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Quantitative Structure- Activity Relationship (QSAR) study on Transport and Extraction of Ions Using Biologically Significant Anthraquinone Derived Ionophores

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ABSTRACT

The interaction of metal cations with specific organic molecules (ionophores) in liquid-liquid extraction and bulk liquid membrane transport is widely used in industry and has biological importance. The present study is the first report of quantitative structure- activity relationship (QSAR) on transport and extraction of Li^+, K^+, Ca^{2+} and Mg^{2+} through ionophores derived from quinone family. The quinone stucture is common in numerous natural products that are associated with antitumor, antibacterial, antimalarial, antifungal activities. Biomodeling of naturally occuring quinones may led to synthetic quinones synthesis that can be tested for potential antimicrobial activity against microbes of medical importance[1].The ions used in the study are biologically important metal ion pairs. A pool of graph theoretical descriptors were calculated and correlations with transport and extraction potential of the ionophores were investigated using correlation analysis. Various statistical parameters (Se, R^2, R^2A and F) were calculated and are used for proposing most appropriate model. The correlation of QSAR with experimental data will be a promising way in molecular designing and tailoring of better ionophores derived from quinone family and helps to predict the selectivity and specificity for metal ions under study.

Keywords: Transport of ions, QSAR, graph theoretical descriptors, correlation analysis, extraction of ions.

INTRODUCTION

Ionophores are the molecules which form stable lipophilic complexes with biologically important metal ions such as Na^+, K^+, Ca^{2+}, Mg^{2+} etc. and the resulting complex possess hydrophobic exterior and hydrophilic interior and thus are able to transport them into lipohilic phases across natural or artificial membranes. The metal ion and ionophore interaction results

into the formation of complex (supermolecule) which led to transport of metal ion through liquid membranes. Supramolecular species are characterized as thermodynamically less stable, kinetically more labile and dynamically more flexible than simple molecules for performing the task of extraction & transport of ions. The search for the most efficient ionophores for selective binding of a given metal is essentially empirical which can be achieved by experimentation. Moreover, the methods based on QSAR play significant role in theoretical design of ionophores with desired characteristics. By varying the molecular topology, desired extraction and transport activities can be attained with respect to metal ions of interest.

The exhaustive[2]-[6] investigations carried out in our laboratories have indicated the structural dependence of transport and extraction of ions through ionophores. The extraction and carrier ability is dependent on flexibility, chain length, redox states etc.

The topological indices are the numbers associated with molecular structure for the purpose of allowing quantitative structure – activity – property – toxicity relationships. A plethora of topological indices are reported in the literature [7]. The goal of this work is to correlate the extraction and transport potential with topological indices and molecular descriptors of a series of seven ionophores derived from anthraquinone that will help to explore the complexation, extraction and transport ability of ionophores. The methodology used is the correlation analysis employing the method of least square [7].

Thus, it can help in monitoring the selectivity and specificity of other ionophores derived from quinone as the study has taken an account of such class of ionophores.

EXPERIMENTAL SECTION

The ionophores V_1 -V_7 have been synthesized using the methodology reported by Echegoyen. Table 1 contains the list of seven ionophores. The ionophore V_1 was synthesized when diethyleneglycol mono ethyl ether (1.62mL, 1.2 mol) in tetrahydrofuran (10 mL) was added to a vigorously stirred suspension of sodium hydride (60% oil dispersion, 0.29g, 7.25 mmol) and the mixture was refluxed for 30 minutes. Then a solution of 1-chloro anthraquinone (2.42g, 1mol) in tetrahydrofuran was added to it and refluxed for 10 h under nitrogen atmosphere with stirring at 80°C. The reaction mixture was then allowed to cool, concentrated and the residue was dissolved in dichloromethane and then washed with water (twice) and finally with brine. The organic phase was separated and dried over magnesium sulphate, filtered and concentrated. The final product (V_1) was separated by column chromatography (silica gel, 2%, methanol/ dichloromethane) followed by recrystallization initially with dichloromethane/hexane and then with ethanol and characterized by m.p., TLC and spectral analysis.

In a similar way ionophores V_2-V_7 have been prepared using mono chloro and dicholoro anthraquinone and glycols of different chain length and end groups.

A pool of 125 topological indices was calculated using DRAGON software. Table 2 contains symbol of descriptors with their name. The structural normalization was carried out using Hyper Chem Software. Out of the pool of these topological indices, variable selection for multiple regression analysis was made with the help of NCSS (Number Cruncher Statistical System)

software. Finally the statistically most significant models were derived using DATA ANALYSIS, PASS (Power and Sample Analysis) and ORIGIN-50 softwares.

RESULTS AND DISCUSSION

The topological indices for V_1 -V_7 were calculated accessing DRAGON software. The variable selection for multiple regression analysis is presented in the Table 3. Three topological indices were employed for modeling the transport and extraction of the ions used (Li^+, K^+, Ca^{2+} and Mg^{2+}). Regression parameters and quality of correlation of transport & extraction of ions by ionophores is presented in Table 4 and Table 5 respectively. A perusal of Table 4 shows that in all the cases better R^2 values are obtained when three topological indices are used for modeling the transport of each of the ions through the ionophore. In case of Li^+ and K^+ fairly good models are obtained. In both the cases $R^2 = 0.42$ indicating that the ionophores are equally good for the transport of Li^+ and K^+. However, a detailed regression analysis has indicated that only one-variable model containing 0χ (Randic connectivity index-zero Order, descriptor that covers information about the number of atoms and therefore size of the molecule) as the correlating parameter is statistically allowed. In case of two and three -variable models, the coefficients of the two correlation parameters were smaller than their respective standard deviation. Since models are not allowed statistically[7]-[12], it is worth mentioning that the transport of Mg^{2+} though slightly better than Li^+ and K^+ is also fairly good then we can only use one-variable i.e. Xu (Xu index, descriptor that indicates the effect of size of molecule and side arms) for modeling its transport behavior.

Excellent results are obtained in case of Ca^{2+}. The one-variable model containing 0χ as the correlating parameter yields the following regression expression:

$$T_{Ca2+} = 36.7275 + 4.5752(\pm 2.0490)0\chi$$

N=7, R= 0.7066, R^2A= 0.3991, F=4.9858

Successive regression has indicated that the better results are obtained when W (Wiener index, topological index accounting for size, shape and side arms in the molecular structure) and J (Balaban distance connectivity index, descriptor that accounts for the shape of the molecule) indices are used in correlation analysis. The regression equation obtained is shown as below:

$$T_{Ca2+} = -408.1893 + 0.0131(\pm 0.0036)W + 293.7099(1 \pm 124.7845)J$$

N=7, R= 0.8752, R^2A= 0.6491, F=6.5507

Finally, excellent results are obtained using ZM_1 (First Zagreb index M1, descriptor related to molecular side arms), ZM_2 (Second Zagreb index M2, descriptor related to molecular side arms) and J as the correlating parameters.

$$T_{Ca2+} = -435.6547 + 14.0605(\pm 4.2307)ZM_1 - 12.2792(\pm 3.9767)ZM_2 + 369.2036(\pm 101.0684)J$$

N=7, R= 0.9506, R^2A= 0.8073, F=9.3862

Extraction potential

On the basis of value of R^2=0.9934,0.7725,0.9784,0.5574 for Li^+, K^+, Ca^2 and Mg^{2+} respectively shown in Table 5, it is clear that the extraction potential of the ionophores(V_1-V_7) is good for Li^+, K^+, Ca^2 except that for Mg^{2+} ion. The results show that ionophores are good for the extraction of Li^+ and Ca^{2+}, moreover slightly better for the extraction of Li^+ than Ca^{2+}. However, in all the three types of regressions (mono-, bi- and tri- parameters) excellent statistics is obtained while good extraction in case of Li^+ is not proved by one-variable model by ionophores.

Extraction of Li^+

As one-variable regression is not possible. So, in case of two-variable model, employing 0χ and ZM_1 as the correlating parameters, very good statistics is obtained:

$$E_{Li^+} = 88.9916 - 2.4836(\pm 0.5132)ZM_1 + 14.5727(\pm 2.8429)0\chi$$

N=7, R= 0.9363, R^2A= 0.8152, F=14.2377

Excellent results are obtained in tri-parametric model only when ZM_2 is added to the above model:

$$E_{Li^+} = 41.4732 - 11.8117(\pm 1.2931)ZM_1 + 6.5582(\pm 0.9039)ZM_2 + 28.4817(\pm 2.0631)0\chi$$

N=7, R= 0.9967, R^2A= 0.9867, F=149.5699

Extraction of K^+

A perusal of Table 5 shows that in this case better one-variable regression is possible. However, statistics is not that much good. Very good results are obtained when two-variables viz ZM_1 and 0χ are used for the extraction of K^+ by the ionophores:

$$E_{K^+} = 71.72.15 - 2.8055(\pm 1.2540)ZM_1 + 17.5901(\pm 6.9460)0\chi$$

N=7, R= 0.8379, R^2A= 0.5531, F= 4.7126

Finally, slightly better results are obtained when W is added to the above model:

$$E_{K^+} = 83.6353 - 0.0120(\pm 0.0157)W - 3.0064(\pm 1.9113)ZM_2 - 11.8206(\pm 32.3790)Xu + 39.6747(\pm 46.1030)0\chi$$

N=7, R= 0.8869, R^2A= 0.3601, F= 1.8441

Since coefficients of W and Xu are smaller than their standard deviation, this model is not allowed statistically.

Extraction of Ca^{2+}

The data displayed in Table 5 shows that the ionophores used are best for the extraction of Ca^{2+}. Excellent statistics is obtained even in one-variable model in that Xu is used for modeling:

$$E_{Ca2+} = 8.9224 + 2.7287(\pm 0.5882)Xu$$

N=7, R= 0.9008, R^2A= 0.7738, F= 21.5210

When a parameter ZM_1 is added to the above model there is tremendous improvement in the statistics such that now R^2 is increased from 0.8115 to 0.9632:

$$E_{Ca2+} = 161.5015 + 27.8624(\pm 5.7515)Xu + 54.3554(\pm 32.3082)J - 29.7050(\pm 6.7078)0\chi$$

N=7, R= 0.9892, R^2A= 0.9568, F= 45.3534

Extraction of Mg^{2+}

Comparison of extraction potential of Mg^{2+} with other ions shows that the ionophores used are least interacting with Mg^{2+}. Fairly good model is obtained when 0χ and ZM_1 are used as the correlating parameters. No improvement in the statistics is resulted in three-variable modeling.

From this, it is observed that in the transport and extraction process, the topological indices found appropriate for modeling are: Xu, 0χ, ZM_1, ZM_2, W and J.(Table 1) Out of these indices, W is the first and the foremost index accounting for size, shape and side arms in the molecular structure of the ionophores used. The regression expression with positive coefficient of W indicates that size, shape and side arms are favorable for the transport as well as extraction of ions under study. The parameter 0χ is the Randic's connectivity index of zero order. It covers information about the number of atoms and therefore size of the ionophore. The Balaban J index is the extended connectivity index and thus accounts for the effect of side arms on the transport and extraction by the ionophore.

Like Balaban J index, Xu index is also a highly discriminatory molecular descriptor. It accounts for molecular size and side arms like W and 0χ indices. Therefore, increase in Xu indicates the effect due to increase in size and side arms of ionophores for transport and extraction of ions through them. Finally, the two Zagreb indices ZM_1 and ZM_2 used are related to molecular side arms. Both are closely related to 0χ and 1χ (Randic connectivity index -first order, descriptor that covers information about the number of atoms and therefore size of the molecule) respectively.

It is clear that the side arm in the ionophore is the most important feature influencing their transport and extraction ability and hence the most important indices for this are Xu, 0χ and ZM_1. It is worthy to mention that the general structure of the ionophores used is as below:

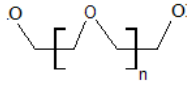

Fig.1

and that the structural moiety responsible for their extraction and transport behavior is

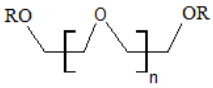

Fig.2

CONCLUSION

It is reported that with increase in the chain length [13]of the ionophore, the transport potential likewise increases shown in Fig.3 & 4. The increase in n (shown in Fig.1 & 2) increases the transport ability due to growth of flexibility. Also from the QSAR study, it is clear that those ionophores are more favorable for transport process for which there is increase in the magnitude of Xu, 0χ and ZM_1. Hence, the transport ability can be monitored while designing and synthesizing new ionophores on the basis of calculated values of Xu, 0χ and ZM_1.

Table 6 shows the values of Xu, 0χ and ZM_1 for D1 as 23.836, 17.485 and 124 respectively that indicates that the hypothetical ionophore D1 will not show the ability as a good carrier for the metal ions taken in account in comparison to the other ionophores under study.

Thus, the correlation of QSAR with experimental data will be a promising way in molecular designing and tailoring of better ionophores derived from quinone family. Thus, one can predict the selectivity and specificity and develop transport and extraction models suitable to be used for the theoretical design of new ionophores. Similar studies with aim to correlate biological activity with structural descriptors have been done.[14]-[17]

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Table 1.Structures of ionophores(V_1 -V_7) and hypothetical ionophore D_1 with their IUPAC name

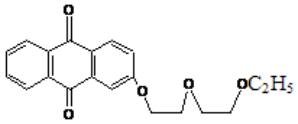
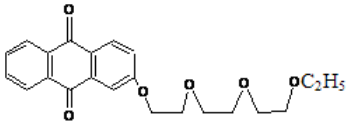
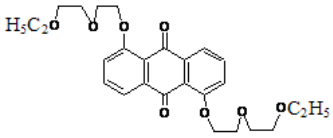
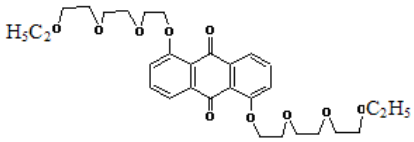
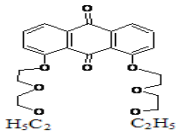
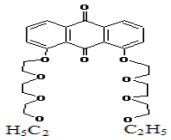
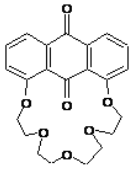
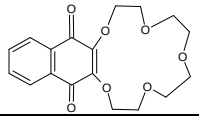
Symbol	Structures of ionophores	IUPAC name
V_1		1-[1-anthraquinonyloxy]-3,6dioxahexane-6-ethane
V_2		1-(1-anthraquinonyloxy)3,6,9trioxanonane-9-ethane
V_3		1, 5 bis (2-(2-(2-ethoxy) ethoxy) ethoxy) anthracene-9-10-dione
V_4		1, 5 bis (2-(2-(2-(2-ethoxy) ethoxy)ethoxy) ethoxy) anthracene -9-10dione
V_5		1,8-bis(2-(2-ethoxyethoxy)ethoxy)anthracene-9,10-dione
V_6		1,8-bis(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)anthracene-9,10-dione
V_7		1,8-oxybis(ethyleneoxyethyleneoxy)athracene-9,10-dione
D_1		2,3,5,6,8,9,11,12-octahydronaphtho[2,3-b][1,4,7,10,13]pentaoxacyclooctadecine-14,19-dione

Table 2. Symbol of descriptors with their name

Symbol	Descriptor
W	Wiener index
ZM_1	First Zagreb index M1
ZM_2	Second Zagreb index M2
Xu	Xu index
J	Balaban distance connectivity index
PW3	Path/ walk3- Randic shape index
PW4	Path/ walk4- Randic shape index
PW5	Path/ walk5- Randic shape index
PJI2	2D petitjean shape index
0χ	Randic connectivity index-zero Order
1χ	Randic connectivity index-I Order
2χ	Randic connectivity index-II Order
3χ	Randic connectivity index-III order
V	Topological valency

Table 3.Variable selection for transport and extraction of ions through ionophores

Parameters used for transport			
Li^+	**K^+**	**Ca^{2+}**	**Mg^{2+}**
0χ	0χ	0χ	Xu
0χ,J	Xu, J	W,J	Xu, 0χ
ZM_2,Xu, 0χ	ZM_1, ZM_2,J	ZM_1, ZM_2,J	W, Xu, 0χ

Parameters used for extraction			
Li^+	**K^+**	**Ca^{2+}**	**Mg^{2+}**
Xu	Xu	Xu	W
ZM_1, 0χ	ZM_1, 0χ	ZM_1, Xu	ZM_1, 0χ
ZM_1, ZM_2, 0χ	W, ZM_2, 0χ	J, 0χ, Xu	ZM_1, ZM_2, 0χ

Table 4. Regression parameters and quality of correlation of transport of ions by ionophores

Ion	Parameters used	Se	R^2	R^2A	F
Li^+	0χ	7.3206	0.2554	0.1065	1.7155
	J, 0χ	7.6605	0.3478	0.0217	1.0665
	ZM_2,Xu, 0χ	8.3831	0.4142	0.1716	0.7070
K^+	0χ	20.8732	0.3367	0.2040	2.5379
	Xu, J	22.5424	0.3811	0.0716	1.2315
	ZM_1, ZM_2,J	25.1368	0.4228	0.1544	0.7326
Ca^{2+}	0χ	21.3766	0.4993	0.3991	4.9858
	W ,J	16.3349	0.7661	0.6492	6.5507
	ZM_1,ZM_2,J	12.1037	0.9037	0.8074	9.3826
Mg^{2+}	Xu	5.2408	0.4170	0.3004	3.5769
	Xu, 0χ	5.5378	0.4793	0.2189	1.8407
	W, Xu, 0χ	6.0905	0.5268	0.0547	1.1134

Table 5. Regression parameters and quality of correlation of extraction of ions by ionophores

Ion	Parameters used	Se	R^2	R^2A	F
Li^+	Xu	10.4464	0.1831	0.0197	1.1204
	ZM_1, 0χ	4.5350	0.8768	0.8152	0.8152
	ZM_1, ZM_2, 0χ	1.2160	0.9934	0.9867	149.5699
K^+	Xu	14.5742	0.3557	0.2268	2.7603
	ZM_1, 0χ	11.0806	0.7021	0.5531	4.7126
	W,ZM_2, 0χ	11.1804	0.7725	0.5450	3.3955
Ca^{2+}	Xu	7.3488	0.8115	0.7738	21.5209
	ZM_1,Xu	3.6294	0.9632	0.9448	52.3649
	Xu, J, 0χ	3.2093	0.9784	0.9569	45.3534
Mg^{2+}	W	13.9388	0.0135	0.1839	0.0682
	ZM_1, 0χ	11.4773	0.4649	0.1973	1.7376
	ZM_1, ZM_2, 0χ	12.0533	0.5574	0.1148	1.2592

Table 6. Comparison of parameters of synthesized ionophores (V_1-V_7) with the hypothetical ionophore (D_1).

Ionophores used	ZM1	Xu	0χ
	First Zagreb indexM1	***Xu index***	***Randic connectivity index-zero Order***
V_1	126	24.498	17.648
V_2	138	27.529	19.769
V_3	164	32.208	24.175
V_4	188	37.458	28.418
V_5	164	32.076	24.175
V_6	188	37.317	28.418
V_7	150	26.799	20.054
D_1	124	23.836	17.485

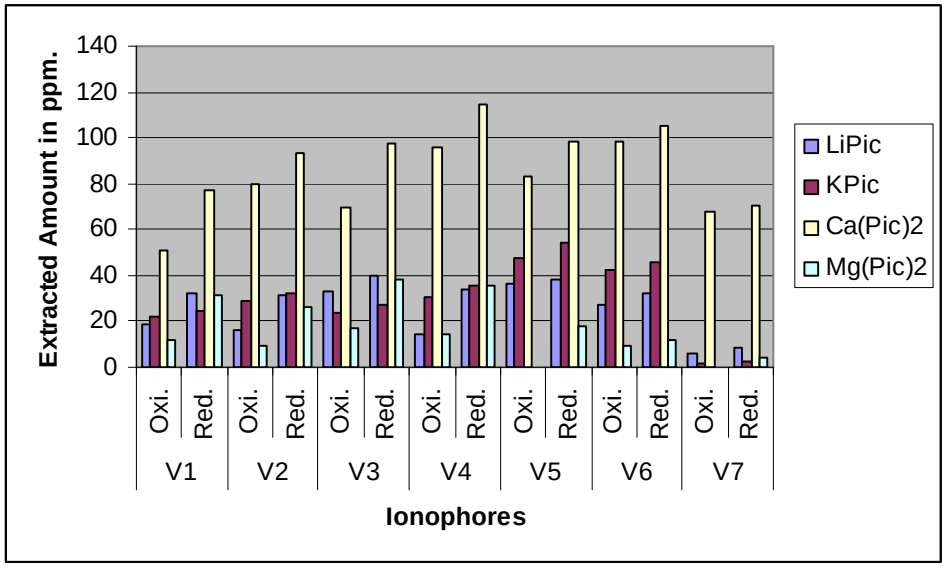

Extracted Amount in ppm.
140
120
100
80
60
40
20
0
Oxi.
Red.
V1
V2
V3
V4
V5
V6
V7
Ionophores
LiPic
KPic
Ca(Pic)2
Mg(Pic)2

Fig. 3

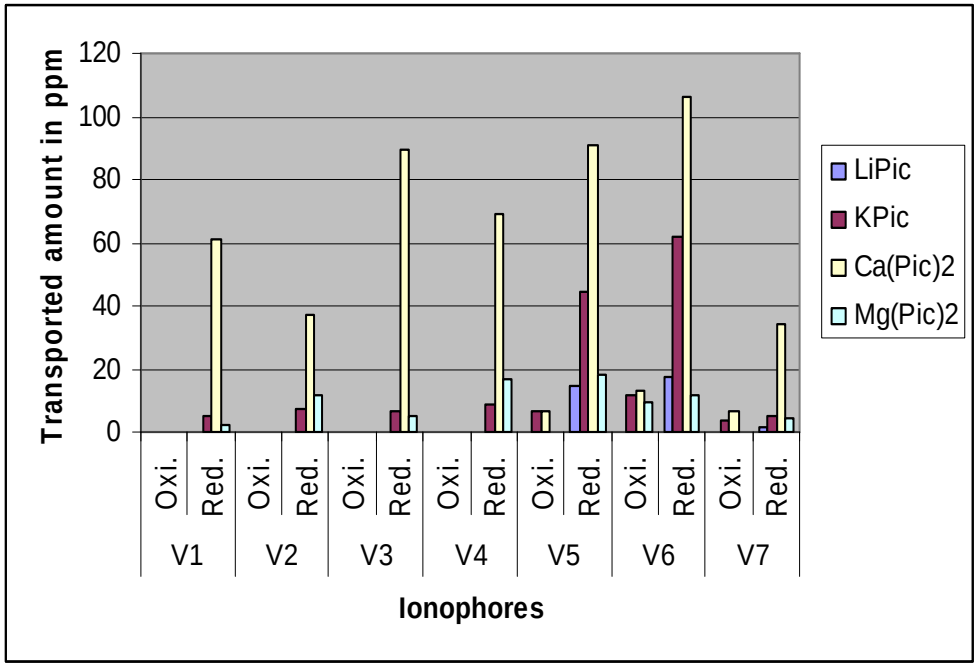

Transported amount in ppm
120
100
80
60
40
20
0
Oxi.
Red.
V1
V2
V3
V4
V5
V6
V7
Ionophores
LiPic
KPic
Ca(Pic)2
Mg(Pic)2

Fig. 4