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Bond and Molecular Polarizabilities in the Structural Studies of Guanosine and its Derivatives

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ABSTRACT
Bond and molecular polarizabilities of Guanosine and its derivatives have been evaluated by quantum mechanical δ-function model and molecular vibration methods. Aliphatic or aromatic nature of carbon atoms present in the molecule has been identified from these bond polarizability studies. The results are discussed in comparison with X-ray structural data, NMR chemical shifts and quantum chemical calculations.

K*ey words:* *Polarizability, purine, alphyl, aryl, free valence index.*

1. INTRODUCTION

Guanosine and its substituents are biologically important molecules. Cyclic GMP (Guanosine3/-5/-cyclic monophosphate) is involved in metabolic control and regulatory functions. Cyclic GMP has been found in a number of mammalian tissues and body fluids [1]. 8-Bromoguanosine, 8-mercaptoguanosine and 7-methyl-8-oxo-7,8-dihydroguanosine compounds have been shown to act as intracellular mitogens in murine splenic B lymphocytes [2]. They are found to augment the proliferation and differentiation of murine T cells in the presence of other stimulating signals [3,4]. 7-methyl-8-oxo-7,8-dihydroguanosine has been shown to be a more potent B-cell mitogen and a more potent adjuvant for humoral immune responses [5]. As a part of structural studies of nucleosides the authors have earlier reported bond and molecular polarizabilities of adenosine, uridine and thymidine [6-8]. In this paper, bond polarizability studies are extended to guanosine molecules to understand the reactivity nature of carbon atoms.

2. MOLECULAR POLARIZABILITY

Mean molecular polarizability is generally determined from refractivity and light scattering techniques. In the present paper, bond and molecular polarizabilities of the molecules considered here are theoretically determined by (i) quantum mechanical δ-function potential model and (ii) molecular vibration method.

2.1. Quantum mechanical δ-function potential model

This method involves the evaluation of (i) a bond parallel component, and (ii) a bond perpendicular component. The bond parallel component is obtained from the contributions of (a) bond region electrons and (b) non-bond region electrons according to the valence bond theory. The perpendicular components of polarizability are evaluated from Pauling's electro negativities and atomic polarizabilities of the atoms of the molecule. The details of this method are given in the earlier papers [9-14]. The appropriate relations are given below.

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

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

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

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

The inter nuclear distance data required for the present work are taken from the literature on x-ray diffraction [1,15-23]. Pauling's electro negativities and Lippincott's [24] atomic polarizabilities are also used in these calculations. The results are presented in Table 1.

2.2. Molecular vibration method

Based on the theory of the Kerr effect, Rao and Murthy [25] developed molecular vibration method. They derived equations relating longitudinal bond polarizability coefficient (b_L) with stretching force constant (K) and transverse bond polarizability coefficient (b_T) with its mean

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amplitude of vibration ($\sigma^{1/2}$). The individual bond polarizability coefficients are obtained by solving the two expressions:

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

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

The meaning of the various terms is given in the earlier papers [9-14].

Using the force constants and mean amplitudes of vibration longitudinal and transverse bond coefficient values of each bond can be obtained.

Finally the molecular polarizability is given by

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

Table 1. Quantum mechanical δ-function potential method (α_M x10^{23} cm^3)

S.No.	Molecule	$\Sigma\alpha_{llp}$	$\Sigma\alpha_{lln}$	$\Sigma 2\alpha_{\perp}$	α_M
1	Guanosine	4.475	0.346	2.332	2.384
2	Guanosine 3′,5′-cyclic monophosphate sodium Tetrahydrate	6.003	0.424	2.322	2.916
3	Disodium deoxyguanosine-5′-phosphate Tetrahydrate	5.85	0.484	2.322	2.885
4	8-Methylguanosine Trihydrate	5.198	0.345	2.336	2.627
5	7-Methyl-8-oxo-7,8-dihydroguanosine Monohydrate	5.337	0.385	2.387	2.703
6	5-aza-7-deaza-2′-deoxyguanosine	4.869	0.306	2.062	2.412
7	2′-Deoxy-6-thioguanosine Monohydrate	5.217	0.388	2.183	2.596
8	2′,3′-*O*- Isopropylidene guanosine Hemihydrate	6.081	0.346	2.507	2.978
9	2′,3′,5′-Tri-*O*-acetylguanosine	6.932	0.464	3.216	3.537
10	Disodium Guanosine 5′-Phosphate Heptahydrate	6.073	0.484	2.366	2.974

Table 2. Molecular vibration method (bx10^{23} Cm^3).

Bond	Force constant (K) m dyne/Å	b_L	b_T	$(b_L+2b_T)/3$
C-N	7.268	0.196	0.074	0.115
C=N	7.607	0.178	0.081	0.113
C-C	6.572	0.144	0.046	0.079
C=C	7.459	0.201	0.120	0.147
C=O	10.264	0.169	0.044	0.086
N-H	5.382	0.093	0.084	0.087
C-H	5.160	0.075	0.063	0.067
N-H (amino)	6.002	0.091	0.081	0.085
N-C′	2.480	0.203	0.128	0.153
C-H (methyl)	4.626	0.076	0.065	0.068
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
P-O	5.698	0.138	0.066	0.090
P=O	5.698	0.127	0.072	0.090
C=S	3.950	0.197	0.058	0.104

Table 3. Molecular polarizabilities of guanosine and its derivatives (α_M x10^{23} Cm^3)

S.No.	Molecule	α_M Lipp	α_M MVM	α_M Le Fevre
1	Guanosine	2.384	2.839 2.833*	2.811
2	Guanosine 3′, 5′-cyclic monophosphate sodium tetrahydrate	2.916	3.471	3.328
3	Disodium deoxyguanosine-5′-phosphate tetrahydrate	2.885	3.541	3.394
4	8-Methylguanosine trihydrate	2.627	3.527	3.288
5	7-Methyl-8-oxo-7, 8-dihydroguanosine monohydrate	2.703	3.689	3.392
6	5-aza-7-deaza-2′-deoxyguanosine	2.412	3.197	2.921
7	2′-deoxy-6-thioguanosine monohydrate	2.596	3.199	2.893
8	2′, 3′-*O*- Isopropylidene guanosine hemihydrate	2.978	3.897	3.543
9	2′, 3′, 5′-Tri-*O*-acetylguanosine	3.537	4.448	4.113
10	Disodium guanosine 5′-phosphate heptahydrate	2.974	3.571	3.428

* Denotes present experimental value.

where n_i is the number of bonds of type i. Since normal coordinate analysis of purines is not attempted the authors have estimated the stretching force constants following the methods of Ladd, Orvillie-Thomas and Cox [26], Decius [27], Susi and Ard [28]. By using force constants data and IR and Raman frequency data [29,30], b_L and b_T values are estimated and presented in Table 2. A comparison of the mean molecular polarizabilities is presented in Table 3 of methods

3. DISCUSSION

The longitudinal and bond polarizability coefficient b_L of C5-C6 bond is 0.144 x 10^{-23} cm^3. It does not coincide either with the alphyl value (=0.099) or the aryl value (=0.224) estimated from Le Fevre for certain chemical bonds. This intermediate value shows that while one of the carbon atoms in the bond has alphyl character, the other possesses aryl nature. This makes the C5-C6 bond a hybrid one. To understand which of the carbon atoms is aryl (C5/C6) with respect to reactivity nature substitutions at these positions needs to be examined. The authors have proved earlier [10,11] that C5 is aryl in nature by estimating the C5-CH_3 bond polarizability coefficient. Since C4 is locked in nine membered rings it does not allow substitution. The higher value (=0.179) of C′-C′ longitudinal bond polarizability coefficient for the C-C bonds in the saturated ribose molecule can be attributed to the presence of electron rich oxygen atom in the C-OH bonds, otherwise the value would have coincided with 0.099 for aliphatic cases. Since the ribose is a saturated ring, the aromatic studies cannot be extended to it. The b_L values of C-N and C=N are 0.196 is 0.178 respectively. These values are less compared to the b_L value (=0.203) of C′-N bond associated with ribose ring. Since nitrogen atoms in the resonance ring affect the ring current or the mobility of the electrons the b_L values are less. The b_L value of C=O is 0.169 x $10^{-23}$$cm^3$ which is less compared to the value of C′-O (=0.185). The lower value of C=O at C6 position is due to the lower electronic charge on C6 due to the effect of the adjacent N1 atom. Since no such nitrogen atom is associated with the sugar ring the b_L values of C′-O are fairly higher.

The above results can be corroborated with the conclusions drawn from X-ray diffraction studies, NMR chemical shifts and quantum chemical calculations.

Shortening of single bonds and elongation of double bonds is a characteristic property of aromaticity. In guanosine and its derivatives considered here, the C-C internuclear distance varies between 1.450 and 1.407 Å and is shorter than the normal value (1.54 Å). In the case of C=C, internuclear distance varies between 1.390 and 1.368 Å and is higher than the normal value (1.34 Å). The internuclear distance values for C-N are in between 1.326 and 1.459 Å, which exhibit alphyl-aryl character of the bond. Since ribose is a saturated ring no resonance character can be associated with the C′-C′ bonds.

The ^{13}C NMR chemical shifts for guanosine are -26.06, -23.82, +10.98, -29.25 and -8.35 for the carbon atoms at 2, 4, 5, 6 and 8 positions respectively. The higher electron density attributed to C5 by Jones et al [31] is based on the theoretical justification. These values compare with the chemical shifts of -23.1, -25.9, +0.4, -15.9 and -19 for the 2, 4, 5, 6 and 8 position respectively in the purine molecules as reported by Pugmire et al [32].

Pullman and Pullman have reported the electron densities at various carbon atoms in guanine. Their values are 0.807; 0.977; 1.176; 0.793 and 0.991 respectively for 2, 4, 5, 6 and 8 positions. From this electron density data of guanine, it is clear that C5 atom exhibits higher electron density. A comparison of electron densities of C6 position of the guanine (purine) with the C4 position of pyrimidine suggests that the electronic

environments of these two atoms in these molecules are the same. These two facts clearly indicate the mixed aliphatic-aromatic character of the corresponding bonds in the bases.

Apart from this, the higher electron density values exhibited by the C4 atom in the purine (guanine) show evidence for C_{ar}-C_{ar} nature of the C4=C5 bond. The bond orders quoted by Pullman and Pullman [33] in guanosine for C4-C5 bond is 0.630 and for C5-C6 bond is 0.373. The free valence index value is 0.221 for guanine at C5 position. Pullman has concluded that C8 and C6 are equally susceptible to nucleophilic substitution, Kuchetkov and Budovskii [34] also concluded that the most reactive atoms to nucleophilic substitution are C8 and C6.Thus quantum chemical calculations agree with the bond polarizability conclusions.

From the Table 3, it can be seen that there is good agreement between the mean molecular polarizabilities estimated by the three methods. The closer agreement between the Le Fevre values and the molecular vibration values indicates that a method based on molecular vibration parameters is more sensitive to structural changes.

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