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Polarizability and Allied Properties of Thymidine and Substituted Thymidines

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ABSTRACT

Molecular polarizabilities and diamagnetic susceptibilities are important for several kinetic aspects of positive ion chemistry. The reactivity nature of a molecule depends in the most general way on the polarization and polarizability of the different atoms of which it is composed. The use of polarizabilities in calculating the effect of perturbation is equivalent to using first order perturbation theory. The ring current associated with the aromatic molecules is responsible for the diamagnetic susceptibility exaltations. In view of these applications molecular polarizabilities and diamagnetic susceptibilities are evaluated for thymidine and its substituents and presented in this paper.

Keywords: *Polarizability, diamagnetic susceptibility, pyrimidine, hetero aromatic nature.*

1. INTRODUCTION

The study of the physical properties of biomolecules plays an important role in understanding of cell structure, metabolism and other physical phenomena. Molecular polarizability is conformation dependent property. Polarizabilities can increase the understanding of structure of biomolecules. Structure plays an important role in understanding the biological activity. Many thymidine analogues are useful in AIDS control treatment. A few are listed here. Stavudine is a potent antiviral drug and is used for the treatment of HIV/AIDS [1,2]. S-Phenyl 0-$3^{\prime}$-thymidinyl methyl phosphonothioate is one of a series of nucleotide synthons directed towards introducing chiral internucleotidic linkages into DNA. DNA modified in this manner has several applications in biology and medicine [3]. AZT, $3^{\prime}$-azido-$2^{\prime}$,$3^{\prime}$-dideoxythymidine, is an effective inhibitor which is in current clinical use with HIV patients [4]. In view of this importance the present studies have been performed on these thymidine derivatives.

1.2. MOLECULAR POLARIZABILITY

The mean molecular polarizabilities of thymidine and its substituents are evaluated using the quantum mechanical δ-function model, molecular dynamics method and experimentally determined by solution technique.

1.2.1. δ-Function Potential model

Lippincott and Stutmann[5] have developed this method as a semi-empirical model for the estimation of molecular polarizability. The details of this method are reported elsewhere[6-8].

The method is based on evaluating the (i) parallel component of polarizability $\Sigma\alpha_{IIp}$, of the various bonds present in the molecule, (ii) the non-bond region electron contribution $\Sigma\alpha_{IIn}$ and (iii) the perpendicular component of polarizability $\Sigma 2\alpha_{\perp}$. The appropriate relations are given below.

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

$$\alpha_{IIn} = \Sigma f_j \alpha_j$$

$$2\alpha_{\perp} = n_{df}\,\frac{\sum_j x_j^2 \alpha_j}{\sum_j x_j^2}$$

The mean molecular polarizability of a molecule is given by the expression:

$$\alpha_M = \frac{1}{3}\left[\Sigma\alpha_{IIP} + \Sigma\alpha_{IIn} + 2\alpha_{\perp}\right]$$

The details of the various parameters and the method of calculation are given by Lippincott and Stutmann. The inter nuclear distances data required in these estimations is taken from the literature on x-ray diffraction[9-19]. The three individual components are evaluated and presented in table-1 along with the average values of molecular polarizability.

1.2.2. Molecular Dynamics Method

Based on the theory of Kerr effect, the authors' school has related bond polarizability coefficients to the molecular dynamics parameters i.e. force

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

S.No.	Molecule	$\Sigma\alpha_{llp}$	$\Sigma\alpha_{lln}$	$\Sigma 2\alpha_{\perp}$	α_M
1	Thymidine	3.914	0.257	2.172	2.098
2	$5^{/}$-Acetyl thymidine	4.965	0.296	2.466	2.576
3	$2^{/}$, $3^{/}$-Dideoxy-$3^{/}$-C, $2^{/}$-N-[(3R, 5R)-5-ethoxy-carbonyl-2-methyl-1, 2-isoxazolidine]-ribothymidine	6.603	0.365	3.051	3.340
4	$2^{/}$,$3^{/}$-Dideoxy-$3^{/}$-nitrothymidine	4.707	0.296	2.159	2.387
5	$2^{/}$-Propoxy-$3^{/}$-nitrothymidine	5.976	0.365	2.878	3.073
6	(Thymidin-$3^{/}$-yl) (N^3-methyl-4-thiothymidin-$5^{/}$-yl) methylphosphonate	10.883	0.634	4.787	5.435
7	Stavudine	4.109	0.217	2.145	2.157
8	$3^{/}$- O-Acetylthymidine	4.999	0.296	2.466	2.587
9	S-Phenyl 0-$3^{/}$-thymidinyl methyl phosphonothioate	8.155	0.417	3.477	4.016
10	Cis-thymidine $3^{/}$, $5^{/}$-cyclic N, N-dimethylphosphoramidate	5.635	0.325	2.698	2.886
11	Calcium thymidine $5^{/}$-phosphate dihydrate	5.449	0.394	2.356	2.733
12	$2^{/}$,$3^{/}$-Didehydro-$3^{/}$-deoxythymidine N-methyl-2-pyrrolidone solvate	6.152	0.286	3.102	3.180

constants and mean amplitudes of vibration of the bonds. The details of this method are given in references[6-8]. The actual relationships are given below.

$$b_L - b_T = A\left[(x_B x_C)^{\frac{1}{2}} \left(\frac{aN}{K-b} \right)^{\frac{2}{3}} \right]^s$$

$$b_L + 2b_T = CP^{j_B} J_B^{n\gamma} \sigma^{\frac{1}{2}}$$

Where n_i is the number of bonds of type i. The force constants are taken from reference[20-21]. The b_L and b_T values along with the average value of bond polarizability of each bond present in the molecules considered here are presented in table-2. A comparison of the molecular polarizabilities is given in table-3.

1.2.3. Solution technique

Polarizability of a substance can be determined by measuring the refractive index of the substance. For solids, they are examined in solution and mixture formulae are applied to the observations. Le Fevre has given this method for solutions.

Let the subscripts 1, 2 and 12 relate respectively to the solvent, solute and solution. If the concentrations are expressed as molar fractions f_1 and f_2 or weight fractions W_1 and W_2, then, the apparent partial molar refraction is given by equation

$$\frac{n_{12}^2 - 1}{n_{12}^2 + 2} \cdot \frac{1}{d_{12}} = W_1 r_1 + W_2 r_2$$

Weight fractions are found to be arithmetically simpler in use than molar fractions. It has often been found by experiment that $(d_{12}-d_1)/d_1W_2 = \beta$ and $\left(n_{12}^2 - n_1^2\right)/W_2 = \gamma n_1^2$ are constant. Hence r_2 at infinite dilution is obtained from the mean values of β and γn_1^2 $\quad {}_{\infty}r_2 = r_1(1-\beta) + C\gamma n_1^2$ and the following equation

Where C = $3/d_1(n_1^2+2)^2$

From this specific refraction of the solute, the molecular polarizability of the solid can be estimated experimentally.

2. EXPERIMENTAL

Thymidine solutions are prepared by dissolving thymidine in distilled water. 0.025 gm 0.125 gm in steps of 0.025 gm of thymidine is dissolved in 25 ml of water. Weight fractions have been estimated by weighing the solute and solvent for each concentration. Refractive indices have been measured at 4358 Å, 5460 Å, 5790 Å and 5893 Å wave lengths by using Pulfrich Refractometer. Densities of these different concentrated solutions and the solvent have been measured at room temperature. Graphs are plotted between $(d_{12}-d_1)/d_1$ versus W_2 (solute weight fraction) and $\left(n_{12}^2 - n_1^2\right)$ versus W_2. The slopes β and γn_1^2 are estimated and substituted in the equation for ${}_{\infty}r_2$. The molar refraction $M\,{}_{\infty}r_2$ = R is estimated and polarizability α is calculated. The results are presented in table-4.

2.1. Diamagnetic Susceptibility

In view of importance of diamagnetic susceptibility in positive ion chemistry, they have been evaluated

Table 2. Force field data and bond polarizability coefficients (b×10^{23}cm^3).

Bond	Force constant (K) m dyne/Å	b_L	b_T	$(b_L+2b_T)/3$
C-C	6.202	0.144	0.048	0.080
C=C	8.702	0.130	0.045	0.073
C-N	6.380	0.196	0.080	0.119
C=O	10.50	0.169	0.044	0.085
C5-C (methyl)	4.889	0.226	0.139	0.168
N-H	5.382	0.093	0.084	0.087
C-H	5.204	0.074	0.062	0.066
C-H (Methyl)	4.626	0.076	0.065	0.068
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$^{/}$=C$^{/}$ (deoxyribose)	9.637	0.131	0.042	0.072
O-H	6.282	0.180	0.049	0.093
C$^{/}$-H	4.681	0.076	0.064	0.068
N=O	12.28	0.148	0.047	0.080
N-O	11.99	0.166	0.038	0.081
C=S	3.400	0.195	0.066	0.109
C-S	4.100	0.246	0.032	0.103
P-C	7.964	0.177	0.118	0.138
P-O	5.698	0.138	0.066	0.090
P=O	5.698	0.127	0.072	0.090
P-S	3.370	0.256	0.162	0.193
P-N	5.026	0.154	0.095	0.115
Phenyl ring:				
C-C	7.910	0.145	0.040	0.075
C=C	7.910	0.130	0.048	0.075
C-H	5.269	0.074	0.062	0.066
Pyrrolidone ring:				
N1-C2	6.500	0.196	0.079	0.118
C2-C3	3.400	0.144	0.069	0.094
C3-C4	3.600	0.144	0.067	0.092
C4-C5	3.065	0.144	0.073	0.096
C5-N1	5.000	0.196	0.091	0.126
C-H	4.527	0.076	0.065	0.069

for Thymidine and its substituents by Pascal's incremental system[22] and authors' polarizability method [8,23]. Diamagnetic susceptibilities are estimated by these two methods and reported in table-5

3. RESULTS AND DISCUSSION

From Table 1, it can be found that the longitudinal bond polarizability coefficient bL of C4-C5 bond is 0.144 x 10-23 cm3. It does not coincide either with the alphyl value (=0.099) or the aryl value (=0.224) estimated by Le Fevre. It predicts a mixed alphyl-aryl character for the C4-C5 bond. To understand which of the carbon atoms i.e., C4or C5 is aryl in character one has to study the substitution effect at C4 and C5 positions. The authors have earlier proved the aromatic character of the C5 position [7,8] with methyl substitution. Hence it has been taken for the present case also. Therefore the C5 position allows electrophilic substitution. bL value of C/-C/ bond is 0.179 x 10-23 cm3 which is higher than the bL value of C4-C5 bond. The higher values of bL for C/-C/ bonds noticed here can be attributed to the presence of oxygen atoms, which possess more electron densities around them and not the resonance effect. The bL value of C-N bond is 0.196 x 10-23 cm3, which is higher. This is true because the nitrogen atoms possess electron-withdrawing effect. Due to this character, the electron density on nitrogen increases and there by C-N bond gains bL value. This value is slightly less compared to the bL value of C/-N (=0.203) associated with sugar ring. The bL value of C=O bond is 0.169 x 10-23 cm3. The bL of C/-O bond is 0.185 x 10-23 cm3, which is fairly higher. Since ribose lacks unsaturation, no resonance character can be associated with the C/-C/ bonds.

Shortening of single bonds and elongation of double bonds is a characteristic property of aromaticity. In thymidine and its derivatives considered here, the C-C internuclear distance varies between 1.401 and 1.456 Å. These are shorter than the normal value of 1.53 Å. The C=C internuclear distance is in between 1.335 and 1.35 Å. This value is higher than the normal value of

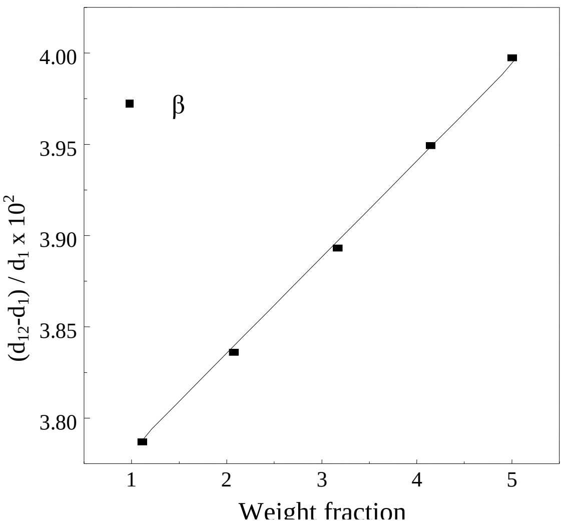

Figure 1: Variation of density ratio with weight

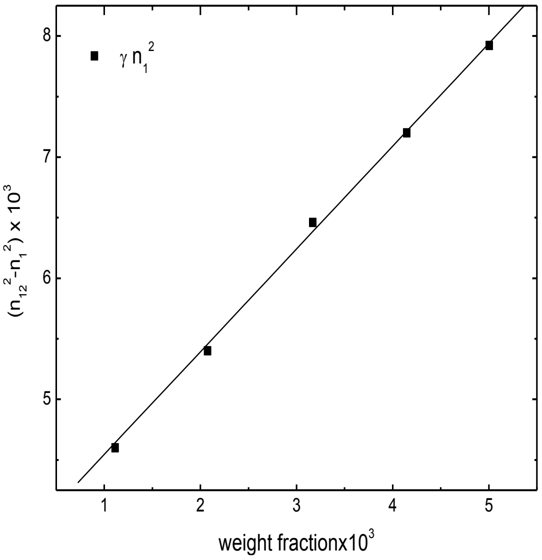

Figure 2: Variation of $(n_{12}^2 - n_1^2)$ with weight fraction of 4358 Å line

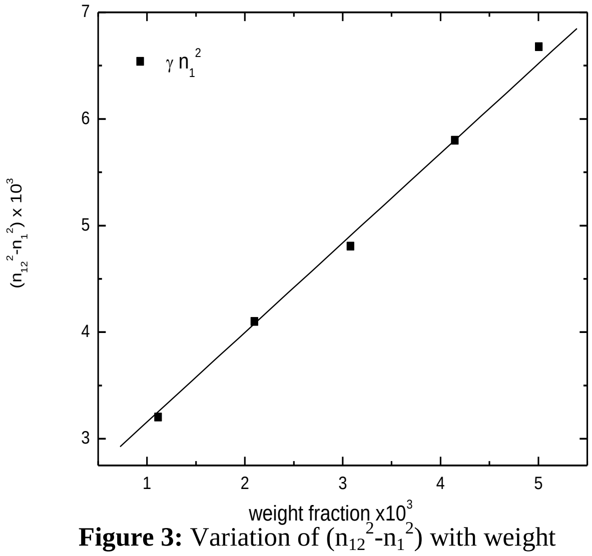

Figure 3: Variation of $(n_{12}^2 - n_1^2)$ with weight fraction of 5460 Å line

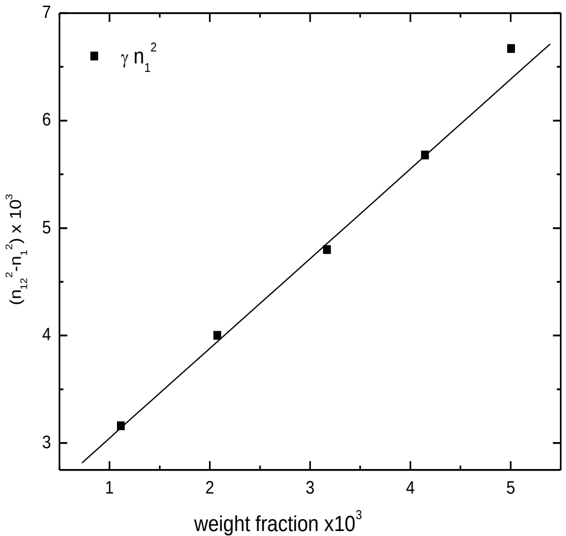

Figure 4: Variation of $(n_{12}^2 - n_1^2)$ with weight fraction of 5790 Å line

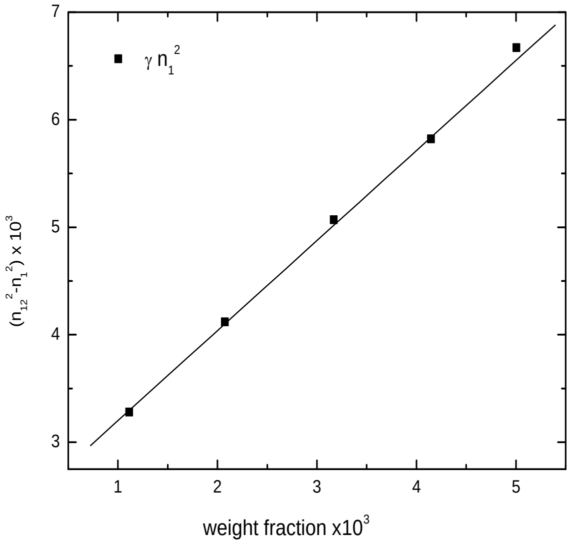

Figure 5: Variation of $(n_{12}^2 - n_1^2)$ with weight fraction of 5893 Å line

1.34 Å. Therefore these bonds are exhibiting the aromatic property. The bond distance values for C-N are in between 1.356 and 1.41 Å, which exhibit alphyl-aryl character of the bond. The bond distance values for C/-C/ bond is in between 1.515 and 1.529 Å. The C/-O bond internuclear distance is in between 1.401 and 1.479 Å. Since ribose is a saturated ring, no resonance studies can be applied to the bonds in the ring.

The NMR chemical shifts for thymidine [24] are -23.58, -36.69, +18.29 and -0.947 for the carbon atoms at the 2, 4, 5 and 6 positions respectively. The high field shift at C5 position therefore points out that this position is rich in electrons and hence acts as a donor and facilitates electrophilic substitutions. The minimal values of shifts at C6

Table 4. Molar refractions of thymidine.

λ Å	r $_1$	C γ $\mathbf{n_1^2}$	r $_1$(1-β)	$_\infty \mathbf{r_2}$	α_M x10^{23} cm^3	Mean α_M x10^{23} cm^3
4358.44	0.209	0.1773	0.0993	0.2766	2.6558	2.638
5460.74	0.2068	0.1769	0.0978	0.2747	2.6380	
5790.66	0.2061	0.1766	0.0975	0.2741	2.6322	
5893	0.2060	0.1761	0.0974	0.2736	2.6268	

Table 5. Diamagnetic susceptibilities of thymidine and its derivatives (-χ_M x10^6 CGS emu mol^{-1})

S.No.	Molecule	Pascal method	Rao et al method
1	Thymidine	126.70	138.14
2	$5^{/}$-Acetyl thymidine	132.90	131.18
3	$2^{/}$, $3^{/}$-Dideoxy-$3^{/}$-C, $2^{/}$-N-[(3R, 5R)-5-ethoxy-carbonyl-2-methyl-1, 2-isoxazolidine]-ribothymidine	175.86	173.34
4	$2^{/}$, $3^{/}$-Dideoxy-$3^{/}$-nitrothymidine	123.17	120.32
5	$2^{/}$-Propoxy-$3^{/}$-nitrothymidine	164.21	169.14
6	(Thymidin-$3^{/}$-yl) (N^3-methyl-4-thiothymidin-$5^{/}$-yl) methylphosphonate	282.51	298.56
7	Stavudine	105.45	105.60
8	$3^{/}$- O-Acetylthymidine	132.90	131.18
9	S-Phenyl 0-$3^{/}$-thymidinyl methyl phosphonothioate	199.23	203.13
10	Cis-thymidine $3^{/}$, $5^{/}$-cyclic N, N-dimethylphosphoramidate	152.10	151.99
11	Calcium thymidine $5^{/}$-phosphate dihydrate	127.16	128.25
12	$2^{/}$, $3^{/}$-Didehydro-$3^{/}$-deoxythymidine N-methyl-2-pyrrolidone solvate	166.51	162.28

and C2 show that these centers allow nucleophilic substitution because they act as electron acceptors.

The electron densities reported at various carbon positions in thymine are: 0.769; 0.789; 0.888 and 1.167 for C2, C4, C6 and C5 atoms respectively. From these electron densities, it is clear that C5 position in thymine has higher electron density compared to the values of C2, C4 and C6 positions. According to Pullman and Pullman [25], free valence indices for thymine are 0.179, 0.183, 0.455 and 0.326 for C2, C4, C6 and C5 respectively. Bond orders for C4-C5 are 0.377 and 0.811 respectively. Kuchetkov and Budovskii [26] on the basis of Huckel approximation and SCF methods, have reported that the most active atom relative to electrophilic substitutions is C5 atom and nucleophilic substitutions are C2, C4 and C6 atoms in thymine. The bond polarizability values are in a position to reflect these predictions. Thus the bond polarizability studies form yet another useful method for studying heteroaromatic nature of carbon atoms in nucleosides.

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