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Dipole moment studies on α-hydroxy-β-lactam derivatives

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In this study, the dipole moment of α-hydroxy-β-lactam derivatives are discussed in detail. Both the hydroxy and acetoxy derivatives of monocyclic *cis* and *trans* β-lactam are considered for this investigation. The influence of the substituted group at N_1 position on the polarity is also investigated. Four quantum mechanical methods (AM1, RM1, PM3 and PM6) are chosen to calculate dipole moment of these molecules. Best of our knowledge, this is the first study on the dipole moment of hydroxy β-lactam derivatives which are related to taxol and taxotere anticancer agents.

Keywords: α-Hydroxy-β-lactam, dipole moment, quantum mechanical methods.

Introduction

β-Lactams are biologically important compounds. They are the core part of important antibiotics such as penicillin derivatives, thienamycins, cephalosporins, monobactams, carbapenem and carbacephem[1,2]. Along with antibiotics application, β-lactams have also other pharmaceutical applications as anti-inflammatory[3], antifungal[4], antihepatitis[5], analgesic properties[6], antihyperglycemic[7], LHRH antagonists[8], cholesterol absorption inhibitors[9], and anticancer agents[10]. In addition, β-lactams also have received significant attention from medicinal and synthetical chemists because of their importance in organic synthesis as versatile synthetic intermediates and chiral synthons[11]. Several research groups have reported a large variety of β-lactam based synthetic methods[12]. The applications of β-lactams have led to the development of numerous syntheses like indolizidine alkaloids, taxoids, paclitaxel, docetaxel, cyptophycins, lankacidins, variety of non-protein amino acids, oligopeptides, peptidomimetics and nitrogen-heterocycles. Among numerous synthetic intermediates, application of β-lactams for taxol (paclitaxel), taxotere (docletaxel) and their analogs[13] have acquired much attention because of the anti-tumor activity of taxol related compounds. α-Hydroxy-β-lactam are the intermediates for the semi-synthesis of taxol and its analogs.

Over the past decades, our group have synthesized and disclosed pharmaceutically important α-hydroxy-β-lactam and their derivatives[14]. Besides, we have carried out synthesis and computational studies of different biologically important compounds[15]. In this study, we present quantum mechanical dipole moment calculations of α-hydroxy-β-lactam derivatives. Both the hydroxy (OH) and acetoxy (OAc) derivatives of *cis* and *trans* β-lactam are considered for this investigation. According to our knowledge, this is the first study on the dipole moment calculation of α-hydroxy-β-lactam derivatives. The dipole moment data has shown a consistent trend in all of these β-lactams regardless of their stereochemical distribution.

Materials and methods

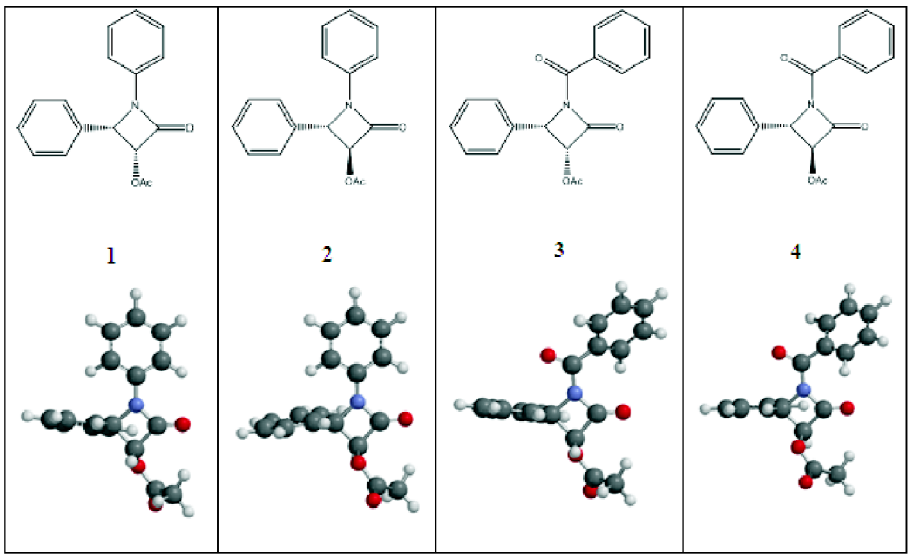
α-Acetoxy-β-lactams:

The molecular structures and energy minimized structure of the α-acetoxy-β-lactams are shown in Scheme 1. Compound **1** and compound **2** have same molecular formula (identical compounds), they are stereoisomers. Since the stereoisomers has showed remarkable difference in the prop-

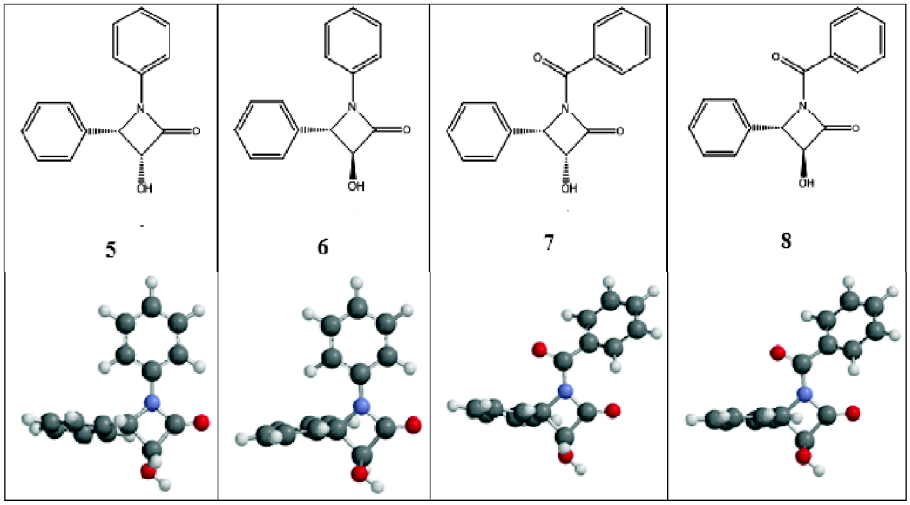
erties, we have included both the *cis* and *trans* isomers in this study. Compound **1** is a *cis* isomer and compound **2** is a *trans* isomer. They have a phenyl group linked to N_1 position of the β-lactam ring, oxygen at the C_2 position, an acetoxy group at the C_3 position of the ring and a phenyl group at the C_4 position. To investigate the influence of the substituted group at the N_1 position, other compounds **4** and **5** are also explored. Compounds **4** and **5** have a CO-phenyl group linked to N_1 position of the β-lactam ring instead of phenyl group. Compounds **4** (*cis*) and compound **5** (*trans*) are stereoisomer.

α-Hydroxy-β-lactams:

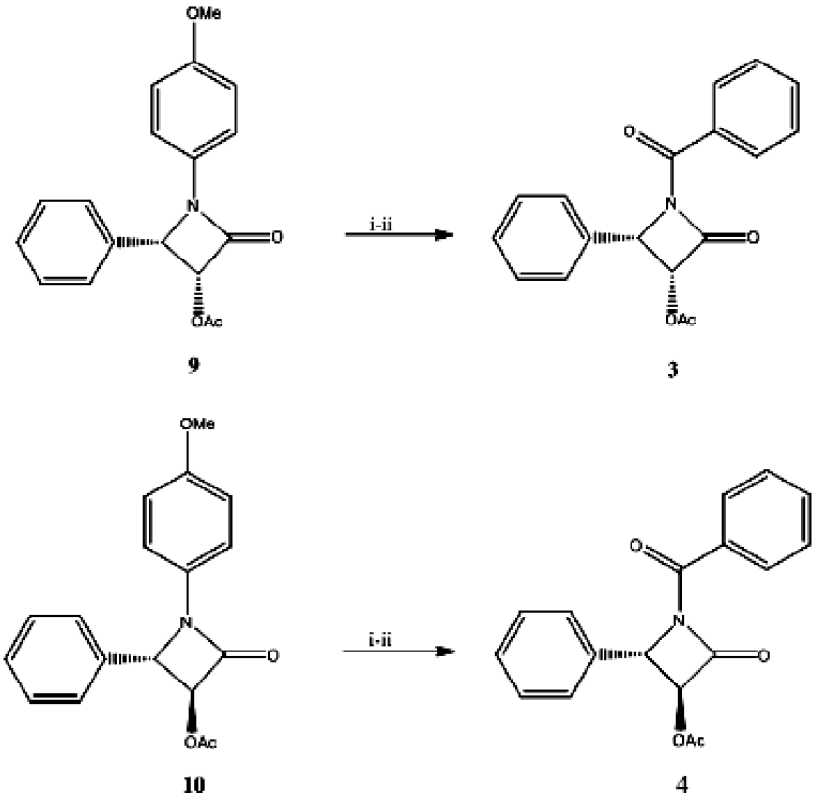
The molecular structures and energy minimized structure of the α-hydroxy-β-lactams are shown in Scheme 2. α-Hydroxy-β-lactams have a hydroxy group (OH) at the C_3 position of the ring. Compound **5** and compound **6** are stereoisomers. They have a phenyl group linked to N_1 position of the β-lactam ring, oxygen at the C_2 position, and a phenyl



Scheme 1. The chemical and optimized structures of the α-acetoxy-β-lactams.



Scheme 2. The chemical and optimized structures of the α-hydroxy-β-lactams.



Scheme 3. Synthesis of compounds **3** and **4**, i-ii: CAN/H_2O/CH_3CN; PhCOCl/TEA.

group at the C_4 position. The other two α-hydroxy β-lactams **7** and **8** have a CO-phenyl group linked to N_1 position of the β-lactam ring instead of phenyl group and they are stereoisomer.

Synthesis of α-hydroxy-β-lactams:

Different methods are available for the synthesis of α-hydroxy β-lactams derivatives[14]. Scheme **3** shows the schematics of the synthesis of compound **3** and **4**[14c-f].

Dipole moment calculation:

In this study all the dipole moment calculations were done using the SPARTAN 18 software package. All the measurements were performed 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). All the methods were based on the Neglect of Differential Diatomic Overlap (NDDO) integral approximation. All the structures were drawn in 2D and then converted into their 3D forms using the same software followed by their optimization procedure.

Results and discussion

The calculated ground-state dipole moment (μ) values in Debye (D) for eight α-hydroxy-β-lactams derivatives are shown in Table 1. The compounds **1, 3, 5** and **7** are *cis* in nature and the compounds **2, 4, 6** and **8** are *trans* β-lactams.

Table 1. Dipole moment values of compounds **1**-**8**

Compounds	Dipole moment in Debye (D)			
	AM1	RM1	PM3	PM6
1	5.6	5.55	5.64	6.35
2	6.29	6.42	5.32	7.08
3	2.64	2.54	2.4	2.67
4	4.81	4.52	4.33	5.2
5	2.57	2.52	2.19	2.72
6	3.04	3	2.18	3.2
7	1.72	2.06	1.75	1.95
8	2.45	2.44	2.22	2.77

From the calculation it is observed that *trans* compounds has higher dipole moment than *cis* regardless of the sub-

stituent present in the N_1 and C_3 position.

The *trans* compound with an acetoxy (OAc) group at the C_3 position showed more dipole moment than corresponding compounds with hydroxyl (OH) group. Following AM1 calculations, *trans* compounds with OAc at C_3 position and phenyl at N_1 position (compound **2**) showed the highest dipole moment (6.29D), followed by the compound **4** (4.81D) that has OAc at C_3 position and CO-phenyl group at N_1 position. Compounds **6** and **8** showed low dipole moment values 3.04D and 2.45D, because of the presence of the OH group. *Cis* compounds also showed the same trend. The compound with OAc showed higher dipole moment than *cis* compound with CO-phenyl and OH compound. For instance, the compound **7** showed the lowest dipole moment (1.72D). All the four quantum mechanical calculations (AM1, RM1, PM3 and PM6) showed comparable dipole moment values. Surprisingly the dipole moment values of all the compounds from the PM3 calculations were lower compared to data from other methods.

Mechanism:

From our dipole moment calculations, it is understood that *trans*-α-hydroxy-β-lactams derivatives have higher dipole moment compared to corresponding *cis*-α-hydroxy-β-lactams derivatives. The energy minimized 3D structure of the acetoxy stereoisomers showed in *cis* isomers **1**, the oxygen in the ring atom and oxygen in the acetoxy group are two close each other (2.9 Å separation) compared to oxygen atoms in *trans* isomer **2** (5.1 Å) as shown in Fig. 1. Because of this close proximity in *cis* isomers, electronic repulsion takes place and therefore polarity decreases due to overcrowding. Highest dipole moment was expected for compound **4**, but because of close proximity of oxygen atoms in the acetoxy group, oxygen at the C_2 position and oxygen at the N_1 position (3.3 Å and 3.9 Å separation), polarity effects counter balance each other and overall effect resulting in a reduced dipole moment.

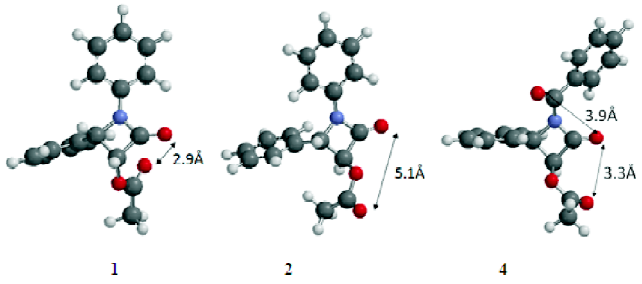


Fig. 1. Separation distance of oxygen atoms in stereoisomers.

Conclusions

In this study eight α-hydroxy-β-lactams derivatives are analyzed with four semi-empirical quantum mechanical dipole moment calculations. Dipole moment is observed to be high for *trans* compounds regardless of the group present in the N_1 and C_3 position. All the quantum mechanical calculations followed the same trend. This study is significant and novel, since dipole moment values have played an important role in determining the biological activity of many compounds. But, this type of study has not been investigated with β-lactams that have a wide range of medicinal properties. These results may open a way to design and synthesize more active β-lactam based drugs.

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Supporting materials

All the supporting materials will be available on request.

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