81	3.43
N_1-H_3	1.01	1.02	1.01	1.02	1.01	1.01	1.01	1.00	1.03	1.03	1.05	1.04
N_1-C_7	3.00	2.15	1.49	1.50	2.13	1.39	3.50	3.32	1.50	1.50	1.56	1.42
C_7-O_8	1.20	1.23	1.38	1.25	1.18	1.22	1.21	1.21	1.40	1.25	1.42	1.22
C_7-O_9	1.35	1.35	1.39	1.65	1.70	2.80	1.37	1.37	1.41	1.64	1.38	2.80
O_9-H_1	0.97	0.97	0.97	1.80	2.40	1.82	1.00	1.00	0.99	1.89	0.99	4.07
O_8-H_2	2.06	1.64	0.98	1.04	1.55	0.96	2.00	1.99	1.02	1.03	1.07	0.97
O_8-H_{11}	2.31	2.28	2.27	0.98	0.97	0.97	2.37	2.37	2.25	1.04	2.32	1.01
C_7-C_{11}	1.53	1.53	1.56	1.55	1.56	1.53	1.53	1.53	1.58	1.57	1.56	1.54
C_{11}-N_{12}	1.47	1.47	1.46	1.48	1.46	1.46	1.48	1.47	1.47	1.47	1.48	1.47
C_{11}-C_{13}	1.56	1.57	1.57	1.55	1.56	1.57	1.55	1.55	1.55	1.55	1.56	1.56
Mulliken charges (ē)												
O_5	-0.32	-0.32	-0.39	-0.40	-0.37	-0.34	-0.57	-0.71	-0.57	-0.57	-0.56	-0.57
N_1	-0.50	-0.55	-0.45	-0.50	-0.65	-0.38	-0.61	-0.54	-0.64	-0.64	-0.62	-0.56
C_6	-0.13	-0.07	-0.13	-0.15	-0.13	-0.14	-0.63	-0.64	-0.62	-0.62	-0.69	-0.70
C_4	0.32	0.36	0.43	0.42	0.40	0.40	0.69	0.64	0.73	0.73	0.73	0.77
H_2	0.24	0.22	0.24	0.27	0.23	0.24	0.27	0.30	0.29	0.29	0.31	0.31
H_3	0.23	0.28	0.27	0.31	0.33	0.28	0.29	0.37	0.39	0.37	0.45	0.34
O_9	-0.31	-0.32	-0.37	-0.38	-0.45	-0.50	-0.53	-0.53	-0.56	-0.57	-0.72	-0.66
O_8	-0.33	-0.45	-0.39	-0.46	-0.23	-0.38	-0.52	-0.50	-0.60	-0.68	-0.60	-0.52
N_{12}	-0.33	-0.33	-0.37	-0.33	-0.35	-0.34	-0.46	-0.45	-0.46	-0.46	-0.45	-0.39
C_{13}	-0.51	-0.51	-0.45	-0.48	-0.48	-0.49	-0.28	-0.29	-0.27	-0.26	-0.27	-0.28
C_{11}	0.38	0.06	0.04	-0.03	0.07	0.05	-0.05	-0.04	-0.06	-0.05	-0.04	-0.08
C_7	0.38	0.46	0.39	0.46	0.38	0.41	0.63	0.63	0.67	0.67	0.67	0.62
H_{11}	0.27	0.25	0.25	0.28	0.28	0.28	0.34	0.34	0.35	0.44	0.34	0.38

Substantial characters of materials are obtained with the quantum chemical calculations. Computational calculation is an alternate choice due to difficulty to measure hyperpolarizability directly, The first order-hyperpolarizability and related properties of sulbactam and tigecycline and sulbactam- tigecycline were calculated using B3LYP/6-311G(d,p) basis set, based on the finite field approach. The mean first-order hyperpolarizability can be calculated using the equation 1.

$$\beta_{total}=\sqrt{((\beta_{xxx}+\beta_{xyy}+\beta_{xzz})^2+(\beta_{yyy}+\beta_{yzz}+\beta_{yxx})^2 +(\beta_{zzz}+\beta_{zxx}+\beta_{zyy})^2)} \quad (1)$$

The DFT/6-31G (d,p) calculated first hyperpolarizability values (β) of for tigecycline-sulbactam, tigecycline, sulbactam are equal to 20.427 10^{-30}, 1.398 10^{-30}, 10.954 10^{-30}esu.

According to Koopman's theorem [17] chemical hardness, electronegativity and chemical potential can be defined as:

$$\eta=1/2\ (E_{LUMO}-E_{HOMO}) \quad (2)$$

$$\mu=-\chi=1/2\ (E_{HOMO}+E_{LUMO}) \quad (3)$$

Global softness which is one of the most important reactivity descriptors is defined as the inverse of global hardness as in the given following equation [18,19]:

$$\sigma=1/\eta \quad (4)$$

Electrophilicity (ω) is another parameter and indicates tendency of the molecule to accept electrons. Electrophilicity index explain the electrophilic and nucleophilic behavior of molecules. Electrophilicity index is defined via equation 5 [20]. A good electrophile means high electronegativity (or chemical potential) and low chemical hardness values.

$$\omega=\mu^2/2\eta \quad (5)$$

The DFT/6-311G(d,p) calculated electrophilicity values (ω) for tigecycline-sulbactam, tigecycline, sulbactam are equal to 5.147, 2.671, 4.915. The values are the largest for the tigecycline-sulbactam than for the alone tigecycline and alone sulbactam. The established order is as follows: tigecycline-sulbactam>tigecycline>sulbactam.

Nucleofugality (ΔEn), Electrofuqality (ΔEe) are useful theoretical descriptors and may be calculated with equation 6 and 7.

$$\Delta E_n=-A+\ \omega=(\mu+\eta)^2/2\eta \quad (6)$$

$$\Delta E\_e=I+\ \omega=(\mu-\eta)^2/2\eta \quad (7)$$

The results in Table 2 establish the influence of tigecycline, sulbactam and tigecycline-sulbactam on the first hyperpolarizability and the other descriptors calculated with B3LYP(6-311G(d,p) and B3LYP(6-311G(2d,2p) levels. The values are the largest for the tigecycline-sulbactam than for the alone tigecycline and alone sulbactam. The established order is as follows: sulbactam>tigecycline>tigecycline-sulbactam

The lowest unoccupied molecular orbital - E_{LUMO}, The highest occupied molecular orbital energies- E_{HOMO}, hardness, softness, electronegativity, energy gap, chemical potential, electrophilicity index, nucleofugality, electrofugality are given in Table 2.

. **Table 2. Some descriptors for tigecycline, sulbactamand tigecyclinesulbactam**

	Tigecycline		**Sulbactam**		**Tigecycline-Sulbactam**	
	6-311 G(d,p)	**6-311 G(2d,2p)**	**6-311 G(d,p)**	**6-311 G(2d,2p)**	**6-311 G(d,p)**	**6-311 G(2d,2p)**
E_{LUMO}	-2.376	-2.342	-0.903	-0.829	-2.481	-2.433
E_{HOMO}	-5.661	-5.689	-7.482	-7.428	-5.859	-5.831
ΔE	3.286	3.347	6.579	6.599	3.379	3.397
η	1.643	1.673	3.290	3.299	1.689	1.699
S	0.304	0.299	0.152	0.152	0.296	0.294
χ	4.018	4.016	4.192	4.128	4.170	4.132
μ	-4.018	-4.016	-4.192	-4.128	-4.170	-4.132
ω	4.915	4.818	2.671	2.583	5.147	5.025
ΔE_n	1.717	1.639	0.124	0.104	1.822	1.743
ΔE_e	4.093	3.982	1.026	0.933	4.303	4.176
β(10^{-30}esu)	10.954	10.873	1.398	2.082	20.427	20.120

Eventual charge transfer interaction is taking place within the molecule is explained with the HOMO and LUMO energy gap. Hardness defined the gap between the HOMO and LUMO orbital energies is associated with the stability of the chemical. The gap energies between E_{HOMO} and E_{LUMO} for tigecycline, sulbactam and tigecycline-sulbactam calculated with the B3LYP/6-311G(d,p) level are 3.286 eV, 6.579 eV, and 3.379 eV, respectively and 3.347 eV, 6.599 eV and 3.397 eV with the B3LYP/6-311G(2d,2p) level. As shown in Table 2, the compound that has the highest HOMO energy is the tigecycline (E_{HOMO}= -5.661 eV). This higher energy allows it to be the best electron donor. The compound that has the lowest LUMO energy is the compound tigecycline-sulbactam (E_{LUMO}= -2.481eV) which signifies that it can be the best electron acceptor.

4. CONCLUSION

The reaction is nucleophilic in nature in which the nitrogen lone pair of tigecycline attacks the carbonyl carbon (C7) of sulbactam to form tigecycline- sulbactam adduct. The two methods are in good agreement with one another since they produced two transition states and one intermediate for stepwise mechanism and one transition for concerted mechanism.

The HOMO–LUMO calculations show that the energy gab increases with the combination of tigecycline- sulbactam. Some quantum chemical descritors such as, energy gap, hardness, softness, electronegativity, chemical potential, electrophilicity, nucleofugality, electrofugality were calculated and compared among themselves.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. B. Pharmacopoeia. British Pharmacopoeia Commission London. The Department of Health. Social Services and Public Safety. 2013;1:719-20.
2. Hoffmann M, De Maio W, Jordan RA, Talaat R, Harper D, Speth J, et al. Metabolism, Excretion, and Pharmacokinetics of [^{14}C] Tigecycline, a First-In-Class Glycylcycline Antibiotic, after Intravenous Infusion to Healthy Male Subjects. Drug Metabolism and Disposition. 2007;35(9):1543-53.
3. Chopra I. Glycylcyclines: Third-generation tetracycline antibiotics. Curr Opin Pharmacol. 2001;1(5):464-9.
4. Zhanel GG, Homenuik K, Nichol K, Noreddin A, Vercaigne L, Embil J, et al. The glycylcyclines: A comparative review with the tetracyclines. Drugs. 2004;64(1): 63-88.
5. Wang YC, Kuo SC, Yang YS, Lee YT, Chiu CH, Chuang MF, et al. Individual or Combined Effects of Meropenem, Imipenem, Sulbactam, Colistin, and Tigecycline on Biofilm-Embedded *Acinetobacter baumannii* and Biofilm Architecture. Antimicrob Agents Chemother. 2016;60(8):4670-6.
6. Jean SS, Hsieh TC, Hsu CW, Lee WS, Bai KJ, Lam C. Comparison of the clinical efficacy between tigecycline plus extended-infusion imipenem and sulbactam plus imipenem against ventilator-associated pneumonia with pneumonic extensively drug-resistant *Acinetobacter baumannii* bacteremia, and correlation of clinical efficacy with in vitro synergy tests. J MicrobiolImmunol Infect. 2016; 49(6):924-33.
7. Cai Y, Bai N, Liu X, Liang B, Wang J, Wang R. Tigecycline: Alone or in combination?. Infectious Diseases. 2016; 48(7):491-502.
8. Falagas ME, Vardakas KZ, Tsiveriotis KP, Triarides NA, Tansarli GS. Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections. Int J Antimicrob Agents. 2014;44(1):1-7.
9. Sayiner HS, Kandemirli F. The Reaction Mechanism Study of Ceftriaxone and Phenylalanine. Journal of International Research in Medical and Pharmaceutical Sciences. 2015;9(2):83-90.
10. Sayiner HS, Kandemirli F. The interaction study with meropenem and phenylalanine. International Journal of Science and

Engineering Investigations. 2017;6(62): 114-117.
11. Slater JC. Quantum Theory of Molecular and Solids. McGrawHill. New York. 1974; 4.f.
12. Fock VZ. Physic. 1930;61:126.
13. Becke AD. Density-functional exchange-energy approximation with correct asymptotic behavior. Phys Rev. A. 1988; 38:3098.
14. Vosko SH, Wilk L, Nusair M. Accurate spin-dependent electron liquid correlation energies for local spin density calculations: A critical analysis. Canadian Journal of Physics. 1980;58(8):1200-11.
15. Lee C, Yang W, Parr. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B. 1988;37:785.
16. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian Inc. Wallingford CT; 2009.
17. Koopmans T. Überdie Zuordnung von Wellenfunktionen und Eigenwertenzu den Einzelnen Elektronen Eines Atoms. Physica. 1934;1(1-6):104-13. German.
18. Yang W, Lee C, Ghosh SK. Molecular softness as the average of atomic softnesses: companion principle to the geometric mean principle for electron-egativity equalization, J. Phys Chem. 1985; 89(25):5412-14.
19. Yang W, Parr RG. Hardness, softness, and the fukui function in the electronic theory of metals and catalysis. Proc Natl Acad Sci. 1985;82(20):6723-6.
20. Parr RG, Sventpaly L, Liu S. Electrophilicity Index. J Am Chem Soc 1999;121(9):1922-4.

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