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Polarizability in Substituted Oxazoles: A PC-Model Data Analysis

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Abstract: A systematic investigation of various Oxazole derivatives has been subjected to a *Polarized Continuums Model* (PCM) for evaluation of their physico-chemical parameters. The data thus obtained have been used to discuss the effect of substituents on polarizability of the oxazole aromatic ring and its possible dependence on the lipophilicity. In view of their biological activity a quantitative dependence of the physico-chemical parameters of the oxazole derivatives with the π – lipophilicity distributive parameter [8] with respect to substituents on the oxazole aromatic ring, have been attempted. These physico-chemical parameters showed a dependence with respect to their X_1, X_2 and X_3 substituents as H, H, H < H, H, Ph < H, Ph, Ph < Ph, Ph, Ph The variations thus obtained have been discussed in light of substitutions and their effect on the polarizability of the oxazole ring.

Key words: Polarizability, Oxazole, PC Model Data analysis

Introduction

Molecule may visualized as the **M**echanics originating out of **O**rientations and **L**ocation of **E**ntities **C**onnected **U**sing **L**evi-able **E**lectrons. The entities include atoms, groups and molecular fragments. The location of such entities is decided by the affinity of the sites and electro negativity of the incoming substituents. In addition to this respective responses of entities with respect to their neighbors give rise to steric adaptations or conformations called as orientations. These orientations develop a mechanics in the molecule, which is the sole cause for their detection using electromagnetic radiations.

Keeping this idea in mind a systematic investigation of various Oxazole derivatives[1,2] have been subjected to a *Polarized Continuums Model* (PCM) for evaluation of their physico-chemical parameters. The data thus obtained have been used to discuss the effect of substituents on polarizability of the oxazole aromatic ring and its possible dependence on the lipophilicity. Similar such reports are cited in literature[3-5].

Experimental

Serena Software[6] Ver 5.13 based on evaluation of molecular mechanics energy (energy closely related to internal energy of molecule) and its breakup into molecular force fields viz.,

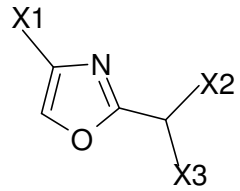
$$E_{MM} = E_{bn} + E_{an} + E_{vdw} + E_{tor} + E_{ch} + E_{misc}$$

The package provides a minimization of E_{MM} over various possible conformations giving rise to the breakup of the force field where Ebn corresponds the bond energy, E_{an} energy of angle, E_{vdw} correspond to Vander Waals forces, Etor torsion, Ech charges and Emisc. Constitute the miscellaneous forces other than mentioned above.

The package is able to produce window compatible output with the help of Quantum Chemistry Program Exchange (QCPE) ver 5.04. The physico-chemical properties calculated by the package include; the dipole moments, Vander Waal forces, molar volume ($^{\circ}$A) and the Z-matrices (Cartesian coordinates) for the hypothetical molecule. Five of these molecules have been synthesized and characterized from our laboratories. The computational out puts thus obtained have been recorded with respect to the substituents in **Table-1**. X1, X2 and X3 are the positions for substitution on the oxazole aromatic ring whereas H, $-CH_3$ (Me), $-C_2H_5$ (Et) and $-C_6H_5$ (Ph) are the substituents. Several such compounds have been reported[7,8] as anti malarial agents.

In view of their biological activity a quantitative dependence of the physico-chemical parameters of the oxazole derivatives with the π – lipophilicity distributive parameter[9] with respect to substituents on the oxazole aromatic ring, have been attempted. The z-matrix obtained after several iterations have been used to express the relative distances in bond lengths with added substituents. The values of the bond lengths are recorded in **Table 3.**

Table 1 Variation in the Physico-chemical properties for substituted Oxazoles as obtained using PC-Model software.



Comp. No.	X1	X2	X3	Physico – Chemical Properties						
				π (a)	Dip. Mom.(b)	Charge –N (c)	Charge –O (d)	Mol. Vol.(e)	vdW (f)	π(Cal.)
1a	H	H	H	0.00	0.893	-0.100	-0.229	104	1.027	0.014
1b	Me	H	H	0.56	0.993	-0.114	-0.242	136	0.114	0.539
1c	Et	H	H	1.02	1.096	-0.122	-0.250	166	1.794	1.032
1d	Ph	H	H	1.96	0.717	-0.124	-0.251	215	5.117	1.932
2a	H	Ph	H	1.96	1.238	-0.124	-0.251	222	2.923	1.968
2b	Me	Ph	H	2.52	1.309	-0.128	-0.255	255	2.862	2.534
2c	Et	Ph	H	2.98	2.044	-0.132	-0.258	286	6.594	2.950
2d	Ph	Ph	H	3.92	1.091	-0.138	-0.264	330	9.532	3.844
3a	H	Ph	Ph	3.92	1.244	-0.138	-0.264	341	26.183	4.015
3b	Me	Ph	Ph	4.48	1.477	-0.134	-0.261	369	40.794	4.525
3c	Et	Ph	Ph	4.94	1.607	-0.136	-0.263	394	9.413	4.943
3d	Ph	Ph	Ph	5.88	1.711	-0.135	-0.262	445	12.182	5.842

π = (a) lipophilicity distributive coefficient, (b) Dipole Moment, (c,d) = partial charges on -N and -O atoms (in esu), (e)= partial molar volume (^{0}A), (f)= Vander Waals force,

Results and Discussion

Table records the magnitudes of physico-chemical constants *viz*., dipole moments, van der Waal forces and the molar volumes. The partial charges (in esu) values for oxygen and nitrogen atoms have also been recorded in their adjacent columns.

A perusal of the values, in general, shows a marked dependence of the physico-chemical parameters on their respective substitutions. Dipole moment value, which is indirectly, related to the molecular des-symmetry of charges show a marked increase with bulkier substituents. These physico-chemical parameters showed dependence with respect to their X_1, X_2 and X_3 substituents as:

H, H, H < H, H, Ph < H, Ph, Ph < Ph, Ph, Ph				
Dip.Moment	1.191	1.238	1.244	1.711
Par.char (N)	0.101	0.1242	0.1382	0.1359
Par.char (O)	0.2291	0.2531	0.2642	0.2621
Me, H, H < Me, H, Ph < Me, Ph, Ph < Ph, Ph, Ph				
Dip. Moment	0.994	1.309	1.477	1.711
Par.char (N)	0.1144	0.1289	0.1346	0.1359
Par.char (O)	0.242	0.2556	0.261	0.2621
Et, H, H < Et, H, Ph < Et, Ph, Ph < Ph, Ph, Ph				
Dip. Moment	1.096	--	1.607	1.711
Par.char (N)	0.1229	0.132	0.1369	0.1359
Par.char (O)	0.250	0.258	0.263	0.2621

This dependence of the physico-chemical parameters with respect to dipole moment values though not very significant on account of their R, R^2 and slope values (**Table 2**, **Section B**), however, the general trend for the variations are almost same.

Table – 2 Variation in the Lipophilicity Distributive parameters and The Dipole Moment values with Dependable parameters with their Slope Values, Intercepts, R and R^2 Values for Binary and Multiple variations

	Y = mX + C			
Correlation in Properties X vs. Y	m X	C Intercept	R	R^2
Section A: Binary Variation				
a vs. b	0.1069 X	1.0057	0.552	0.3047
a vs. c	0.0054 X	0.1117	0.870	0.7709
a vs. d	0.0051 X	0.2398	0.883	0.7791
a vs. e	55.51 X	105.41	1.000	0.9989
b vs. c	0.013 X	0.1101	0.407	0.1664
b vs. d	0.0126 X	0.2377	0.425	0.1809
b vs. e	171.83 X	46.811	0.568	0.3232
Section B : Multiple Variation – Three Parameters				
a vs. b,c,d	0.802 (b) -4.664 (c) 641.4 (d)	-102.0	0.908	0.824
Section C: Multiple Variation – Four Parameters				
a vs. b,c,d,e	-0.169 (b) -37.604 (c) 34.23 (d) 0.0179 (e)	-5.88	1.001	0.999

Table 3 Variation in the inter-dependence of the correlation parameters in the multiple four parameter variation

Model/ Correlation	Parameter	Molar Volume	Dipole Moment	Partial Charge – N (esu)	Partial Charge - O (esu)
Section C: Multiple Variation – Four Parameters	Molar Volume	1.000	-0.317	0.170	0.220
	Dipole Moment	0.317	1.000	0.479	-0.467
a vs. b,c,d,e	Charge – N(esu)	0.170	0.479	1.000	-0.998
	Charge - O (esu)	-0.220	-0.467	-0.998	1.000

To observe the role of these physico-chemical parameters on the biological activities, an attempt has been made to observe the variation in these physico-chemical parameters with respect to the lipophilicity coefficient π^{**} (as reveled by Hansch[9]). The individual variations of these parameters with π - parameter though fail to show any significant dependence (R, R2 and slope values) **Table 2** section- A. Similarly a multi-component variation of these parameters with π - values have been attempted (both with and without molar volumes. The interdependence of these parameters (matrix) **Table 3** show a poor relationship in all the values except the molar volumes. The two multi-component equations express that the dipole moment and the molar volumes are the significant parameters in affecting the lipophilicity values and thus in turn the biological activities.

The effect of the X_1, X2 substituents as polarizability properties of the ring may also be observed from the changes in their respective bond-length values of the ring structure. **Table 4** records the relative variation in the bond – length values as evaluated using the Cartesian coordinates for different molecules.

Table 4 The bond length values for the X1, X2 and X3 Positions as obtained from the Z-matrix parameters developed by PC-Model

Comp. No.	X1	X2	X3	Bond Lengths (in ^{0}A)					
				N-C	C-C	C-O	O-C	C-N	C-C
1a	H	H	H	1.261	1.331	1.388	1.401	1.335	1.098
1b	Me	H	H	1.271	1.334	1.364	1.382	1.329	1.496
1c	Et	H	H	1.261	1.331	1.384	1.401	1.336	1.499
1d	Ph	H	H	1.73	1.336	1.363	1.382	1.341	1.484
2a	H	Ph	H	1.272	1.334	1.364	1.381	1.334	1.099
2b	Me	Ph	H	1.271	1.334	1.365	1.382	1.334	1.496
2c	Et	Ph	H	1.273	1.345	1.366	1371	1.331	1.506
2d	Ph	Ph	H	1.274	1.335	1.363	1.381	1.344	1.484
3a	H	Ph	Ph	1.272	1.334	1.364	1.381	1.340	1.098
3b	Me	Ph	Ph	1.271	1.333	1.364	1.383	1.344	1.496
3c	Et	Ph	Ph	1.272	1.334	1.364	1.382	1.344	1.500
3d	Ph	Ph	Ph	1.273	1.335	1.363	1.380	1.343	1.484

** π is the lipophilicity coefficient or distributive parameters used for the evaluation of hydro- phobicity values by Hansch [8]

It may be stated that the polarizability of the oxazole ring structure is greatly affected by the substituents in the X_1, X_2 and X_3 positions which is order of $H < CH_3 < C_2H_5 <$ phenyl. The relative influences of X_1, X_2 and X_3 positions have been observed to be $X_1 < X_3 < X_3$. Similar correlations are being attempted for the ir and NMR data for the synthesized compounds.

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