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POLARIZABILITY OF SOME PENICILLIN CLASS OF COMPOUNDS USING EMPIRICAL APPROACH

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Abstract

Antibiotics refers to a substance produced wholly or partly by chemical synthesis which in low concentration inhibits the growth or destroys micro-organisms by intervening in their metabolic processes. The molecular polarizabilities of few penicillin and their derivatives have been calculated using a new empirical approach based on the square of the sum of the atomic hybrid components (ahc), namely $\alpha(\text{ahc}) = 4/N [\sum_A \tau_A]^2 (\text{\AA})^3$, where the summation proceeds over all atoms $A = 1, 2, 3, \dots$, and N is the total number of electrons in the molecule. Common trends and patterns are recognized and discussed. The results have been compared with those calculated by using semi-empirical δ – function model and molecular vibration methods.

Keywords : Atomic hybrid component, δ – function model, Polarizability, Penicillin,

Introduction

Penicillin is a group of antibiotics derived from penicillium fungi including penicillin G, procaine penicillin, benzathine penicillin and penicillin V. Penicillin antibiotics are historically significant because they are the first drugs¹ that were effective against many serious diseases. All penicillins are β -lactum antibiotics and are used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms.

Computational details

1. δ – function model

Lippincott and Stutman² have developed a semi-empirical model. The details of this method are reported elsewhere³⁻⁵. According to this method the parallel component of polarizability $\Sigma_{\parallel p}$ can be obtained as:

$$\sum \alpha_{\parallel p} = \frac{4nA}{a_0} \left[\frac{R^2}{4} + \frac{1}{2C_R^2} \right]^2 \quad \dots (1)$$

The non-bond region electron contribution to parallel component is given by the relation:

$$\sum \alpha_{\parallel p} = \sum_j f_j \alpha_j \quad \dots (2)$$

The perpendicular component of polarizability is given by the relation:

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

for a given molecule. The mean polarizability of the molecule is obtained as α_M by averaging all these quantities as follows.

$$\alpha_M = \frac{1}{3} \left(\sum \alpha_{\parallel p} + \sum \alpha_{\parallel n} + \sum 2\alpha_{\perp} \right) \quad \dots (4)$$

The details of the various parameters and the method of calculating are reported by Lippincott et al² in detail.

2. Molecular Vibration Method

Based on the theory of Kerr effect, the author's school has developed relationships between bond polarizability coefficients and force constant/ mean amplitude of vibrations of the corresponding bond⁶⁻¹¹. The relations are quoted below.

$$b_L - b_T = A \left[(x_1 x_2)^{\frac{1}{2}} \left(\frac{aN}{k-b} \right)^{\frac{2}{3}} \right]^s \quad \dots (5)$$

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

The individual and longitudinal and transverse bond polarizability coefficients b_L and b_T can be estimated by these two relations and averaged to get bond polarizability ellipsoid components. The mean value of the molecule is given by

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

where n_i is the number of bonds of the type i . The force constants are borrowed from the nearest environment¹²⁻¹⁴. The authors estimated the mean amplitudes of vibration from I.R. and Raman frequency data. The force constant (k) of each bond, the individual b_L and b_T values and the average polarizability .

3. Atomic Hybrid Component

A new empirical approach to the calculation of the average molecular polarizability as a square of a sum of atomic hybrid components is presented by Miller & Savchick¹⁵. It requires a few parameters than other methods and has the functional form

$$\alpha_{(ahc)} = \frac{4}{N} \left[\sum_A \tau_A \right]^2 (\text{\AA})^3 \quad \dots (8)$$

where N is the number of electrons in the molecule and ahc refers to the atomic hybrid components τ_A of α for each atom in a particular hybrid configuration. The summation proceeds over all atoms A in the molecule. In the present formulation τ_A does not depend on atoms which are bonded to A , but it does depend on the type of bonding through the hybridization of atomic orbitals on A .

3.1 Rationalization of the Empirical Approach

The functional form of the empirical formula proposed in this investigation can be rationalized, with the variational-perturbation approach proposed by Hylleraas¹⁶ and Hasse¹⁷ and approximated by Hirschfelder, Curtiss and Bird¹⁸ for the calculation of the x component of molecular polarizability;

$$\alpha_{xx} = \frac{4}{Na_0} \left[\overline{(x_1 - \bar{x})^2} - (N-1) \overline{(x_1 - \bar{x})(x_2 - \bar{x})} \right]^2 \quad \dots (9)$$

where N is the number of electrons, \bar{x} is the average position of an electron in the x direction, $\overline{(x_1 - \bar{x})^2}$ is the mean square deviation of an electron from its average position and $\overline{(x_1 - \bar{x})(x_2 - \bar{x})}$ is the average correlation between two electrons in the x direction. The average value of the operator q

$$\bar{q} = \int \psi^* q \psi \, d\tau \quad \dots (10)$$

is calculated with the zeroth-order wave function ψ obtained from perturbation theory. If the term in brackets in eq. 9 is rewritten to include a summation over all electrons $i, j = 1, 2, 3, \dots, V$, then

$$\alpha_{xx} = \frac{4}{Na_0} \left[\sum_{ij} \overline{(x_i - \bar{x}_i)(x_j - \bar{x}_j)} \right]^2 \quad \dots (11)$$

$$= \frac{4}{Na_0} [L_{xx}]^2 \quad \dots (12)$$

The term in brackets in eqs. 11 and 12 reduces to

$$L_{xx} = \sum_{ij} (\bar{x}_i \bar{x}_j) - \left(\sum_i \bar{x}_i \right)^2 \quad \dots (13)$$

For closed-shell systems the zeroth-order wave function may be approximated by an anti-symmetrized product of molecular orbitals ψ_μ , $\mu = 1, 2, 3 \dots$ and spin function η and $\bar{\eta}$ with z components equal to $\pm 1/2$

$$\psi = (N!)^{-1/2} A \{ \psi_1(1) \eta(1) \psi_1(2) \bar{\eta}(2) \dots \} \quad \dots (14)$$

substituting eq.14 in eq.13 yields

$$L_{xx} = -2 \sum_{\mu} \sum_{\nu} \int \psi_{\mu}^* x \psi_{\nu} d\tau \int \psi_{\mu}^* x \psi_{\mu} d\tau + 2 \sum_{\mu} \int \psi_{\mu}^* x^2 \psi_{\mu} d\tau \quad \dots (15)$$

where μ and ν refer to the occupied molecular orbitals. The molecular orbitals are expanded as a linear combination of atomic orbitals χ_{At}

$$\psi_{\mu} = \sum_A \sum_t C_{At\mu} \chi_{At} \quad \dots (16)$$

where t may refer to s, p_x, p_y and p_z atomic orbitals or to hybrid atomic orbitals on atoms $A = 1, 2, 3 \dots$. Substituting eq.16 into eq.15 and using the zero differential overlap approximation yields

$$L_{xx} = \sum_A \sqrt{a_0} \tau_{Axx} \quad \dots (17)$$

where $\sqrt{a_0} \tau_{Axx}$

$$= -2 \sum_B \sum_t \sum_u \sum_v \sum_w \sum_{\mu} \sum_{\nu} C_{At\mu}^* C_{Auv} C_{B\nu\nu}^* C_{Bw\mu} \times \int \chi_{At}^* x \chi_{Au} d\tau \int \chi_{B\nu}^* x \chi_{Bw} d\tau$$

$$+ 2 \sum_{t,u} \sum_{\mu} C_{At\mu}^* C_{Au\mu} \times \int \chi_{At}^* x^2 \chi_{Au} d\tau \quad \dots (18)$$

provides the link between the proposed empirical formula, eq.8 and a molecular orbital model, Atomic orbitals t, u, v and w are centered on atoms A and B in At, Au, Bv and Bw.

It is convenient to assume that ψ_{μ} , $\mu=1,2,3,\dots$ are the localized molecular orbitals studied extensively by England et al¹⁹⁻²⁰. Their orbitals, confined to the region of a chemical bond, are written as a sum of hybrid atomic or π orbitals. For acyclic hydrocarbon two-center localized molecular orbitals are found, whereas for condensed hydrocarbons two-to-four center localized molecular orbitals connected through a set of adjacent atoms are obtained.

Now, the contributions to τ_{Axx} consist of two types of terms: the first eq.18 connects atomic orbitals on a pair of atoms A and B, and the second involved only atomic orbitals on each atoms A. The first term may be viewed as a bond contribution because the coefficients $C_{At\mu}^* C_{Bw\mu}$ and $C_{Au\mu} C_{Bv\mu}^*$ connected through common localized molecular orbitals ψ_{μ} and ψ_{ν} are largest if A and B are adjacent atoms. If these bond contributions, which arise for each hybrid atomic orbital in ψ_{μ} on atom A connecting adjacent atoms, are partitioned between the two atoms A and B, then one has a rationale for the assignment of a unique value of τ_{Axx} for each hybrid atomic state. If eq.18 is written as

$$\begin{aligned} \sqrt{a_0} \tau_{Axx} &= -\frac{1}{2} \sum_B \sum_t \sum_u \sum_v \sum_w P_{AtBw} P_{AuBv}^* \int \chi_{At}^* x \chi_{Au} d\tau \\ &\times \int \chi_{Bv}^* x \chi_{Bw} d\tau \sum_t q_{At} \int \chi_{At}^* x^2 \chi_{At} d\tau \quad \dots (19) \end{aligned}$$

where

$$P_{AtBw} = \sum_{\mu} C_{At\mu}^* C_{Bw\mu} \quad \dots (20)$$

is the bond order for doubly occupied orbitals $q_{At} = P_{AtAv}$. which arises because symmetry requires that $t = u$ in the second term of eq.18, is the electronic charge, then the bond and atomic terms are more obvious. Bond orders are small unless A and B are adjacent atoms.

This approximation ought to work well for covalently bonded systems in which the electron pairs are nearly equally shared by two atoms. For very polar systems, some modification of τ_{Axx} will be required. However, in this investigation, eq.8 reproduces experimental values of average molecular polarizabilities of organic compounds quite well.

To complete the rationalization of eq. 8 the component of polarizability α_{xx} obtained with eq. 9, and similarly α_{yy} and α_{zz} are assumed to be calculated with the xyz coordinate system oriented along the principal axes of the polarization ellipsoid. If the contribution of τ_A along each principal axis is assumed to be given by

$$\tau_{Akk} = \sqrt{3} \cos \gamma_{kk} \tau_A \quad (k = x, y, \text{ or } z) \quad \dots\dots(21)$$

where

$$\sum_k \cos^2 \gamma_{kk} = 1 \quad \dots\dots(22)$$

then the average molecular polarizability

$$\alpha = \frac{1}{3} \sum_k \alpha_{kk} \quad \dots\dots(23)$$

is obtained from

$$\alpha_{kk} = \frac{4}{N} \left[\sum_k \tau_{Akk} \right]^2 \quad \dots\dots(24)$$

by combining eq.12 with eq.17 and 21 for $k = x$ and similarly for $k = y$ and z . The component τ_{Akk} are projections of $\sqrt{3}\tau_A$ onto the principal axes $k = x, y$ and z , or the components of the polarizability

$$\sqrt{\alpha_{kk}} = \cos \gamma_{kk} \sqrt{3\alpha} \quad \dots\dots(25)$$

is the projection of 3α onto the principal axes.

In the case of condensed hydrocarbons, the localized molecular orbitals are delocalized over more than two atoms. The contribution of each atomic hybrid component is still obtained by partitioning the effect term involving A and B over each states of carbon $\tau_C = 1.428$ for one with a C—H bond and $\tau_C = 1.800$ for one in which branched configuration as in graphite. This is the only exception made in the formulation of the average molecular polarizability with parameters τ_A for atoms, A , in their conventional states of hybridization and it is required to achieve agreement between $\alpha(\text{ahc})$ and $\alpha(\text{exp})$.

An alternate approach to that proposed in this investigation, in which τ_A represents atomic hybrid contributions, would be a summation over bond contributions with a formula like eq.8 in eq.18 or eq.19, terms involving orbitals on atoms would be partitioned into pairs of atoms connected by a bond or several atoms encompassed by the localized molecular orbital in the case of condensed hydrocarbons, and τ would be accordingly redefined. The terms connecting pairs of atoms A approach was not explored. It would require a set of parameters τ_A for every pair of atoms with each particular bonding type, and consequently there would be greater number of parameters than required in the present empirical approach.

The van der Waals radii can be correlated to the atomic polarizability

$$\alpha_A = \frac{4}{N_A} (\tau_A)^2 \quad \dots\dots(26)$$

calculated with eq.8 for each atomic hybrid contribution τ_A . Combining eq.26 with the Slater-Krikwood approximation²¹.

$$\alpha_A = \frac{4}{a_0} \left[\frac{\bar{r}_A^2}{3} \right]^2 \quad \dots (27)$$

yields

$$\sqrt{\bar{r}_A^2} = \frac{\sqrt{3}}{2} \sqrt[4]{a_0 \alpha_A} \quad \dots (28)$$

Results and discussion

The calculated values of molecular polarizabilities penicillin and their derivatives are given in **Table 2** along with the values obtained by using Lippincott & Stutman's method and molecular vibration methods. The bond polarizability values are quoted in 10^{-25} cm^3 units. The empirical approach proposed with $\alpha_{(ahc)} = \frac{4}{N} [\sum_A \tau_A]^2 (\text{\AA})^3$ resulted from an attempt to obtain molecular polarizabilities for atoms in various hybrid states. For each atom A, one value of τ_A is used for each hybridization and the number of and type of bonds as well as lone pairs are incorporated in to the hybrid state of each atom determined systematically and given in **Table 1**.

In general there is a good agreement between the polarizability values obtained by different methods. There is a little deviation due to the environmental effect. But for this agreement quote good.

The close agreement between these methods shows that the method proposed in this investigation is competitive with other approaches and shows that structural differences can be predicated by empirical calculations of polarizabilities.

The empirical approach proposed in this investigation appears to have several advantages over other methods like:

- (i) Fewer parameters are required.
- (ii) τ_A does not depend on atoms to which atom A is bounded, but rather bonding is contained implicitly in the choice of atomic hybrid component τ_A .
- (iii) only one component τ_A is needed for each atomic hybrid configuration. For each atom A, one value of τ_A is needed for each type of bond as well as lone pairs are automatically incorporated into a parameter τ_A by the hybrid state of each atom. In the determination of τ_A , for example, from the average polarizability of H_2 , one obtains $(\alpha_{\text{H}}/8)^2 = \tau_{\text{H}} = 0.314 \text{\AA}^{3/2}$ and then from α_{CH_4} , $\tau_{\text{C}} = [\sqrt{10/4\alpha_{\text{C}}} - 4\tau_{\text{H}}] = 1.294 \text{\AA}^{3/2}$, for carbon in the tetrahedral hybrid configuration τ_{C} (tetetete). Then ethylene ($\tau_{\text{C}} = 1.436 \text{\AA}^{3/2}$) and benzene ($\tau_{\text{C}} = 1.428 \text{\AA}^{3/2}$) for the hybrid state C (trtrtr π), finally acetylene yields $\tau_{\text{C}} = 1.393 \text{\AA}^{3/2}$ for C (didi $\pi\pi$).

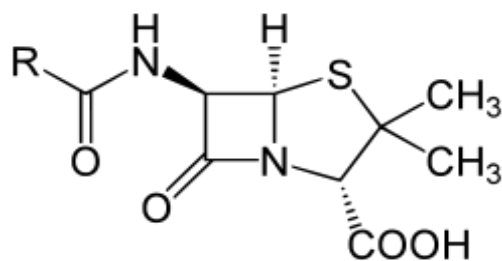


Figure 1. The general structure of penicillin nucleus

Table 1. Atomic Component τ_A for atoms in various hybridization state used in the calculation of the average molecular polarizability

Atom (A)	Hybridization (A)	Group	τ_A ($\text{\AA}^{3/2}$)
H	σ	-H	0.314
C	tetetete	>C<	1.294
C	trtrtr π	>C-	1.428
C	trtrtr π	>C-	1.800
C	didi $\pi \pi$	-C \equiv	1.393
N	te ² tetete	->N:	1.435
N	tr ² trtr π	>N:	1.262
N	trtrtr π^2	>N-	1.220
N	di ² di $\pi \pi$	\equiv N -	1.304
O	te ² te ² tete	>O:	1.290
O	tr ² tr ² tr π	=O:	1.216
O	tr ² trtr π^2	>O:	1.099
S	te ² te ² tete	>S:	3.496
S	tr ² trtr π^2	>S:	2.982
S	tr ² tr ² tr π	=S:	3.967

Table 2. Comparison of the molecular polarizabilities of the pencillin class of compounds
(10^{-25} cm^3)

Compound Name	Lippincott & Stutman's Method	Molecular Vibration Method	Miller Method
Penicillin	525.46	550.64	548.06
Penicillin F	315.37	345.23	318.74
Penicillin G	325.35	347.21	343.31
Penicillin K	364.31	401.53	357.88
Penicillin V	322.28	350.97	350.54
Oxacillin	345.45	373.80	413.55
Ampicillin	342.12	366.77	362.20
Amoxicillin	335.53	374.73	248.07
Nafcillin	407.22	421.11	430.15
Ticarcillin	339.05	357.89	366.57
Piperacillin	481.11	570.53	513.74
Sodium salt of Penicillinic acid	195.82	202.57	238.24
Du (Phenyl-2-Thiazola[3,2-5][1,2,4] triazolyl-6)-2 thiazolocarboxylate-4d', Ethyl(PMTT)	310.97	342.73	337.27

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