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Molecular Polarizability in the Structural Studies of Cytidine and its Derivatives

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ABSTRACT
Bond and molecular polarizabilities of cytidine and its derivatives have been evaluated by quantum mechanical δ-function potential model and molecular vibration methods. By using bond polarizability coefficients, the electrophilic or nucleophilic nature of carbon atoms present in the molecules are discussed. These results are discussed in relation to X-ray diffraction studies, NMR chemical shifts, and quantum chemical calculations.

Key words: *Polarizability, Nucleoside, Nucleotide, Alphyl, Aryl, Free valence index.*

1. INTRODUCTION

Cytidine analogs are of therapeutic interest. Ex: 2,2/-Anhydro-1-*β*-D-arabinofuranosylcytosine-3/,5/-diphosphate is a derivative of 2,2/-anhydro-1-*β*-D-arabinofuranosylcytosine. It possesses strong antitumor activity against leukemia and various tumor cells [1]. 3,4-etheno-5-methoxymethyl-2/-deoxycytidine, (I), is a structural analog of 5-methoxymethyl-2/-deoxycytidine, which is a nanomolar inhibitor of the herpes simplex I virus [2-5]. N^4-Aminocytidine is a potent mutagen in phages and bacteria [6], in cultured mammalian cells [7,8] and *Drosophila* [9]. Cytidine analogs are chosen for the present study due to their medicinal importance.

2. POLARIZABILITY

2.1. The δ-function Model

The details of the method are given in the earlier papers [10-15]. The appropriate equations for estimating the parallel, nonbond region contribution and perpendicular components of polarizability are given below.

$$\alpha_{llb}=\frac{4nA}{a_0}\left[\frac{R^2}{4}+\frac{1}{2C_R^2}\right].\exp\left[-\frac{(x_A-x_B)^2}{4}\right] \quad (1)$$

$$\alpha_{11n}=\sum_j f_j\alpha_j \quad (2)$$

$$\sum 2\alpha_{\wedge}=n_{df}\frac{\sum x_j^2\alpha_j}{\sum x_j^2} \quad (3)$$

The mean molecular polarizability is obtained as

$$\alpha_M=\frac{1}{3}\left(\sum\alpha_{llp}+\sum\alpha_{llp}+\sum 2\alpha_{\wedge}\right) \quad (4)$$

The internuclear distances required for the present work are taken from the literature [16-26]. The δ-function strengths are estimated, and the parallel, non-bond region electron contribution, and the perpendicular components of polarizability are evaluated and presented in Table 1.

2.2. The Molecular Vibration Method

The details of this method, which relate the bond polarizability coefficients b_L and b_T with the bond stretching force constant K and the mean amplitude of vibration $\sigma^{1/2}$, are given in the earlier papers [10-15]. The bond polarizability coefficients are obtained by solving the following expressions:

$$b_L-b_T=A\left[(x_1x_2)^{\frac{1}{2}}\left(\frac{aN}{K-b}\right)^{\frac{2}{3}}\right]^{K/3b-2k} \quad (5)$$

and

$$b_L+2b_T=Cp^{j_B}J_B^{n\gamma}\sigma^{\frac{1}{2}} \quad (6)$$

The force constant and mean amplitude data needed in the present work are taken from the references [27,28].

The mean molecular polarizability is evaluated from the expression

$$\alpha_M=\sum_i\frac{n_i(b_L+2b_T)_i}{3} \quad (7)$$

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Table 1: δ-function potential method ($\alpha_M \times 10^{23}$ cm^3).

Molecule	$\Sigma\alpha_{allp}$	$\Sigma\alpha_{lln}$	$\Sigma 2\alpha_{\perp}$	α_M
Cytidine	3.955	0.257	2.087	2.099
5-methyl-2/-deoxycytidine-5/-monophosphate dihydrate	5.874	0.365	2.576	2.938
2,2/-anhydro-1-β-D-arabinofuranosylcytosine-3/,5/-diphosphate monohydrate	6.547	0.503	2.456	3.169
5/-hydroxymethyl-2/-deoxycytidine	4.883	0.286	2.238	2.469
5-methyl-6-aza-2/-deoxyisocytidine	4.379	0.276	2.104	2.253
2/-deoxy-5-methylisocytidine	4.609	0.247	2.189	2.348
5-methyl-2/-deoxycytidine	4.608	0.247	2.189	2.348
β-cytidine	4.543	0.286	2.015	2.281
N4,5-dimethyl-2/-deoxycytidine	5.164	0.246	2.413	2.608
3,4-etheno-5-methoxymethyl-2/-deoxycytidine	6.019	0.286	2.505	2.937
N4-aminocytidine hemihydrate	4.590	0.316	2.154	2.353

Where n_i is the number of bonds of Type I. The longitudinal and transverse bond polarizability values are given in Table 2. The mean molecular polarizabilities are given in Table 3 along with the results obtained from δ-function model and Le Fevre methods.

3. DISCUSSION

Molecular polarizabilities obtained from two theoretical methods are compared with the values obtained by summing Le Fevre [29] bond polarizability coefficients. These are known to yield experimental results with a deviation of 4% or less. Good agreement among the three values lends satisfactory support to the reliability of two theoretical methods.

Here, the b_L and b_T values are used to discuss the alphyl-aryl nature of carbon atoms in the title compound. From Table 2, it is evident that the b_L value of C4-C5 bond is 0.144×10^{-23} cm^3. It falls in between the b_L C-C values of Le Fevre aliphatic value of 0.099 in C_6H_{12} and aromatic value of 0.224 in C_6H_6. This shows that the C4-C5 bond is a mixed aliphatic-aromatic bond. With the substitution at C5 position Subbaiah et al. [10,11] have proved the aromatic character of C5 position. The position helps the electrophilic substitutions rather than nucleophilic substitutions due to its higher electron density. The X-ray diffraction studies exhibit the bond lengths for these C4-C5 bonds in between 1.472 and 1.419 Å. These are shorter than the normal value of 1.54 Å. Therefore, it is a proof for the mixed aliphatic-aromatic character. The b_L value of C-N bond is 0.196×10^{-23} cm^3, which is higher. This is due to nitrogen atom present in the bond. Nitrogen atom locks the ring current. This value is less compared to the b_L value (=0.203) of C/-N bond associated with ribose ring. The bond distance data for C-N are in between 1.287 and 1.394 Å, which exhibit alphyl-aryl character of the bond. The b_L value of C=O bond is 0.172×10^{-23} cm^3. The b_L of C/-O bond is 0.185×10^{-23} cm^3, which is fairly higher. The X-ray data for C/-O bond vary between 1.340 and 1.455 Å. Ribose is a saturated ring, so resonance studies cannot be applied to it. However, the higher values of b_L for C/-C/bonds are due to the effect of oxygen atoms, which possess more electron densities around them.

Table 2: Molecular vibration method ($b \times 10^{23}$ cm^3).

Bond	Force constant K m dyne/Å	b_L	b_T	$(b_L+2b_T)/3$
C-N	6.746	0.196	0.078	0.117
C=N	10.359	0.177	0.069	0.105
C-C	6.191	0.144	0.048	0.080
C=C	10.621	0.131	0.039	0.070
C=O	14.123	0.172	0.033	0.079
C-NH_2	8.363	0.196	0.068	0.111
N-H (amino)	8.179	0.085	0.075	0.078
N-CH_3	4.889	0.077	0.065	0.069
C-H	6.408	0.072	0.059	0.063
N-N	5.950	0.135	0.049	0.078
N-C/	2.480	0.203	0.128	0.153
C/-C/	3.761	0.179	0.047	0.091
C/-O	6.227	0.185	0.054	0.098
C/-H	4.674	0.076	0.064	0.068
C-H (methyl)	4.889	0.075	0.064	0.067
O/-H	6.640	0.104	0.096	0.099
P=O	5.698	0.127	0.072	0.090
P-O	5.698	0.138	0.066	0.090

The ^{13}C NMR chemical shifts for cytidine are −28.42, −38.17, +32.85, and −14.29 for the carbon atoms at the 2, 4, 5, and 6 positions, respectively. Thus, higher electron density can be observed at C5 position compared to C2/C4 and C6 positions from NMR

Table 3: Molecular polarizabilities of Cytidine and its derivatives $\alpha_M \times 10^{23}$ cm^3.

Molecule	α_M Lipp	α_M MVM	α_M Le Fevre
Cytidine	2.099	2.556	2.144
		2.386*	
5-methyl-2/-deoxycytidine-5/-monophosphate dihydrate	2.938	3.343	3.236
2,2/-anhydro-1-*β*-D-arabinofuranosylcytosine-3/,5/-diphosphate monohydrate	3.169	3.495	3.463
5/-hydroxymethyl-2/-deoxycytidine	2.469	3.016	2.837
5-methyl-6-aza-2/-deoxyisocytidine	2.253	2.820	2.462
2/-deoxy-5-methylisocytidine	2.348	2.884	2.537
5-methyl-2/-deoxycytidine	2.348	2.887	2.671
β-cytidine	2.281	2.798	2.574
*N*4,5-dimethyl-2/-deoxycytidine	2.608	3.118	2.863
3,4-etheno-5-methoxymethyl-2/-deoxycytidine	2.937	3.509	3.379
*N*4-aminocytidine hemihydrate	2.353	2.954	2.725

*Denotes present experimental value

chemical shifts. Hence, C5 is predicted as the most reactive atom in the cytidine and its analogs with respect to electrophilic reactions. The C2, C4, and C6 are predicted as active centers for nucleophilic reactions.

The electron densities at various carbon atoms in the cytosine are 0.796; 0.828; 0.835, and 1.169, respectively, for 2, 4, 6, and 5 positions. According to Pullman and Pullman [30], free valence indices in cytosine are 0.146, 0.101, 0.445, and 0.449 for C2, C4, C6, and C5 positions, respectively. Bond orders for C4-C5 and C5-C6 bonds are 0.525 and 0.758, respectively. Kuchetkov and Budovskii [31] on the basis of Huckel's approximation and SCF methods, have reported that the most active atom relative to electrophilic reactions is C5, and the most reactive atoms relative to nucleophilic reactions is C6>C2>C4 in cytosine. From the above electron densities, free valence indices and bond orders, it has been concluded that C5 atom has higher values compared to C2, C4, and C6 atoms.

Thus, all the experimental studies (X-ray and NMR) and theoretical studies on quantum chemical calculations lend support to the conclusions drawn from polarizability studies. Hence, bond polarizabilities form yet another useful study to understand reactivity nature of the carbon atoms in nucleosides/nucleotides.

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****Bibliographical Sketch***

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