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β-Lactams: Geometry, dipole moment and anticancer activity

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This research has aimed to analyze the geometry and dipole moment (μ) of β-lactams by theoretical calculations and to investigate its relationship with anticancer activity. The semi-empirical quantum mechanical method (AM1, PM3, and MNDO) has been performed for the dipole moment calculation of five lactams. To the best of our knowledge, this is the first report on the relationship between dipole moment and anticancer activities of β-lactams. Notably, the active compounds have shown a significantly higher dipole moment value (ranging from 5.12 D to 4.3 D) compared to inactive compounds (below 3.4 D). These data indicate that dipole moment data may be a useful parameter for the realization and prediction of novel anticancer β-lactams. Along with the dipole moment data, other physicochemical parameters of β-lactams are calculated using density functional theory (DFT).

Keywords: β-Lactam, dipole moment, DFT, AM1, PM3, MNDO.

Introduction

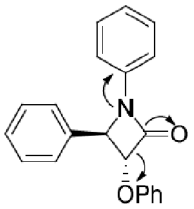
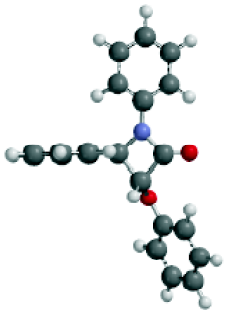
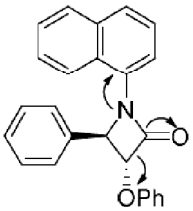
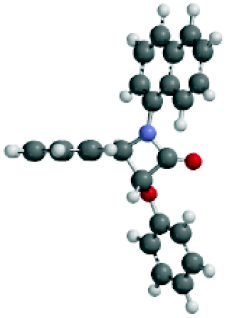
β-Lactam, the four-membered cyclic amide has been extensively used for the synthesis of several biologically active heterocyclic compounds, such as anti-inflammatory[1], anti-hepatitis[2], antibacterial[3], cholesterol absorption inhibitors[4], antifungal[5], analgesic[6], antihyperglycemic[7], and anticancer agents[8]. Cancer remains as one of the leading causes of death in the world. Therefore, there is a growing need for the development of novel and effective anticancer drugs. Our group has been studied the synthesis[9] and the anticancer activities[8] of β-lactam derivatives for the past many years.

From our results on β-lactam anticancer agents, it is apparent that studies of both intramolecular and intermolecular electronic interactions of β-lactams are required. Toward this goal, in this study, we have performed theoretical calculations to predict the optimized geometry and ground-state dipole moment of several β-lactams. This work also reveals the correlation between dipole moment and anticancer activity of β-lactams. This study aims to develop more active anticancer lactam by determining the influence of different substitutional groups on the lactam rings. To our knowledge, this is the first and only study on the correlation between dipole moment and anticancer activities of β-lactams. Thus, this current work has tremendous significance for further development. We also had reported computational studies on the physicochemical and structural properties of various biologically active compounds using classical mechanical as well as quantum mechanical methods to explore the cause of their biological activities[10].

Materials and methods

Five different β-lactams were used for dipole moment calculation (Table 1). β-Lactam **1** has a phenyl group linked to the N_1 position, oxygen at the C_2 position, a phenoxy group (OPh) at the C_3 position, and a phenyl group at the C_4 position of the ring as shown in **1(a)**. Four more compounds, **2**, **3**, **4**, and **5** were also studied to explore the influence of the substituted groups for anticancer activity. In detail, **2** has naphthalene group at the N_1 position, **3** has anthracene group at the N_1 position and **4** has phenanthrene group at the N_1 position of the ring. Compound **5** has a phenanthrene group

Table 1. Compounds used for the calculations

	
1(a)	1(b)
	
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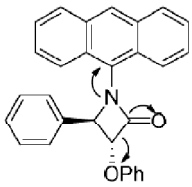
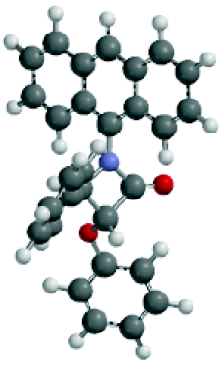
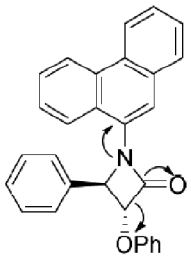
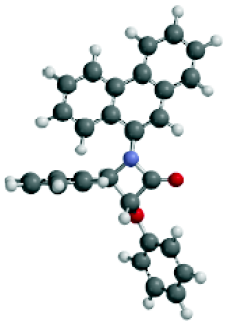
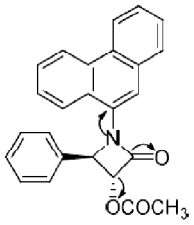
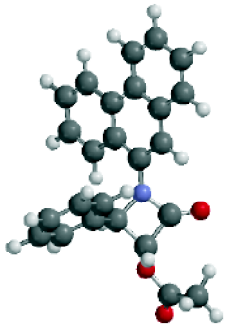
	
3(a)	3(b)
	
4(a)	4(b)

Table-1 (contd.)

	
5(a)	5(b)

at the N_1 position of the ring with a different substitution at the same C_3 position (acetoxy group). The electron movement in each structure is indicated by arrows.

Knowledge of the dipole moment reflects the charge distribution and it is strongly affected by the geometry of the molecule. There are various techniques available for the determination of dipole moment experimentally. But the use of most of the techniques is limited and not reliable because they are equipment-sensitive and are affected by huge error factors. Thus, in this work, we are making theoretical predictions for dipole moment calculation with optimized geometry.

The most successful and frequently used methods for calculating dipole moment are AM1 (Austin Model 1)[11], MNDO (modified neglect of differential overlap)[12], and PM3 (Parametric Model number 3)[13] semi-empirical methods. All were based on the Neglect of Differential Diatomic Overlap (NDDO) integral approximation. All the calculations were done with the SPARTAN 18 software package.

The measurements were performed with equilibrium geometry at the ground state by changing AM1, PM3, and MNDO Hamiltonians. The structures were drawn in 2D and then converted into their 3D forms using the same software followed by their energy minimization procedure. These methods were used to identify the most stereochemically stable structure of each compound, **1(b)**, **2(b)**, **3(b)**, **4(b)**, and **5(b)**. These are represented in Table 1.

Results and discussion

The calculated ground-state dipole moment (μ) value in Debye (D) for the five β-lactam compounds is given in Table 2. It is observed that β-lactam **5**, showed the highest dipole

moment, ranging from 5.12 to 4.3 D. The dipole moments of all other compounds were below 3.46 D. It was also observed that the calculated values by the AM1 method were in between the values obtained from PM3 and MNDO calculations (except in **5**, AM1 calculation gave highest dipole moment values).

Table 2. Calculated dipole moment values (in Debye)

Compounds	AM1	PM3	MNDO
1	3.44	2.77	3.46
2	3.16	2.48	3.23
3	2.99	2.31	3.36
4	2.83	2.58	3.45
5	5.15	4.89	4.3

The anticancer activities of these β-lactams are shown in Table 3. Tests were done against nine human cancer cell lines. The details of synthesis and anticancer activity are discussed elsewhere[8]. The data from cisplatin, the anticancer chemotherapy drug, is considered as the reference value. It was revealed that **1**, **2**, **3**, and **4** are inactive against any of these cell lines and showed maximum activity at concentrations above 20 μM/mL (a level not considered to have a significant effect).

From the dipole moment calculation and anticancer activity data, it is shown that there is a direct relationship between dipole moment and anticancer activity of β-lactams. Only **5** (phenanthrene group at the N_1 position of the ring

Table 3. *In vitro* cytotoxicity of β-lactams on human cancer cell lines (μM)

Compounds	SKOV	K-562	OVCAR	HT-29	PC-3	BRO	HL-60	MDA-231	MCF-7
Cisplatin	5.99	2.33	3.99	16.99	4.66	7.66	1.66	12.33	10.05
5	18.0	4	18.0	10.49	9.3	10.48	5.21	12.49	10.09
1, 2, 3, 4	> 20	> 20	> 20	> 20	> 20	> 20	> 20	> 20	> 20

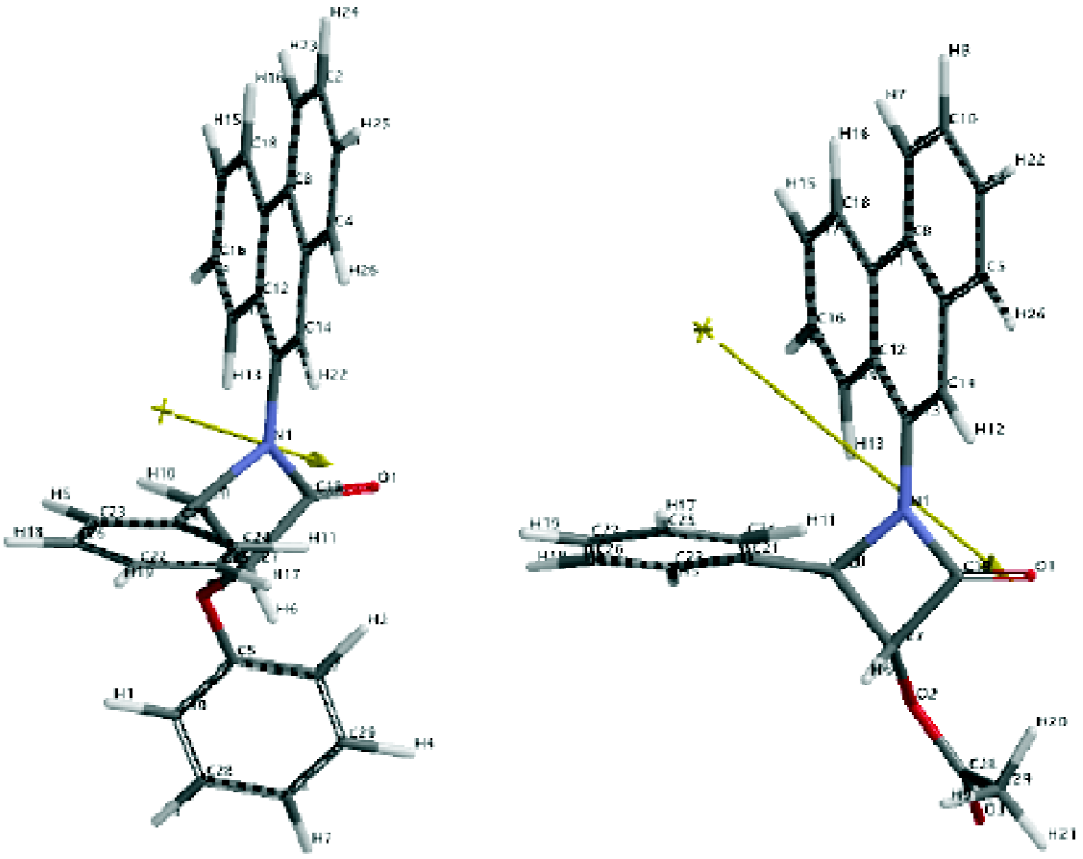


Fig. 1. Optimized structure of compounds **4** and **5**.

and an acetoxy group (OAc) at the C_3 position) demonstrated anticancer activity and the dipole moment of this molecule was high (above 4.3 Debye) compared to all other β-lactams. A difference of 2.3 Debye was observed in **4** when we replaced the acetoxy group at the C_3 position by phenoxy group (in AM1 and PM3 calculation) and the molecule was biologically inactive.

Since the shape of a molecule and the polarity of its bonds determine the overall polarity of that molecule, the dipole moment is strongly dependent on the substitution at the N_1 and C_3 sites. It is noticed that the dipole moment is directly affected by the arrangement of aromatic rings at the N_1 site. Linear arrangements of aromatic rings (anthracene group, naphthalene group) make the compound less polar. Angular arrangements of aromatic rings (phenanthrene group) make the compound more polar by making a large separation of charges in β-lactam. Anticancer activity test also had determined that the minimal structural requirement of the aromatic moiety for cytotoxicity is at least three aromatic rings in an angular configuration (e.g. phenanthrene group). It is also observed that the acetoxy group at the C_3 position has also a significant role in anticancer activity.

The substituted β-lactam ring plays an important role in electron density variation. Angular arrangements of aromatic rings in the phenanthrene group at the N_1 and acetoxy group at the C_3 of the ring act as strong electron-withdrawing groups that result in a strong polar compound.

*Detailed ground state geometry of **4** and **5**:*

The tube model structures of **4** and **5** are shown in Fig. 1. The arrow represents the dipole vector. These structures were optimized using the 6-31G* basis sets at the B3LYP level. The physicochemical properties obtained from Density Func-

Table 4. Geometrical parameters obtained from Density Functional Theory (DFT) calculations

Parameters	Compound 4	Compound 5
Molecular weight (amu)	415.49	381.43
Molecular volume (Å^3)	440.96	395.33
Surface area (Å^2)	440.84	398.81
PSA (Å^2)	36.35	21.69
Ovality	1.57	1.53
log P	6.28	4.32
Polarizability	76.07	72.41
HOMO (eV)	–5.83	–5.81
LUMO (eV)	–1.29	–1.46

Table 5. Calculated bond orders for compound **4**

Bond	Löwdin	Mulliken	Bond	Löwdin	Mulliken	Bond	Löwdin	Mulliken
C1-C2	1.576	1.492	C10-C28	1.517	1.448	C20-C27	0.970	0.935
C1-C8	1.367	1.348	C10-H1	0.894	0.921	C20-H10	0.879	0.908
C1-H23	0.888	0.910	C11-C12	1.299	1.320	C20-N1	0.985	0.896
C2-C3	1.414	1.354	C11-C18	1.364	1.348	C21-C23	1.450	1.425
C2-H24	0.901	0.929	C12-C13	1.177	1.178	C21-C24	1.428	1.401
C3-C4	1.587	1.500	C12-C15	1.353	1.323	C22-C25	1.488	1.437
C3-H25	0.899	0.929	C13-C14	1.631	1.564	C22-C26	1.512	1.458
C4-C7	1.346	1.312	C13-N1	1.067	0.812	C22-H19	0.902	0.929
C4-H26	0.894	0.923	C14-H22	0.883	0.910	C23-C26	1.497	1.425
C5-C9	1.430	1.401	C15-C16	1.576	1.491	C23-H5	0.895	0.921
C5-C10	1.420	1.412	C15-H13	0.888	0.909	C24-C25	1.520	1.446
C5-O2	1.172	0.865	C16-C17	1.423	1.357	C24-H11	0.893	0.919
C6-C28	1.491	1.438	C16-H14	0.899	0.929	C25-H17	0.901	0.929
C6-C29	1.509	1.457	C17-C18	1.575	1.492	C26-H18	0.900	0.928
C6-H7	0.902	0.931	C17-H15	0.899	0.929	C27-H6	0.878	0.897
C7-C8	1.296	1.328	C18-H16	0.889	0.911	C27-O2	1.127	0.890
C7-C14	1.243	1.167	C19-C27	0.928	0.859	C28-H3	0.901	0.929
C8-C11	1.167	1.133	C19-N1	1.289	1.072	C29-H4	0.900	0.929
C9-C29	1.496	1.425	C19-O1	2.158	1.829			
C9-H2	0.875	0.885	C20-C21	1.042	0.980			

tional Theory (DFT) calculations are presented in Table 4. The details of the geometries are presented in Tables 5–8. These data are helpful in the identification of several parameters of these two compounds and a similar series of compounds. Some quantitative differences in the values of these parameters are obtained. A combination of these parameters has resulted in widely significant overall dipole moment values. Therefore, this type of information is required to advance an explanation of the differences in the bioactivity of organic molecules of similar structures.

Table 6. Calculated atomic charges for compound **4**

Atom Label	Natural charge	Mulliken charge	Electrostatic charge	Atom Label	Natural charge	Mulliken charge	Electrostatic charge
C1	–0.207	–0.194	–0.131	C28	–0.224	–0.137	–0.018
C2	–0.226	–0.135	–0.154	C29	–0.218	–0.143	–0.047
C3	–0.232	–0.130	–0.066	H1	+0.245	+0.134	+0.164
C4	–0.203	–0.202	–0.269	H2	+0.259	+0.178	+0.145
C5	+0.306	+0.349	+0.459	H3	+0.237	+0.130	+0.109
C6	–0.256	–0.128	–0.219	H4	+0.239	+0.134	+0.119
C7	–0.057	+0.133	+0.295	H5	+0.238	+0.136	+0.143
C8	–0.028	+0.086	–0.051	H6	+0.238	+0.167	+0.072
C9	–0.301	–0.188	–0.304	H7	+0.236	+0.126	+0.131
C10	–0.272	–0.171	–0.347	H10	+0.252	+0.162	+0.126
C11	–0.029	+0.036	+0.051	H11	+0.239	+0.138	+0.124
C12	–0.053	+0.144	+0.089	H13	+0.243	+0.147	+0.167
C13	+0.156	+0.218	+0.129	H14	+0.241	+0.136	+0.118
C14	–0.184	–0.218	–0.404	H15	+0.239	+0.132	+0.118
C15	–0.206	–0.198	–0.216	H16	+0.231	+0.135	+0.131
C16	–0.225	–0.130	–0.094	H17	+0.240	+0.136	+0.122
C17	–0.226	–0.133	–0.114	H18	+0.240	+0.137	+0.114
C18	–0.206	–0.191	–0.171	H19	+0.239	+0.135	+0.128
C19	+0.680	+0.589	+0.415	H22	+0.245	+0.143	+0.183
C20	–0.050	–0.065	–0.161	H23	+0.232	+0.137	+0.126
C21	–0.072	+0.205	+0.314	H24	+0.239	+0.132	+0.126
C22	–0.230	–0.126	–0.162	H25	+0.239	+0.133	+0.116
C23	–0.214	–0.186	–0.299	H26	+0.236	+0.134	+0.145
C24	–0.232	–0.199	–0.243	N1	–0.490	–0.556	–0.140
C25	–0.226	–0.132	–0.086	O1	–0.581	–0.480	–0.449
C26	–0.225	–0.130	–0.043	O2	–0.542	–0.537	–0.384
C27	+0.029	+0.008	+0.092				

Table 7. Calculated bond orders for compound **5**

Bond	Löwdin	Mulliken	Bond	Löwdin	Mulliken	Bond	Löwdin	Mulliken
C5-C6	1.587	1.502	C14-H12	0.881	0.904	C22-C26	1.504	1.453
C5-C7	1.343	1.308	C15-C16	1.575	1.492	C22-H19	0.901	0.928
C5-H26	0.894	0.922	C15-H13	0.886	0.910	C23-C26	1.503	1.432
C6-C10	1.413	1.353	C16-C17	1.423	1.359	C23-H5	0.894	0.922
C6-H22	0.900	0.929	C16-H14	0.899	0.929	C24-C25	1.516	1.448
C7-C8	1.292	1.325	C17-C18	1.574	1.491	C24-H11	0.894	0.919
C7-C14	1.251	1.179	C17-H15	0.900	0.929	C25-H17	0.899	0.928
C8-C9	1.367	1.347	C18-H16	0.889	0.910	C26-H18	0.900	0.928

Table-7 (contd.)

C8-C11	1.169	1.136	C19-C27	0.939	0.871	C27-H6	0.878	0.900
C9-C10	1.576	1.491	C19-N1	1.290	1.088	C27-O2	1.104	0.855
C9-H7	0.889	0.911	C19-O1	2.137	1.790	C28-C29	1.070	0.976
C10-H8	0.901	0.929	C20-C21	1.039	0.970	C28-O2	1.226	0.984
C11-C12	1.297	1.329	C20-C27	0.973	0.939	C28-O3	2.216	1.956
C11-C18	1.365	1.348	C20-H10	0.874	0.900	C29-H9	0.923	0.925
C12-C13	1.178	1.168	C20-N1	0.983	0.900	C29-H20	0.904	0.891
C12-C15	1.354	1.319	C21-C23	1.446	1.420	C29-H21	0.927	0.937
C13-C14	1.603	1.534	C21-C24	1.432	1.404			
C13-N1	1.096	0.835	C22-C25	1.495	1.443			

Table 8. Calculated atomic charges for compound **5**

Atom Label	Natural charge	Mulliken charge	Electrostatic charge	Atom Label	Natural charge	Mulliken charge	Electrostatic charge
C5	–0.204	–0.203	–0.276	C29	–0.809	–0.579	–0.728
C6	–0.230	–0.130	–0.058	H5	+0.238	+0.138	+0.150
C7	–0.054	+0.136	+0.281	H6	+0.240	+0.172	+0.058
C8	–0.033	+0.082	–0.042	H7	+0.232	+0.136	+0.127
C9	–0.207	–0.193	–0.140	H8	+0.239	+0.133	+0.122
C10	–0.228	–0.136	–0.145	H9	+0.248	+0.173	+0.189
C11	–0.025	+0.039	+0.038	H10	+0.253	+0.174	+0.188
C12	–0.056	+0.131	+0.120	H11	+0.238	+0.137	+0.148
C13	+0.162	+0.254	+0.050	H12	+0.251	+0.159	+0.185
C14	–0.201	–0.246	–0.358	H13	+0.234	+0.137	+0.122
C15	–0.211	–0.198	–0.208	H14	+0.240	+0.135	+0.119
C16	–0.225	–0.129	–0.087	H15	+0.240	+0.134	+0.123
C17	–0.226	–0.134	–0.132	H16	+0.232	+0.137	+0.128
C18	–0.203	–0.190	–0.151	H17	+0.241	+0.138	+0.117
C19	+0.679	+0.603	+0.402	H18	+0.241	+0.138	+0.115
C20	–0.046	–0.075	–0.354	H19	+0.240	+0.137	+0.129
C21	–0.080	+0.196	+0.394	H20	+0.274	+0.222	+0.195
C22	–0.228	–0.125	–0.172	H21	+0.269	+0.192	+0.206
C23	–0.214	–0.183	–0.325	H22	+0.240	+0.134	+0.114
C24	–0.225	–0.193	–0.319	H26	+0.237	+0.137	+0.148
C25	–0.224	–0.129	–0.045	N1	–0.466	–0.556	–0.043
C26	–0.225	–0.130	–0.030	O1	–0.584	–0.487	–0.455
C27	+0.019	+0.001	+0.222	O2	–0.560	–0.457	–0.449
C28	+0.832	+0.596	+0.834	O3	–0.557	–0.429	–0.504

Conclusions

Our present study indicates that there is a direct relationship between the dipole moment and the anticancer activity of β-lactam compounds. Our work was done using three different dipole moment calculation methods on five different compounds. The dipole moment is observed high, above 4.3 Debye, for the active compound. This study also revealed that the substitutional group at the β-lactam ring plays an important role in its anticancer activity especially the groups at the N_1 and C_3 sites. Furthermore, we believe that this study opens up a new research field to discover new active anticancer lactam compounds and therapeutics to treat cancer

cells. This study is unique since such explorations with β-lactams and their anticancer activities have never been performed. Taken up together, we have identified a correlation between the dipole moment and the anticancer activity of β-lactams. However, further investigations in this area are required to define the role of the polarity and other physical parameters in anticancer activity.

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