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MOLECULAR CONNECTIVITY OF ORGANOMETALLIC CHELATES AND INCLUSION OF VALENCE DELTA : CORRELATION WITH MOLAR REFRACTION

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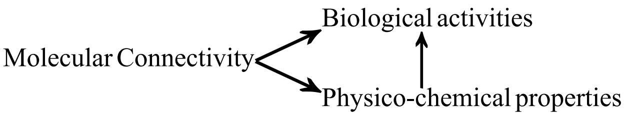
ABSTRACT

Molecular connectivity calculations have been carried out for highly anisotropic chelates of the formulae, R_2MLx type (where R is any alkyl group and L is a highly anisotropic bidentate ligand). Multiple Chi terms ${}^m\chi_t$ for hydrogen suppressed graphs (skeletal structures) and ${}^m\chi_t^v$ (multiple chi terms with the inclusion of valence delta, δ^v instead of vertex valence δ_i) have been correlated to the molar refraction, R_m by the stepwise multiple regression analysis of the first order. These correlations will play an active role in the SAR (Structure Activity Relationships) studies of the chelate molecules and also in finding potential use of bidentate ligands in removing metallic poisons from the human body.

KEYWORDS : Molecular connectivity, molar refraction, organometallics, chelates, valence delta

The light scattering studies on anisotropic ligands suggest that highly anisotropic chelates of the formulae R_2ML_x type can be synthesized by coordinating R_2M^{+n} moieties with anisotropic bidentate ligands, L. Many ligands show biological activity e.g. 8-hydroxyquinoline (oxine) and salicylic acid (Perrin., 1958) show antibacterial action while 2,2'bipyridyl shows marked curariform action during chelation. There are many R_2M^{+n} moieties which retain their cis structure even after co-ordination and act as agonist molecules (Saksena, 1988). Polarizability of these molecules is not only additive but is transferable from one conformation to the other as shown by Laser Rayleigh and Phonon Scattering studies (Brahma et al., 1986) Therefore SAR have been worked out in this paper using the simple concept of molecular connectivity utilizing graph theory .

The relationship (Murray et al., 1976) between molecular connectivity, and physico-chemical properties and biological activities can be shown as follows:



The index, χ is additive and constitutive and related to the shape and size of molecules. The conformation of a molecule provides a specificity with regard to the receptor molecule in the biophase. Distances between the receptor and biologically active molecules can be calculated with the knowledge of polarisability, of the active molecule. Polarisability is directly related to molar refraction, R_m which is easy to dcetermine experimentally. Hence the correlationships of R_m have been developed with the main graph term ${}^1\chi$ and subgraph terms e.g. ${}^m\chi_t$ or ${}^m\chi_t^v$ depending upon the vertex valence, δ^1 and valence delta, δ^v respectively.

Randic' (Randic', 1975) devised an index relating to a topological property of a hydrocarbon, the degree of branching or the connectivity in the molecule. Kier and Hall have discussed the correlation of connectivity and pharmacological action in detail. Efforts have been made to correlate biological activity (Saksena et al.,2009; Frieberg et al., 2005; Murakami et al.,2003, Agarwal et al.,2008; Singh et al., 2010) with calculated physical parameters and compared with measured IC_{50} values. In recent studies (Agarwal et al., 2009; Shaik et al., 2011) topological descriptors for a limited edge values have been used besides physical and biological parameters (Saksena et al. 2009) in correlating biological observed and calculated activities.

EXPERIMENTAL

A series of highly anisotropic organometallic chelates using $R_2Tl(III)$ and $R_2Sn(IV)$ moieties have been synthesized using organometallic substrates and highly anisotropic bidentate ligands tropolonate (trop), 8-hydroxyquinolinate (ox), dibenzoyl methanate (dbzm), acetylacetonate(acac), salicaldehyde (sal), 1, 10-

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phenonthroline(phen) and 2,2'-bipyridyl(bpy).

The purity of the synthesized organometallic chelates has been improved by crystallization from the saturated solution in cyclohexane. Cyclohexane obtained from B.D.H. has been redistilled in a quick-fit vertical column and the fraction distilling between 80-81^{0}C was used for preparing solutions.

Refractive index of fairly dilute solution has been measured on a calibrated Bausch and Lomb Model 33-45-03 series 021 precision refractometer at 25+0.1^{0}C. A He-Ne Laser of 3mW has been used as light source. Temperature has been controlled by circulating water in the outer cell jacket from an NBE type ultrathermostat. Density measurements have been made on a westphal type balance in a temperature controlled room at 25+0.1^{0}C. The uncertainty in refractive index, n and density d is of the order of +0.00001 and 0.1% respectively. Refractive index n2 and d2 of chelates have been derived from the experimental value n and density d for fairly dilute solutions.The following equations have been used which hold good in this concentration range.

For fairly dilute solutions, the following equations hold good,

$$n = n_1 w_1 + n_2 w_2 \qquad (1)$$

or

$$n_2 = \frac{n - n_1 w_1}{w_2}$$

$$d = d_1 w_1 + d_2 w_2 \qquad (2)$$

or

$$d_2 = \frac{d - d_1 w_1}{w_2}$$

and

$$R_m = \frac{n_2^2 - 1}{n_2^2 + 2} \cdot \frac{M_2}{d_2} \qquad (3)$$

here 1 refers to the solvent, 2 refers to the solute and w_2 is weight fraction of solute. In a few cases R_D has been taken as $R_{m'}$ calculated from the bond refraction additivity.

RESULTS AND DISCUSSION

According to Randic' for hydrogen suppressed graphs of hydrocarbons, the connectivity index between two vertices v_i & v_j can be written as,

$$\chi = (\delta_i . \delta_j \, i)^{-1/2}$$

The total molecular connectivity is equal to $\sum\chi$ i.e. sum of all connectivity indices for all distinct paths. The term 'Chi' depends on type of paths, therefore, are evaluated for all subgraphs. The hydrogen suppressed graphs known as skeletal structure for the Organothallium (III) and Tin (IV) chelates respectively. These graphs also labelled with ${}^i\chi$ terms per bond. The chain subgraphs are defined by m vertices and all other by m+1 vertices, where m is the subgraph order. The ${}^m\chi_t$ terms can be defined as,

$$ {}^m\chi_t = \overset{m}{\underset{G}{\Sigma}} \; \overset{m+1}{\underset{i}{\pi}} (\delta_i)^{-1/2} \qquad (5)$$

w ted subgraphs with m edges, the product is over the vertices of subgraph G, and δ_i is the valence of vertex i in hydrogen suppressed graph.

While evaluating ${}^m\chi_t$ terms, all bonds are considered to be single bonds. The hetero atoms, metallic or non-metallic have been retained in the hydrogen suppressed subgraphs and the vertex valencies, δ_i are calculated in the same way as has been done for a carbon atom in hydrocarbons. This is an extension of the original concept given by Randic' in his scheme. In evaluating ${}^1\chi$ for cyclic molecules, 0.5 is subtracted for each ring. This is calculated by spanning trees of a graph for a cyclic molecule. Amidon and Anik used this modification terms in treating hydrocarbon solubility data (Amidon, 1976).

One approach of valence delta δ^v has been introduced with the objective to develop valence values for hetero atoms that are nonempirical in the sense of formal connectivity and consonant with the underlying electronic structures of heteroatoms in molecules. Thus $\delta_i^v = z^v - h_i$ where z^v is the number of valence electrons and hi is the number of hydrogen atoms suppressed. ${}^m\chi_t^v$ terms have been calculated in the same way as ${}^m\chi_t$ terms have been evaluated after labelling vertices by δ^v instead of δ_i. The terms ${}^m\chi_t$ & ${}^m\chi_t^v$ for $R_2T1^{III}L$ type chelates are described in tables 1 and 2 and for $R_2SN^{IV}L_2$ type chelates are described in table 3 and 4

Table 1 : Molar Refraction and ${}^{m}\chi_{t}$ terms for stepwise multiple regression analysis $\left(R_2Tl^{III}L\right)$

S. No.	Chelates	R_m cm^3 mol^{-1}	${}^1\chi$	${}^2\chi$	${}^3\chi_P$	${}^3\chi_C$	${}^4\chi_P$	${}^4\chi_{PC}$	${}^4\chi_{CH}$
*1.	Et_2Tl (trop)	48.354	5.17	6.20	3.83	1.01	2.29	1.07	0.14
*2.	Et_2Tl (ox)	59.993	6.49	5.38	3.67	2.72	1.87	0.95	0.10
*3.	Et_2Tl (dbzm)	91.673	10.67	9.15	6.13	2.66	3.69	1.40	0.00
**4.	Me_2Tl (acac)	38.524	4.45	3.41	1.52	2.16	1.00	0.77	0.00
**5.	Me_2Tl (Sal.)	47.244	3.84	5.42	2.86	2.13	1.74	1.11	0.00

*1. R_m calc. is determined by the feedback of variables.

**2.$R_m$obs. have been taken as RD value obtained from the bond refraction additivity, other R_m values have been evaluated from the experimental data of n.

3.Due to 5 equations & 7 variables; ${}^4\chi_P$, ${}^4\chi_{PC}$ & ${}^4\chi_{CH}$ could not be included. However, it would not affect R_m calc. since r is almost one and s is practically zero.

Table 2 : Molar Refraction and ${}^{m}\chi_{t}^{v}$ terms for stepwise multiple regression analysis $\left(R_2Tl^{III}L\right)$

S. No.	Chelates	R_m cm^3 mol^{-1}	${}^1\chi$	${}^1\chi^v$	${}^2\chi^v$	${}^3\chi_P^v$	${}^3\chi_C^v$
1.	Et_2Tl(trop)	46.354	5.17	5.97	3.50	2.02	1.65
2.	Et_2Tl (ox)	69.993	6.49	6.11	3.38	1.75	0.78
3.	Et_2Tl (dbzm)	91.673	10.67	8.66	4.41	2.38	0.67
4.	Me_2T1 (acac)	38.524	4.45	3.94	2.58	1.18	0.80
5.	Me_2T1 (sal)	47.244	3.84	4.15	2.53	0.95	0.76

1. Regression upto $3\chi_C^V$ is not done due to short of equivalent equations.
2. Here, trop = tropolonate, $C_7H_5O_2^-$; Ox = Oxinate or 8-hydroxyquinolinate, $C_9H_6NO^-$; dbzm = dibenzoyl methanate, $C_{15}H_{11}O_2^-$; acac = acetylacetonate, $C_5H_7O_2^-$; sal = salicaldehyde ligand, $C_7H_5O_2^-$.

TABLE 3 : Molar Refraction and ${}^{m}\chi_{t}^{v}$ terms for stepwise multiple regression analysis $\left(R_2Sn^{IV}L_2\right)$

S. No.	Chelates	R_m cm^3 mol^{-1}	${}^1\chi$	${}^2\chi$	${}^3\chi_P$	${}^3\chi_C$	${}^3\chi_P$	${}^4\chi_{PC}$	${}^4\chi_{CH}$
**1.	Me_2SnCl_2 (phen)	105.702	7.11	7.05	4.22	2.32	2.56	1.39	0.00
**2.	Me_2SnCl_2 (bpy)	73.170	4.97	5.39	3.31	2.19	1.76	1.38	0.00
**3.	$Et_2T_1(ox)_2$	110.768	11.82	9.96	6.67	3.40	3.97	2.21	0.17
*4.	$Bu_2Sn(trop)_2$	94.120	12.82	9.96	5.86	3.06	3.66	1.74	0.17
*5.	$Bu_2Sn(ox)_2$	125.640	14.75	10.66	6.65	2.95	4.23	1.76	0.17
*6.	$Bu_2Sn(dbz)_2$	201.756	18.32	16.99	10.72	3.99	6.69	2.53	0.00
*7.	$Bu_2Sn(sal.)_2$	114.224	10.95	10.07	6.06	2.37	3.57	1.51	0.00
**8.	n-Oct_2.$Sn(ox)_2$	162.760	18.43	14.37	8.87	3.11	6.32	1.91	0.14
**9.	n-Oct_2.$Sn(dbzm)_2$	179.312	20.68	17.92	11.60	3.18	9.70	2.50	0.00

*1. Rm calc. is determined by the feedback of variables.

**2.Rmobs. has been taken as the RD value obtained from the bond refraction additivity and other Rm values have been evaluated from the experimental data of n.

3.Here, phen = 1,10'-phenonthroline; bpy = 2,2'-bipyridyl.

Table 4: Molar Refraction and $^{m}\chi_{t}^{T}$ terms for stepwise multiple regression analysis $\left(R_2Sn^{IV}L_2\right)$

S. No.	Chelates	R_m cm^3 mol^{-1}	$^1\chi$	$^1\chi^v$	$^2\chi^v$	$^3\chi_P^v$	$^3\chi_C^v$	$^4\chi_P^v$	$^4\chi_C^v$	$^4\chi_{CH}^v$
1.	Me_2SnCl_2 (phen)	105.702	7.11	6.61	3.87	1.71	0.54	0.92	0.33	0.00
2.	Me_2SnCl_2 (bpy)	73.170	4.97	6.19	2.70	1.24	0.79	0.64	0.42	0.00
3.	$Bu_2Sn(trop)_2$	110.768	11.82	8.79	4.36	2.17	1.18	1.30	0.66	0.04
4.	$Bu_2Sn(trop)_2$	94.120	12.82	9.82	6.08	4.29	0.54	0.60	0.20	0.04
5.	$Bu_2Sn(ox)_2$	125.640	14.75	11.40	6.11	3.33	1.34	1.63	0.57	0.05
6.	$Bu_2Sn(dbzm)_2$	201.756	18.32	16.15	8.81	4.40	1.17	1.88	0.33	0.00
7.	$Bu_2Sn(sal.)_2$	114.224	10.95	9.80	5.16	3.05	0.81	1.38	0.29	0.00
8.	n-Oct_2.Sn$(ox)_2$	162.760	18.43	15.36	8.93	5.11	0.83	2.96	0.39	0.04
9.	n-Oct_2.Sn$(dbzm)_2$	179.312	20.68	20.01	12.66	6.22	0.69	3.30	0.33	0.04

TABLE 5 : Best correlations for molar refraction R_m

S. No.	Chelates	Correlations
1.	$R_2Tl^{III}L$	(i) $R_m = 2.8897\,^1\chi + 4.9535\,^2\chi + 0.5757\,^3\chi_p + 8.1746\,^3\chi_c - 9.7690$ n = 5, r = 0.9999, s = 7.6834e-09, P.E. in r=1.0051e-09 (ii) $R_m=2.5816\,^1\chi + 14.0349\,^1\chi^v + 5.8509\,^2\chi^v - 33.2173\,^3\chi^v{}_p - 4.1605$ n=5, r=1.0000, s=-1.6764e-08, P.E. in r= -1.6961e-09
2.	$\left(R_2Sn^{IV}L_2\right)$	(i) $R_m = -2.0316\,^1\chi - 43.1479\,^2\chi + 85.4325\,^3\chi_p + 123.7941\,^3\chi_c + 13.2600\,^4\chi_p - 233.1412\,^4\chi_{PC} - 164.7593\,^4\chi_{CH} + 63.7664$ n=9, r=0.9991, s=1.2475e-03, P.E. in r=1.3222e-04 (ii) $R_m = 27.7133\,^1\chi - 57.0189\,^1\chi^v + 63.7918\,^2\chi^v - 10.08\,^3\chi^v{}_p + 48.0965\,^3\chi_C{}^v + 11.4387\,^4\chi_P{}^v + 76.5988\,^4\chi_C{}^v - 2204.95\,^4\chi^v{}_{CH} - 5.8872$ n=9, r=1.0000, s=5.6159e-07, P.E. in r=-4.2088e-08

TABLE 6 : Molecular Connectivity increment in the formation of a structure of Chelate/molecule

S. No.	Molecules	$^1\chi$	$^1\chi_S + n\,^1\chi_L$	$\Delta\chi = \,^1\chi_C - \left(^1\chi_S + n\,^1\chi_L\right)$
		$^1\chi_L$		
1.	Tropolone	3.80		
2.	8-hydroxyquinoline	4.38		
3.	Dibenzoylmethane	7.73		
4.	Salicaldehyde	4.05		
		$^1\chi_S$		
5.	Et_2SnCl_2	3.12		
6.	Bu_2SnCl_2	5.12		
7.	n-Oct_2SnCl_2	7.91		
8.	Et_2TlCl	3.12		
		$^1\chi_C$		
9.	$Et_2Sn(ox)_2$	11.82	11.88	–0.06
10.	$Bu_2Sn(ox)_2$	14.75	13.88	–0.11

(cont.)

11.	n-Oct$_2$Sn(ox)$_2$	18.43	16.67	+1.96
12.	Bu$_2$Sn(dbzm)$_2$	18.32	20.58	–2.26
13.	n-Oct$_2$Sn(dbzm)$_2$	20.68	23.37	–2.69
14.	Bu$_2$Sn(trop)$_2$	12.82	12.72	+0.08
15.	Bu$_2$Sn(sal)$_2$	10.5	13.22	+2.27
16.	Et$_2$Tl (trop)	6.17	6.92	–0.75
17.	Et$_2$Tl(ox)	6.49	7.50	–1.01
18.	Et$_2$Tl (dbzm)	10.67	10.85	–0.18

where s = substrates, L = ligands, C = chelates; = connectivity increment in main graph.
Similarly calculations can be made for (phen) & (bpy) derivatives.

whereas the molecular connectivity increments are described in the table 6.

Stepwise multiple regression analysis has been carried out on molar refraction R_m and $^m\chi_t$ or $^m\chi_t^v$ terms. Best correlations have been described in the table 5.

CONCLUSION

In the evaluation of molecular connectivity indices, known rigid planar structures have been taken into consideration i.e. two dimensional concept of structure rather than a conformation. It appears that molar refraction depends more on subgraph terms than on $^1\chi$ i.e. main graph terms. Inclusion of valence delta, δ^v improves t23he quality of a correlation as is demonstrated in table 5. Even this concept can be improved if the valence delta for a hetero atom; δ_N^v, δ^v_{Tl} and δ^v_{Sn} is also included as an additional variable in the regression analysis. Randic' has slightly improved $^1\chi^V$ calculations by including bond order in summing up bond connectivity terms, C_k values.

The molar refraction is proportional to the electronic polarisability α_E of a molecule which is directly related to the intermolecular forces taking part in drug-receptor interactions (Norrington et al., 1975). It can be safely presumed that molecular connectivity is additive and constitutive in nature as the molar refraction. SAR studies on chelates have a bright future in the removal of heavy metals from the human body by selectively choosing anisotropic ligands as demonstrated by the above studies.

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