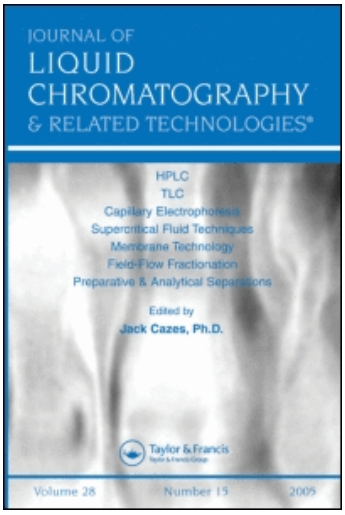

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REVIEW OF RESEARCH ON QUANTITATIVE STRUCTURE-RETENTION RELATIONSHIPS IN THIN-LAYER CHROMATOGRAPHY

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ABSTRACT

A review is given on the quantitative structure-retention relationship (QSRR) in TLC. The establishment of QSRR equations is described, which is based on physico-chemical parameters, non-specific parameters, topological indices, and a combination of physico-chemical parameters. The application of QSRR for prediction of retention, determination of lipophilicity, evaluation of some physico-chemical parameters of chemicals, evaluation of biological activity of compounds, and explanation of separation mechanisms are also reviewed.

INTRODUCTION

Research on the quantitative structure-retention relationship (QSRR) is one of the most important part of the theories of chromatography, and it has become a new investigation branch of chromatographic science. The early investigation of QSRR can be traced back to 1950; Martin[1] suggested that a substituent changes solute retention by a factor dependent on the nature of the substituent (but not on the remaining part of the molecule) and on both the mobile and stationary phases.

After that, with the development of chromatographic techniques, the rules of the retention behavior of solutes, which is correlated to some extent, are further recognized. Research about this field is attracting more and more researchers. Especially in recent years, QSRR studies are making good progress, along with the developments in research of QSAR (quantitative structure activity relationship). Basically, the research methods used in QSRR studies were derived from QSAR studies, but in QSRR studies, the emphasis is placed on chromatographic parameters of structure-property relationships.

In general, the relationship between chromatographic retention data and solute-related structural parameters does not strictly obey the thermodynamic theory. It is based on linear free-energy relationships (LFERs), i.e., it is not necessarily a consequence of thermodynamics. However, the existence of LFERs demonstrate a real connection between some correlated quantities, and the nature of this connection can be identified.

In QSRR studies, two kinds of input data are needed: one is chromatographic retention data for a number of solutes, acting as dependent variables; the other is accurate solute-related parameters, which can reflect the structural features of the solutes being studied, acting as independent variables. Then, the QSRR equations can be obtained using computational techniques.

The goals of QSRR studies are:[2,3]

1. prediction of retention for a new solute;

2. identification of the most informative structure descriptors;

3. explanation of the molecular mechanism of the separation operating in a given chromatographic system;

4. evaluation of complex physico-chemical properties of the compounds;

5. estimation of relative biological activities.

QSRR studies are widely investigated in high-performance liquid chromatography (HPLC), gas chromatography (GC), and thin-layer chromatography (TLC). Here, we put the emphasis on TLC, which has a number of advantages: it is rapid, relatively simple, low cost, and easy to perform; there are a wide choice of adsorbents and developing solvents; and very small amounts of sample are needed. The main parameters used in QSRR studies in TLC are physico-chemical parameters, non-specific parameters, and topological indices. In this paper, the establishment of QSRR equations in TLC is reviewed according to these parameters.

ESTABLISHMENT OF QSRR EQUATIONS

Based on Physico-Chemical Parameters

Physico-chemical parameters are widely used in QSRR studies.[4-6] Among physico-chemical parameters, lipophilicity is one of the most widely used. One of the reasons why lipophilicity can be determined by TLC is that there is a linear relationship between R_m ($R_m=\log(1/R_f-1)$[7]) values and the connection of organic modifier in the mobile phase

$$R_m=R_{m0}+bc$$

where c is the concentration of organic modifier in the mobile phase and b is the slope, which is the decrease of R_m values when the concentration of organic modifier in the mobile phase increases 1%. R_{m0} is the intercept of the TLC equation which represents the extrapolated R_m value, i.e., the theoretical R_m value at 0% organic solvent. This linear relationship has been verified in many studies.[8,9]

Biagi et al.[10] studied the relationship between R_m values and log P values of 5-nitroimidazoles in reversed phase (RP)-TLC. The R_m values, obtained from a 5% silicon oil impregnated thin-layer plate, related with log P values as expressed in the following equation:

$$R_m = -0.364+0.304\log P+0.292\Sigma MR_{1\text{-}2}$$
$$N = 22 \quad r = 0.869 \quad s = 0.345 \quad F = 29.23 \quad p < 0.005$$

(n is the number of compounds being studied; r is the correlation coefficient; s is standard deviation; F is the overall F-test for the regression; p is the level of significance). $\Sigma MR_{1\text{-}2}$ is the molar refractivity summed over the R_1 and R_2 groups. Guerra et al.[11] studied the relationship between log P values and R_m values of xanthone derivatives:

$$\log P = 0.530+1.445R_m$$
$$n = 43 \quad r = 0.837 \quad s = 0.517 \quad F = 96.0 \quad p < 0.005$$

If calculation was made without the log P and R_m values for the compounds bearing a Cl or NH_2 group, which deviate most from linearity, a higher correlation equation was obtained:

$$\text{Log}P = 0.870+1.327R_m$$
$$N = 32 \quad r = 0.907 \quad s = 0.354 \quad F = 139.3 \quad p < 0.005$$

In addition, hydrophobicity (π) also has a high correlation with R_m values:

$$\pi = -0.069+1.456R_m$$
$$n = 22 \quad r = 0.928 \quad s = 0.363 \quad F = 124.6 \quad p < 0.005$$

Pliška et al.[12] first described the theoretical relationship between R_f and P values and the details of the computational procedure. Experimental R_{m0} values for 48 mono- to penta- substituted phenols were determined by Butte et al.[13] using RP-HPTLC, and the R_{m0} values are significantly correlated with log P values.

$$R_{m0} = 1.0988(0.0599)\log P_{oct}-0.2426(0.1335)$$
$$N = 28 \quad r = 0.9634 \quad s = 0.2500 \quad F = 336.09 \quad \alpha < 0.1\%$$

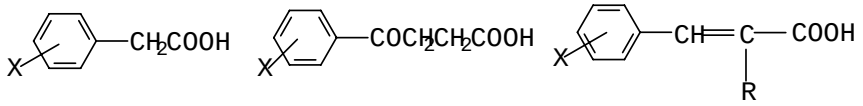
The slope and intercept of this equation are near to 1 and 0, respectively, which supports the hypothesis that the octadecylsilylated (C_{18}) silica phase, as used in HPTLC, has nearly the same property in respect to phenols as does octanol. This verifies that chromatographic methods can be used to measure lipophilicities of chemicals.[14]

Boyce and Milborrow[9] suggested that R_m values obtained in TLC can be used to represent the lipophilicities of chemicals, in order to avoid the difficulties that are involved in measuring the partition coefficients in octanol-water. From above, we can see that there is a real relationship between R_m values and log P values, which exists between the polar mobile phase and the non-polar stationary phase. At the same time, the relationship between the intercept R_{m0} and the slope b in the TLC equation has also been studied by many researchers. Biagi et al.[15-18] found that R_{m0} values were not dependent on the nature of the organic solvent and that it does not make much difference whether the organic solvent is acetone, or methanol, or acetonitrile.

In addition, there is a linear relationship between the intercept (R_{m0}) and the slope (b). Biagi et al. considered that the existence of the linear relationship is another reason why the chromatographic method can be used to determine lipophilicity. He thought that the intercept of the TLC equation can be considered as a measure of the partitioning of the compounds between a polar mobile phase and a non-polar stationary phase,[15] i.e., as the result of the balance between the interactions with the non-polar phase and the interactions with the polar phase, while the slope of the TLC equation indicates the rate at which the solubility of the compound increases in the mobile phase.

Murakami[19] explained the slope in terms of a "displacement model." He emphasized the polar and non-polar interactions in determining the retention behavior of a compound. There are many studies about this aspect.[20,21] For

example, Biagi et al.[17,18] have found that the slopes of TLC equations are related to the reciprocal of the solvent strength ($1/E_0$). Kucher et al.[22] studied the relationship between log P values and the R_m and R_{m0} values of the following acids. They also found that there is also good linear relationship between R_m values and



the slope b in the TLC equation and that R_{m0} and b also have the same relationship.

Szogyi and Cserhati[23] studied the lipophilicity of 17 non-ionic surfactants by RP-TLC. They found the same relationship. Cserhati [24] studied the retention behavior of 3,5-dinitrobenzoic acid esters, using methanol-water mixture as mobile phase and impregnated silica gel, aluminium oxide, and cellulose plates as stationary phases. The relationship between R_m values and the organic modifier concentration in the mobile phase, the relationship between the R_{m0} and π, the relationship between the slope in the TLC equation and π were all studied.

Based on Nonspecific Parameters

There is a relationship between the number of carbon atoms and retention data in GC[25] and HPLC,[26] and a similar relationship was also found in TLC.

Boyce et al.[9] found that there was a linear relationship between the R_m values and the number of carbon atoms in R group of N-n-alkyltritylamines (ph_3CNHR). Janjic et al.[27,28] carried out a series of studies on the relationship between transition metal complexes and the number of carbon atoms in the complexes.

They studied the relationship between the number of carbon atoms and the R_m values of mixed aminocarboxylato cobalt (III) complexes in salting-out TLC on silica gel,[29] polyacrylonitrile,[30] and cellulose.[31] They found the same linear relationship between R_m values and the number of carbon atoms. Zhao et al.[32] presented a theoretical explanation to this phenomenon.

Tyihak et al.[33] studied the same relationship for 2,4-dinitrophenylhydrazones using overpressured layer chromatography (OPLC). The relationship between R_m values and the number of carbon atoms in RP-TLC is a little better than that of normal phase (NP)-TLC. Ekiert et al.[34] found that the R_f values of barbiturate derivatives and the number of carbon atoms also had a linear relationship.

Based on Topological Indices

Topological indices have been used in many fields, such as the studies of correlation between structure and physico-chemical and pharmacological properties,[35-37] especially the relationship between structure and retention behavior,[38-42] and evaluation of the hydrophobicity of organic compounds by chromatographic methods.[43,44]

The calculation methods of molecular connectivity indices were proposed by Kier and Hall.[45] Soler Roca et al.[46] established the relationship between R_f values and molecular connectivity indices of benzodiazepines. Anton-Fos et al.[47] studied the retention behavior of sulfamides in RP-TLC under four different conditions and examined the relationship between R_f values and the connectivity indices. They also studied the relationship between R_f values of substituted anilines[48]and barbiturates[49] and their molecular connectivity indices. In addition, they[50] studied the relationship between the R_m values obtained in NP-TLC for a group of natural phenolic derivatives and their molecular connectivity indices. All of these results indicate that the R_f or R_m values are highly correlated with molecular connectivity indices. Zhao et al.[51] applied molecular connectivity indices to the investigation of retention behavior of 10 amino acids, 11 sulfoethers, 6 thioalcohols, and 22 2,4-dinitrophenylhydrazones in TLC and found that they are well correlated.

Pyka[38,52-60] did a series of studies in applying topological indices to QSRR studies in TLC. Topological indices, such as Gutman, Randic, Wiener indices, and other indices he proposed were used. A new optical index (I_{opt}) was proposed by him,[38,52] which enables distinction between isomers of D and L configuration. Pyka also established a new stereoisomeric topological index (I_{STI}),[56] which enables distinction between stereoisomers with hydroxyl groups in axial and equatorial positions. Using this index, the retention behavior of stereoisomeric menthols and thuyjols have been studied. He[58] also studied the relationship between the R_m values and topological indices of α,β-naphthol, α,β-naphthylamine, propyl and isopropyl oleate, propyl and isopropyl elaidate, 6,7,8-methylquinoline, alkoxyphenols and some polycyclic aromatic hydrocarbons.

Śliwiok et al.[61] studied the relationship between R_f values and topological indices of α- β- γ- and δ-tocopherols and presented the possibility of separating DL-α tocopherol into the individual enantiomers using commercial chiral layers. Bazylak[62] studied the relationship between topological indices and retention data of diethanolamine isomers in four types of RP-TLC. Introducing topological indices to QSRR studies widens the possibility of correlation analysis. Firstly, if the molecular structure is known, topological indices can be obtained without synthesis of the compound; secondly, using topological indices, the molecular

structure can be described by some parameters which have physico-chemical meanings. In addition, the application of computer techniques makes calculations easier. But there is also limitation in the range of application of topological indices. They can be applied as the sole parameter only when they are correlated with other features of molecular structure, such as volume, ring size, carbon chain length, etc. In general, topological indices are combined with other parameters that characterize other properties of the compounds.

Combination of Physico-Chemical Parameters

Wang et al.[63] studied the correlation between the molecular structures of O-ethyl-O-aryl-N-isopropyl phosphoroamidothioates and their retention factors in HPTLC. Four physico-chemical parameters, hydrophobicity (π), electric effect (σ), field effect (F) and steric effect (E_S), were used in the QSRR equations. There is a good agreement between predicted data and experimental data. In another paper, they[64] established a computer-assisted retardation factor predictive system for 16 O-ethyl, O-isopropyl phosphoro(thioureido) thioates in HPTLC. The system is based on three physico-chemical parameters (hydrophobicity π, substituent length L, and substituent maximum width B_5), which have a high correlation to retardation factor (R_f).

APPLICATION OF QSRR STUDIES IN TLC

Prediction of Retention and Separation

All the QSRR equations established above can be used to predict R_f or R_m values of chemicals. Baranowska et al.[65] studied the retention behavior of substituted phenols in RP-TLC and NP-TLC and separated these compounds.

Determination of Lipophilicity

From the examples in Part 2, it can be seen that there is a linear relationship between R_m values and log P. In addition, R_{m0} values also can be used to measure the lipophilicity of chemicals.

Using R_{m0} values, Gocan et al.[66] determined the lipophilicity sequence of some plant growth-stimulating amino esters of ethanolamine, which is in agreement with the sequence determined by their log P values. Kuchar et al.[67] investigated the influence of different stationary phases on changes in lipophilicity of the dialkoxy and phenylalkoxy derivatives through the

relationships between π and the retention data (R_m, log k') in RP-TLC and RP-HPLC. Grunbauer et al.[68] studied the influence of mobile phase composition upon lipophilicity determination in RP-TLC.

Evaluation of Some Physico-Chemical Parameters of Chemicals

Ahmad et al.[69] found that there was a linear relationship between the R_f values of nitroaniline, nitrophenol, and picric acid and their $\log E_{T(30)}$ values. It is possible to predict $\log E_{T(30)}$ values through their R_f values. In addition, pK_a values can be predicted by the R_m values of some compounds. Pyka[57] predicted the pK_a values of substituted phenols by use of biparameteric equations employing R_m values and the topological indexes M or ^0B. Good agreement was obtained between predicted pK_a values and experimental pK_a values.

Evaluation of Biological Activity of Compounds

As early as 1965, Boyce and Milborrow[9] studied the relationship between R_m values of N-n-alkyltritylamines (ph_3CNHR) and their LD_{50} values. It was found that LD_{50} decreased first and then increased with increasing R_m values. There is an R_m value that corresponds to the lowest LD_{50} value. Hansch and Fujita[70] believed that this was due to an increase and decrease in the rate of penetration as the R_m values in a series change progressively and pass through an optimum. The lowest point is the so called "optimum activity point."

Biagi et al.[10] found that there is a quadratic relationship between R_m values and log 1/C for xanthone:

$$\log 1/C = -13.526+13.096R_m-2.712R^2_m$$
$$n = 25 \quad r = 0.848 \quad s = 0.316 \quad f = 28.1 \quad p < 0.005$$

A higher correlated equation was obtained if a compound which deviated most from the equation was omitted:

$$\log 1/C = -14.102+13.567R_m-2.800R^2_m$$
$$n = 24 \quad r = 0.911 \quad s = 0.243 \quad f = 51.3 \quad p < 0.005$$

Pyka[54] studied the relationship among R_m values, topological indices and biological activity (log 1/C). All of the equations he obtained have good correlations. There is a good agreement between predicted log 1/C values and experimental log 1/C values. Most recently, the investigation of structure-activity relationship through the intercept (R_{m0}) and slope b in TLC equations is attracting more and more researchers. Darwish[71] and Forgacs[72] et al. did some research in this area.

Explanation of Separation Mechanism

Cserháti studied the retention behavior of 3,5-dinitrobenzoic acid esters on thin layers prepared from β-cyclodextrin polymer (BCDP). It was found that there was still a linear relationship between Rm values and the concentration of organic modifier in mobile phase, while only the esters with short alkyl chains (methyl and ethyl derivatives) follow the general rule of RP-TLC that their retention decreases with increasing concentration of methanol in the mobile phase. Esters with longer alkyl chains display anomalous retention behavior, their retention increasing with increasing methanol concentration. The authors thought that methanol can enter the cyclodextrin cavity and promote the formation of cyclodextrin-solute-methanol ternary complexes. The stability of the ternary complex increases with increasing concentration of methanol, which results in enhanced retention. But up to now, there is no experimental proof to support this hypothesis. Cserhati et al.[74,75] reported other research which illustrates the high impact of steric interactions on retention.

CONCLUSIONS

QSRR play a vital role in chromatographic research, and the research and application fields of QSRR studies are growing rapidly. TLC is a good method for lipophilicity determination: it is simple and rapid and requires minute amounts of substances that need not necessarily be very pure; it does not require quantitative analysis; the nature of the organic modifier does not affect the measurement of the lipophilicity character, because the R_{m0} value is not affected by the organic modifier; and, most of all, it can avoid the practical difficulties that are involved in direct measurement of log P.

The unique parameter log P plays an important role in describing the relationship between molecular structure and biological activity. How to obtain meaningful log P values that correspond to biomembranes is a challenging problem. We can imagine that if the stationary phase was made from materials similar to biomembranes, log P values obtained in this way will become more valuable and instructive for predicting the biological activity of chemicals. This will make it possible to predict biological activity of chemicals through QSRR equations, which will have a far-reaching influence on molecular design investigation.

Up to now, compounds used in QSRR studies are homologous. Establishing QSRR equations that fit different kinds of compounds requires more effort. This will make QSRR equations have general meaning.

From the viewpoint of application, QSRR equations in TLC are mainly used for retention prediction. Explanation of separation mechanisms remains for further investigation. With the application of different statistical methods, it is possible to select the main retention-effect factors from a number of solute-related factors, which will give convenience for explanation of separation mechanism.

In conclusion, QSRR studies are making a good progress in recent years. We can anticipate that QSRR studies will become more and more important in future studies.

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