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Studies on dipole moment of penicillin isomers and related antibiotics

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In this study, the relationships between dipole moment and medicinal activity of penicillin derivatives are discussed. Four derivatives of penicillin and the stereoisomers of penicillin G are considered for this investigation. Other classes of β-lactam antibiotics like cephalosporin C and thienamycin are also investigated along with penicillin derivatives for comparison purposes. Four semi-empirical quantum mechanical method (AM1, RM1, PM3 and PM6) and a molecular mechanical method (MMFF) are chosen to calculate dipole moment of these molecules. To our knowledge, this is the first study on dipole moment calculation on penicillin and related molecules. All the compounds, including the isomers, demonstrate a direct correlation between biological activity and dipole moment. This study indicates that dipole moment is a useful parameter for the studies of the biological activity of β-lactam antibiotics.

Keywords: Dipole moment, medicinal activity, penicillin, β-lactam.

Introduction

Antibiotics are the most useful and important family of drugs used for human health issues. They are widely used for the infections caused by animals and plants[1]. Among them β-lactam antibiotics are one of the most widely used and frequently prescribed antimicrobial agents. Penicillin derivatives are the most crucial groups of β-lactam antibiotics. Penicillin G, a member of β-lactam antibiotics, was the first antibiotic discovered and used for treatment of a broad-spectrum of bacterial infections. It was discovered in 1929 by Alexander Fleming[2]. The general structure of penicillin consists of a fused thiazolidine ring with a β-lactam ring to which an aminoacyl side chain is attached. It has been hypothesized that a compound requires a ring of sufficient strain with possibilities for electron delocalization outside ring and specific conformational features[3] for efficient antibacterial activity. The reactive β-lactam ring is one of the most important structural moieties for antibacterial activity of penicillin and related compounds against most Gram-negative and Gram-positive bacteria[4,5].

Since their introduction in the early 1940s penicillins have remained the single most important class of antibiotics among the wider family of β-lactams. They were the first drugs that were effective against many serious diseases including Syphilis and Staphylococcus infections[6] and the demand for penicillin is increasing rapidly day by day[7,8]. Penicillin binds and inactivate the penicillin binding protein in bacterial cells, and inhibits the cross linking of peptidoglycans, necessary for cell wall formation[9]. Thus, penicillin controls bacteria by inhibiting their cell division. The two main metabolites of penicillin are penicilloic acid and penilloic acid[10]. Among the many penicillin derivatives, only few compounds have significant biological activity with less side effects and lower environmental exposure levels. Many group had intensively investigated the relationships between the structure of penicillins and their biological activity[11,12]. A minor change in the structure of racemic and optically active forms of these antibiotics can alter the medicinal activity of these compounds. Thus, it is important to identify the principal causes of biological activity. Many theories have been proposed by researchers to

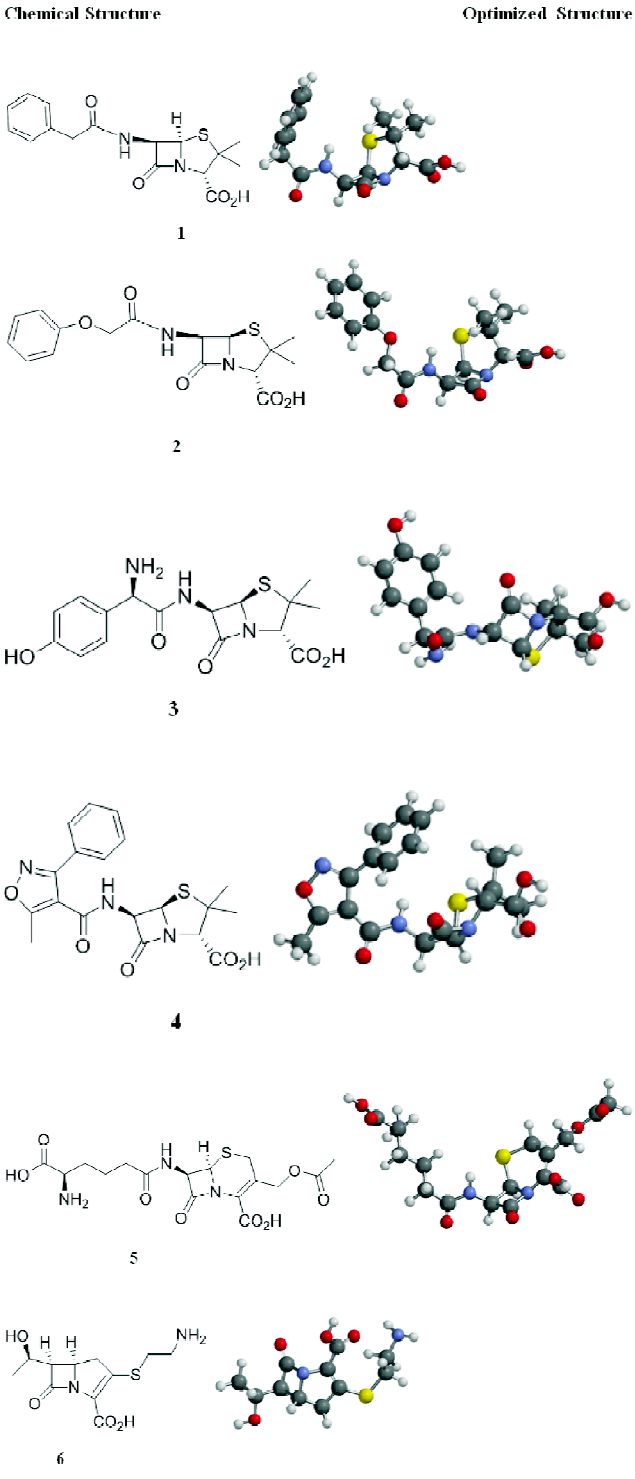
identify the cause of biological activity of medicinally important compounds. Among those, dipole moment values are found to have effects on the medicinally active and inactive compounds.

Over the past decade, the synthesis and biological activities of β-lactams derivatives have been widely studied by our group[13]. This paper describes quantum mechanical and classical mechanical dipole moment calculations to correlate the biological activity of penicillin antibiotics. In this study four derivatives of penicillin and stereoisomer of penicillin G are considered. According to our knowledge, this is the first study on correlating the dipole moment values and biological activity of penicillin derivatives.

Materials and methods

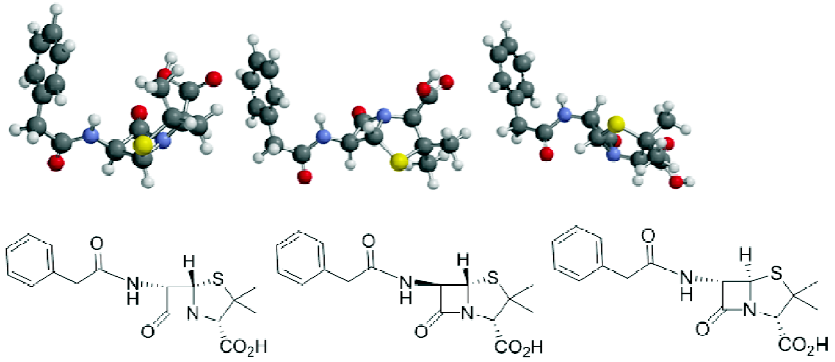
Many compounds have shown a direct correlation between dipole moment and biological activity[14–18]. For examples, tetraoxanes, quinazolinone, indolylpyrimidines and quinolones derivatives have demonstrated a higher dipole moment for active compounds compared to relatively inactive compounds[14,15]. In contrast, thiazolidines, phenothiazines, azole-derivatives, and pyrazolopyridines compounds with lower dipole moment have better activity than the related compounds with higher dipole values[16–18].

We have considered four penicillin derivatives and three isomers of penicillin derivatives for dipole moment calculation. The penicillin derivatives include natural penicillins: penicillin G (benzylpenicillin) and penicillin V (phenoxymethylpenicillin); aminopenicillin: amoxicillin; and penicillinase-resistant penicillin: oxacillin. The chemical and optimized structures of all these derivatives are shown in Scheme 1. In benzylpenicillin (**1**), the substituent at position 6β of the penam ring is a phenylacetamido group. Phenoxymethylpenicillin (**2**) is the phenoxymethyl analog of penicillin G. In amoxicillin (**3**), 2-amino-2-(4-hydroxyphenyl) acetamido group is substituted at position 6β of the penam ring. The antistaphylococcal penicillin, oxacillin (**4**) carries a 5-methyl-3-phenylisoxazole-4-carboxamide group at 6β position of the penam ring. For comparison purposes we have also considered two other classes of the most commonly used β-lactam antibiotics like cephalosporin C (**5**) and thienamycin (**6**). Both these compounds are closely related to penicillin. Along with that *cis* and *tran* sisomers of penicillin are chosen to identify



Scheme 1. The chemical and optimized structures of the four penicillin derivatives, cephalosporin and thienamycin analogue.

the relationships between the structure of penicillins and their biological activity.



Scheme 2. The chemical and optimized structures of the isomers of penicillin G.

The chemical and optimized structures of the stereoisomers of penicillin G are shown in Scheme 2. Compound **7** is the enantiomer of compound **1** and compound **8** and **9** are diastereomers of compound **1.** Thus compound **1** and **7** are *cis* isomers and compound **8** and **9** are *trans* isomers.

Dipole moment calculations for the compounds were done using the SPARTAN 18 software package. All the measurements are done with equilibrium geometry at ground state, using four semi-empirical quantum chemistry methods, Austin Model 1 (AM1), Recife Model 1 (RM1), Parametric Model number 3 (PM3), and Parametric Model number 6 (PM6), the methods are based on the Neglect of Differential Diatomic Overlap (NDDO) integral approximation. To confirm the result, the dipole moment calculations were also done using a classical mechanics method, Merck Molecular Force Field (MMFF) method. All the structures were drawn in 2D and then converted into their 3D forms using the same software followed by their energy minimization procedure.

Results and discussions

The calculated ground-state dipole moment (μ) value in Debye (D) for the four penicillin derivatives, cephalosporin and thienamycin is shown in Table 1. The compounds **1-6** are *cis* in nature. The compounds **1-5** showed dipole moment values ranging from 5.1D to 6.71D in AM1 method and the dipole moment value of compound **6** was 3.07D. According to literature, the compounds**1-5** were highly active antibacterial agents. No results were known on the biological activity of *cis*-thienamycin (**6**), however *trans*-thienamycin had demonstrated the greatest antimicrobial activity. From the data it is clear that there is a direct correlation between the biological activity and dipole moment of these molecules. For example, the higher dipole moment values indicated better potent drugs. The compound **4** showed highest dipole moment value, 6.71D. Probably, the higher dipole moment is due to the isoxazole group in the side chain which may cause charge separation in this molecule more effectively.

All the four quantum mechanical calculations (AM1, RM1, PM3 and PM6) showed identical trend, dipole moment values were higher for active compound. Only a slight variation in the data is observed when comparing the four calcula-

Table 1. Calculated dipole moment values of penicillin derivatives, cephalosporin and thienamycin analogue. Values are in Debye (D)

Compounds	Quantum mechanical methods				Molecular mechanics method	Activity
	AM1	RM1	PM3	PM6	MMFF	
1	5.39	5.02	4.77	5.77	6.06	Active
2	5.1	4.84	4.59	5.31	5	Active
3	6.21	5.45	5.39	6.17	5.55	Active
4	6.71	5.98	5.93	6.5	7.3	Active
5	6.17	5.68	5.44	6.55	5.5	Active
6	3.07	2.14	1.66	2.81	3.3	Inactive

Table 2. Calculated dipole moment values of stereoisomers of penicillin G; active and inactive wording is used from the scientific literature. It does not reflect the quality of any research papers and the authors

Compounds	Quantum mechanical methods				Molecular mechanics method	Activity
	AM1	RM1	PM3	PM6	MMFF	
1	5.39	5.02	4.77	5.77	6.06	Active
7	3.7	3.35	3.33	4.25	3.7	Inactive
8	2.78	2.53	2.26	2.42	3.11	Inactive
9	2.99	2.57	2.29	2.79	3.03	Inactive

tions for each compound. Along with that for all the compounds dipole moment values from the PM3 calculations were lower compared to data from other methods. The classical mechanical method (MMFF) also followed the same trend, compound **6** showed lowest dipole moment 3.3D and the highest dipole moment 7.3D was for compound **4**.

The calculated dipole moment values of stereoisomers of penicillin G compound are shown in Table 2. The data showed that in all calculation the *cis* isomers **1** and **7** have higher dipole moment than the both *trans* isomers **8** and **9**. The dipole moment values of the two *trans* isomers were close to each other whereas the value of dipole moment in the *cis* isomers differed considerably. *cis* penicillin G (**1**), the active isomer has higher dipole moment than the enantiomeric *cis* penicillin G (**7**), which is considered to be inactive. Both the *trans* isomers **8** and **9** are inactive.

From the calculations it is also observed that a minimum value of dipole moment is required to have antibacterial effects and the minimum value may differ by each method. For instance, from our calculations the minimum values by each method are: AM1 (4±0.2D), RM1 (3.6±0.2D), PM3 (3.6±0.2D), PM6 (4.5±0.2D) and MMFF (4±0.2D).

Table 3

Molecular mechanics method	Quantum mechanical methods
Run type: Optimization	Run type: Geometry optimization
Method: MMFF94	Model: RHF/AM1
Stoichiometry: $C_{16}H_{18}N_2O_4S$	Number of shells: 64
Number of atoms: 41	(41 S shells, 23 P shells)
Point group: C_1	Number of basis functions: 110
Degrees of freedom: 117	Number of electrons: 122
	Point group = C1
	Degrees of freedom: 117
T1 heat: –533.98 kJ/mol	T1 heat: –533.98 kJ/mol
Weight: 334.39 amu	Weight: 334.39 amu
Area: 342	Area: 345.25
Volume: 320.38	Volume: 320.76
PSA: 74.85A2	PSA: 75.03A2
Ovality: 1.51	Ovality: 1.51
log P: 0.84	log P: 0.84
Solvation energy: –118.68	Heat of formation: –400.444 kJ/mol

Calculation details:

Details of the molecular mechanics and quantum mechanical calculations for compound **1** are given in Table 3. Other physicochemical parameters obtained from the calculations are also included.

Conclusions

In this study we have demonstrated that there is a direct relationship between the dipole moment and medicinal activity of penicillin and related compounds. Four derivatives of penicillin and stereoisomers of penicillin G are analyzed with four semi-empirical quantum mechanical as well as one classical mechanical dipole moment calculations. Dipole moment is observed to be high, above 4.5 Debye, for active compounds. Interestingly, all the active compounds are *cis* isomers of the corresponding β-lactams. The *trans* compounds which are considered to be inactive or partially active have shown lower dipole moment. Both the quantum mechanical and classical mechanical dipole moment calculations followed same trend. This study also revealed that dipole moment values have played an important role in determining the biological activity of β-lactam antibiotics including cephalosporin and thienamycin analogue. These results may open a way to design and synthesize more active β-lactam antibiotics. Even though, we have described the significance of dipole moment in determining the biological activity of penicillin related compounds, it is obvious that the activity can also be affected by other parameters.

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Supporting materisls

All the supporting materials will be available on request.

References

1. J. L. Martinez, *Environ. Pollut.*, 2009, **157**, 2893.
2. J. W. Bennett and K. T. Chung, *Adv. Appl. Microbiol*., 2001, **49**, 163.
3. J. M. Ghuysen, J. M. Frere, M. Leygh-Bouille, J. Coyette, J. Dusart and M. Nguyen-Disteche, *Ann. Rev. Biochem*., 1979, **48**, 73.
4. S. G. Waley, *Biochem. J*., 1974, **139**, 789.
5. W. E. Farrar (Jr.) and N. M. O'Dell, *J. Infect. Dis*., 1976, **134**, 245.
6. S. J. Andersen and J. C. Frisvad, *Lett. Appl. Microbiol*., 1994, **19**, 486.
7. R. Quinn, *Am. J. Public Health*, 2013, **103**, 426.
8. M. Ferech, S. Coenen, S. Malhotra-Kumar, K. Dvorakova, E. Hendrick, C. Suetens and H. Goossens, *J. Antimicrob. Chemother*., 2006, **58**, 401.
9. E. Fuste, G. J. Galisteo, L. Jover, T. Vinuesa, T. G. Villa and M. Vinas, *Future Microbiol*., 2012, **7**, 781.
10. D. Li, M. Yang, J. Hu, Y. Zhang, H. Chang and F. Jin, *Water Res*., 2008, **42**, 307.
11. A. Nangia and G. R. Desiraju, *J. Mol. Str.*, 1999, **474**, 65.
12. N. Dýaz, D. Suarez and T. L. Sordo, *J. Comp. Chem*., 2003, **24**, 1864.
13. (a) B. K. Banik, ed. Heterocyclic Scaffolds I. *Top. Heterocycl. Chem.*, *Springer,* 2010, **22**, 1-379; (b) B. K. Banik, *Top. Heterocycl. Chem., Springer*, 2012, **30**, 1-226; (c) I. Banik and B. K. Banik, Springer, Berlin, Germany, 2012, **88**, 781-1007; (d) B. K. Banik, ed. Springer, 2017, 1-419; (e) P. T. Parvatkar, P. S. Parameswaran and B. K. Banik, Solid Phase Synthesis of β-Lactams: Results and Scope in B. K. Banik, Beta Lactams: Novel Synthetic Pathways and Applications, ed. Spinger, 2017, 253-284; (f) S. Basu and B. K. Banik, Beta Lactams as Clinically Active Molecules in B. K. Banik, Beta Lactams: Novel Synthetic Pathways and Applications, ed. Springer, 2017, 285-310; (g) B. K. Banik, Synthesis and Biological Studies of Novel β-Lactams, CRC Book, 2013, 31-72.
14. M. C. de Paula, M. S. Valle and J. R. Pliego (Jr.), *Med. Chem. Res*., 2014, **23**, 5197.
15. A. G. Al-Sehemi, A. Irfan, S. A. Alrumman and A. El-LatifHesham, *Bull. Chem. Soc. Ethiop*., 2016, **30**, 307.
16. R. K. C. de Paiva, J. F. da Silva, H. A. Moreira, O. G. Pinto, L. T. F. M. Camargo, P. L. F. Naves, A. J. Camargo, L. Ribeirod and L. M. Ramos, *J. Braz. Chem. Soc*., 2019, **30**, 164.
17. R. A. Murcia, S. M. Leal, M. V. Roa, E. Nagles, A. M. – Castro and J. J. Hurtado, *Molecules*, 2018, **23**, 2013.
18. J. Quiroga, Y. Villareal, J. Gálvez, A. Ortíz, B. Insuasty, R. Abonia, M. Raimondi and S. Zacchino, *Chem. Pharm. Bull. (Tokyo)*, 2017, **65**, 143.