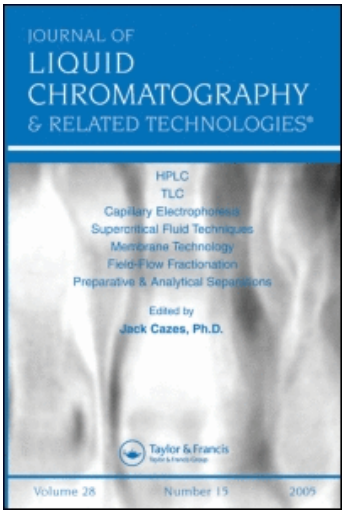

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Automatic Selection of Mobile Phases. VI. Thin-Layer Chromatography on Silica of Libraries of Piperidinones

N. T. Burdzhiev[a]; Ch. E. Palamarev[ab]; M. D. Palamareva[a]
[a] Department of Chemistry, University of Sofia, Sofia, Bulgaria [b] RadioSoft, Edgewater, FL, USA

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Automatic Selection of Mobile Phases. VI. Thin-Layer Chromatography on Silica of Libraries of Piperidinones

N. T. Burdzhiev, Ch. E. Palamarev[1], and M. D. Palamareva
Department of Chemistry, University of Sofia, Sofia, Bulgaria

Abstract: Avoiding trial and error experiments, the LSChrom software incorporating the Snyder theory was applied successfully to automatic selection of mobile phases for thin-layer chromatography (TLC) on silica of two libraries of substituted *trans*-piperidinones comprising amidolactames **1**–**15** and aminolactames **16**–**22**. The procedure takes into account the adsorption properties of the mobile phase (parameter ε), stationary phase, and sample structure expressed by relevant groups. The recommended software value of ε was 0.460 for compounds **1**–**15** and 0.371 for compounds **16**–**22**. Within about 190 measurements on silica using 13 computer selected mobile phases having these values of ε, the retention of any compound fell within a favorable range ($0 < R_F < 1$). Separation of all adjacent components of any library failed in the chromatograms developed once for the majority of the mobile phases. The separation efficiency for compounds **1**–**15** was improved by application of triple development where the mean absolute value of log α increased from 0.16 to 0.23, corresponding to a complete separation.

Keywords: Normal-phase liquid chromatography, Thin-layer chromatography, Silica, N-containing heterocycles, *Trans* isomers, Mobile-phase selection, Snyder theory in LSChrom software

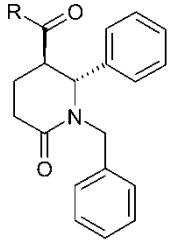
[1]Present address: RadioSoft, 109 West Knapp Avenue, Edgewater, FL 32132, USA.

Address correspondence to M. D. Palamareva, Department of Chemistry, University of Sofia, 1, James Bouchier Avenue, Sofia 1164, Bulgaria. E-mail: mpalamareva@chem.uni-sofia.bg

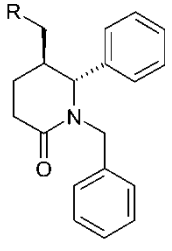
INTRODUCTION

The present series of papers[1–5] specifies the scope and limitation of the well-known Snyder theory[6–8] and the relevant software LSChrom[9–11] for automatic selection of mobile phases for normal-phase liquid chromatography (NPLC). The problem is of great practical importance, since TLC and HPLC on silica or alumina are used daily in the analysis of organic compounds. The procedure used in LSChrom, Version 2[11] includes the approximate calculation of retention by the Snyder theory on the basis of the adsorption properties of the stationary phase (adsorbent), mobile phase, and compound X. The procedure is free from any trial and error experiments prior to the final analysis.

This paper describes the application of LSChrom to predict suitable mobile phases for TLC on silica of two libraries of piperidinones, namely the *trans* compounds **1**–**15** and **16**–**22**. The new point in this paper is the study of the retention and separation of libraries of organic compounds. Trying to rationalize the selection of biologically active compounds, combinatorial chemistry uses preparations of various products in one vessel, the so-called library, where a specific compound reacts with various analogues of another compound. The most important point in this approach is the analysis of the individual compounds of the library (see for instance Ref. 12).



1 - 15



16 - 22

THEORY AND EXPERIMENTAL

LSChrom calculates retention by the following equation

$$R_M = \log k = R_{M(shift)} + \alpha'\left(\sum Q_i^o - \varepsilon \cdot \sum \alpha_i\right) \qquad (1)$$

It contains dimensionless parameters related to the adsorption properties of the three components of the chromatographic system (see details for instance in Ref. [5]).

The adsorbent is characterized by parameters $R_{M(shift)}$ and selectivity, α'.

The mobile phase is characterized by the main parameter strength ε (energy of adsorption) and the tuning parameters: localization, m and

polarity, P'. The greater is the ε value, the weaker is the sample retention. Changes in m modify mobile phase selectivity. An increase in P' decreases retention and vice versa.

The analyzed compound X is characterized by the additive parameters energy of adsorption $S_X = \sum Q_i^o$ and its area under adsorption $A_X = \sum \alpha_i$; the additivity is spread over the relevant parameters Q_i^o and α_i of the functional groups i participating in the structure of X.

Compounds **1**–**15** and **16**–**22** were prepared[13] from two libraries. Their structures and *trans* configurations were determined by ^{1}H-NMR spectra.

The stationary phase for TLC was Polygram sil G/UV$_{254}$ (Macherey-Nagel, Germany) on pre-coated TLC plastic sheets. TLC was performed as described in Ref. [5] with a travelling distance of 8 cm if otherwise is not stated.

The computer program used was LSChrom, Version 2.1, for Windows[11] where the calculation procedure 3.1 was made active.

Tables 1–5 summarize the data obtained in this study.

Table 1 shows the structures of compounds **1**–**22** expressed by the composing structural elements and their adsorption properties. The numbering of the compounds follows from their structures. The mobile phases selected by LSChrom are summarized in Table 2. These mobile phases are composed of two to four solvents. They were prepared from solvents of analytical reagent grade. The experimental values of R_F (a single measurement or arithmetic means of two measurements), using the computer selected mobile phases are shown in Table 3 for compounds **1**–**15** and in Table 4 for compounds **16**–**22**. Table 5 gives data for separation α of the adjacent zones for the cases when the chromatograms were developed from one to three times. The last parameter is calculated from R_F by Eqs. (2) and (3).

$$R_M = \log\left(\frac{1}{R_F} - 1\right) \tag{2}$$

$$\log \alpha = R_{M(m)} - R_{M(n)} \tag{3}$$

where subscripts m and n denote adjacent pair of zones and m has a greater retention than n.

RESULTS AND DISCUSSION

We would like to point out that the studied compounds **1**–**22** were prepared in two libraries from a parent acid by two procedures as shown in Scheme 1.[13] The last step in any procedure involves addition of various secondary amines to a given compound, leading to preparation of the corresponding library in one vessel. Alternatively, any compound was prepared as a single product enabling the study of its individual retention and separation.

Table 1. Structure description by functional groups and adsorption properties of compounds **1–22**

			Number of relevant functional groups in compound																					
Group i^a	Q_i^o	α_i	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Silica: R_M(shift) = −1.76, $\alpha' = 0.57$																								
C =	0.25	1.00	12	12	12	20	12	12	12	12	12	12	12	18	18	18	18	12	12	12	18	18	18	18
Al-CH_2-Al	−0.05	0.90	5	7	17	7	9	10	9	9	9	11	9	9	9	9	9	11	10	10	10	10	10	10
Al-CH_3	5.80	10.50		4					−1		1		2						−1	2				
Al-N (tert)	9.60	10.30				1				1	1	1		1	1	1	1	1	1	1	2	2	2	2
Al-$CONH_2$	3.61	9.00	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2	1	1	2	1	1	1	1
Al-O-CH_3	0.07	1.60							1										1					
Al-OH	5.60	8.50										1												
Al-F	1.54	1.2					–										3							3
Al-CO_2-CH_3	5.27	10.50											1							1				
Ar-F	−0.15	0.4														1							1	
Ar-Cl	−0.2	0.7													1							1		
$\sum Q_i^o$			21.95	22.13	21.35	29.65	21.75	21.70	25.29	27.55	27.62	33.05	36.76	29.05	28.85	28.90	33.67	17.85	21.44	32.91	25.20	25.00	25.05	29.82
$\sum \alpha_i$			37.10	45.30	47.90	57.40	40.70	41.60	48.10	51.20	52.80	61.50	64.70	57.20	57.90	57.60	60.80	42.70	49.20	65.80	58.30	59.00	58.70	61.90
R_F (calc. at $\varepsilon = 0.460$)			0.09	0.91	0.99	0.45	0.52	0.67	0.48	0.23	0.42	0.10	0.01	0.61	0.76	0.71	0.03							
R_F (calc. at $\varepsilon = 0.371$)																		0.81	0.47	0.00	0.35	0.49	0.44	0.01

^{a}Al = Alkyl; Ar = Aryl.

Table 2. Mobile phases used in TLC on silica and the corresponding computer-calculated values of strength, ε, localization, m, and polarity, P'

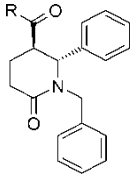
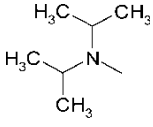
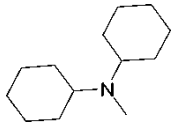
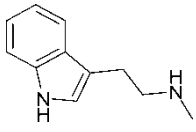
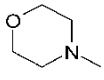
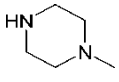
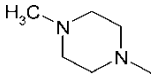
No.	Composition	Vol.%	ε	m	P'
For compounds ***1–15***					
1.	Hexane-isopropanol	69.95 : 30.05	0.460		1.24
2.	Tetrachloromethane-dioxane	36.76 : 63.24	0.460		3.62
3.	Tetrachloromethane-isopropanol	68.01 : 31.99	0.460		2.34
4.	Toluene-dioxane	42.60 : 57.40	0.460		3.78
5.	Toluene-isopropanol	76.24 : 23.76	0.460		2.76
6.	Dichloromethane-tetrahydrofuran	14.46 : 85.54	0.460	0.98	3.87
7.	Toluene-1,2-dichloroethane-tetrahydrofuran-ethyl acetate	41.51 : 10.00 : 15.00 : 33.49	0.460	0.65	3.42
For compounds ***16–22***					
8.	Hexane-ethyl acetate	62.42 : 37.58	0.371	0.59	1.72
9.	Hexane-tert.-buthyl methyl ether	54.03 : 45.97	0.371	0.80	
10.	Hexane-isopropanol	84.45 : 15.55	0.371		0.69
11.	Toluene-ethyl acetate	80.43 : 19.57	0.371	0.51	2.79
12.	Hexane-methylene chloride-tetrahydrofuran	42.91 : 50.00 : 7.09	0.371	0.61	1.88
13.	1,2-Dichloroethane-dioxane-acetone	96.47 : 2.00 : 1.53	0.371		3.55

Automatic Selection of Mobile Phases

The automatic selection of mobile phases performed by LSChrom requires the values for all parameters of Eq. (1), except ε, to be known in advance for the selected adsorbent. In the cases studied, this was accomplished by selection of a TLC silica included in a list of the software having $R_{M(shift)} = -1.76$ and $\alpha' = 0.57$. These values have given good results for the same adsorbent used also in the recent paper of this series.[5] The adsorption properties (the values of S_X and A_X) of compounds **1–22** were calculated by LSChrom on the basis of data input by the user for the structural elements and their number, as shown in Table 1. These data are given since the values of Q_i^o and α_i for some structural elements are not established and such elements have to be replaced by available elements (see details in Refs. [4] and [5]).

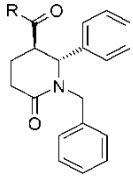
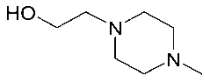
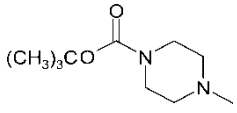
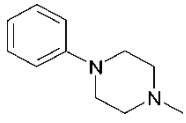
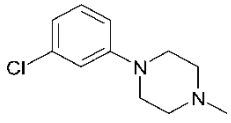
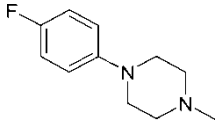
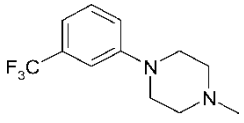
LSChrom, Version 2, calculates retention R_M by Eq. (1) of non-ionic organic compounds as a function of the mobile phase strength ε in the entire range of ε. The software analyzes the retentions of all compounds studied and proposes a recommended value of the mobile phase strength ε ($\varepsilon_{recommended}$) for their separation. The latter value meets two criteria: achievement of a proper retention in the range $0 < R_F < 1$ and best separation of the poorest separated pair of compounds. The selection of concrete mobile phases

Table 3. Experimental R_F values of amidolactams **1–15** with computer selected mobile phases 1–7

Compound			R_F for a given mobile phase[a]						
R	No.		1	2	3[b]	4	5	6	7
		ε	0.46	0.46	0.46	0.46	0.46	0.46	0.46
		m	–	–	–	–	–	0.98	0.65
		P'	1.24	3.62	2.34	3.78	2.76	3.87	3.42
NH_2	**1**		0.30	0.34	0.41	0.38	0.44	0.68	0.08 0.13[c] 0.18[d]
	**2**		0.68	0.78	0.80	0.83	0.75	**0.89**	0.44 0.65[c] 0.78[d]
	**3**		0.81	0.84	0.78	0.97	0.80	0.91	0.63 0.84[c] 0.94[d]
	**4**		0.50	0.59	0.71	**0.68**	**0.69**	**0.89**	0.19 0.33[c] 0.44[d]
	**5**		**0.31**	0.54	0.58	0.61	0.59	0.76	0.15 0.24[c] 0.33[d]
	**6**		0.45	0.66	0.68	***0.73***	***0.69***	***0.84***	0.26 0.41[c] 0.54[d]
	**7**		0.16	0.53	0.37	0.59	0.46	0.72	0.12 0.21[c] 0.28[d]
	**8**		0.02	0.01	0.02	0.03	0.04	0.05	**0.01** ***0.01***[c] 0.01[d]
	**9**		***0.03***	0.06	0.04	0.06	***0.06***	0.11	**0.01** 0.02[c] 0.03[d]

(*continued*)

Table 3. Continued

Compound			R_F for a given mobile phase[a]						
R	No.		1	2	3[b]	4	5	6	7
		ε	0.46	0.46	0.46	0.46	0.46	0.46	0.46
		m	–	–	–	–	–	0.98	0.65
		P'	1.24	3.62	2.34	3.78	2.76	3.87	3.42
	**10**		***0.03***	0.05	0.03	0.08	***0.06***	0.10	**0.01** ***0.01***[c] 0.02[d]
	**11**		*0.43*	**0.69**	0.63	0.75	0.68	***0.84***	0.23 0.35[c] 0.46[d]
	**12**		0.38	**0.69**	0.62	***0.73***	*0.73*	0.86	0.21 0.34[c] 0.45[d]
	**13**		*0.43*	0.72	0.64	0.74	0.76	0.88	0.24 0.39[c] 0.51[d]
	**14**		**0.31**	0.67	0.56	**0.68**	*0.73*	0.85	0.16 0.26[c] 0.38[d]
	**15**		0.42	0.71	0.61	0.71	0.78	0.87	*0.23* 0.36[c] 0.49[d]

[a]The equal values of R_F for a concrete mobile phase are given in Bold, Bold/Italic or Italic.

[b]Developing distance 18 cm.

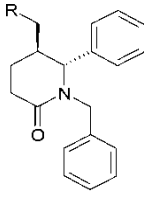
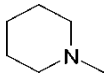
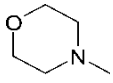
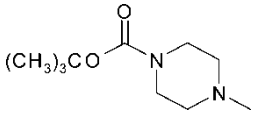
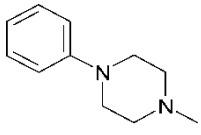
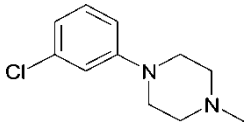
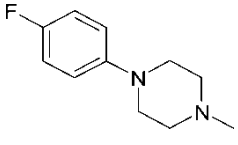
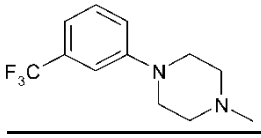
[c]Developed twice.

[d]Developed three times.

having the recommended value of ε is the most difficult calculation problem that is successfully solved. Thus, LSChrom lists numerous mobile phases with the desired ε and different values of m and P'.

For silica, LSChrom calculated $\varepsilon_{recommended}$ of 0.460 for compounds **1**–**15** (see Figure 1) and of 0.371 for compounds **16**–**22**. Figure 1 illustrates

Table 4. Experimental R_F values of aminolactams 16–22 with computer selected mobile phases 8–13

Compound			R_F for a given mobile phase[a]					
R	No.		8	9	10	11	12	13
		ε	0.371	0.371	0.371	0.371	0.371	0.371
		m	0.59	0.80	–	0.51	0.61	–
		P'	1.72	–	0.69	2.79	1.88	3.55
	**16**		0.02 0.04[b] 0.06[c]	0.11	0.26	0.06	**0.15**	0.03
	**17**		0.06 0.12[b] 0.16[c]	0.04	0.36	0.04	0.09	0.05
	**18**		0.13 0.21[b] 0.27[c]	**0.08**	0.53	0.08	0.13	**0.07**
	**19**		0.14 0.24[b] 0.30[c]	0.10	0.57	0.11	**0.15**	**0.07**
	**20**		0.16 0.25[b] 0.34[c]	0.09	0.59	**0.14**	0.21	0.11
	**21**		0.11 0.19[b] 0.24[c]	0.07	0.58	0.09	0.14	0.06
	**22**		0.18 0.27[b] 0.36[c]	**0.08**	0.61	**0.14**	0.23	0.10

[a]The equal values of R_F for a concrete mobile phase are given in Bold.
[b]Developed twice.
[c]Developed three times.

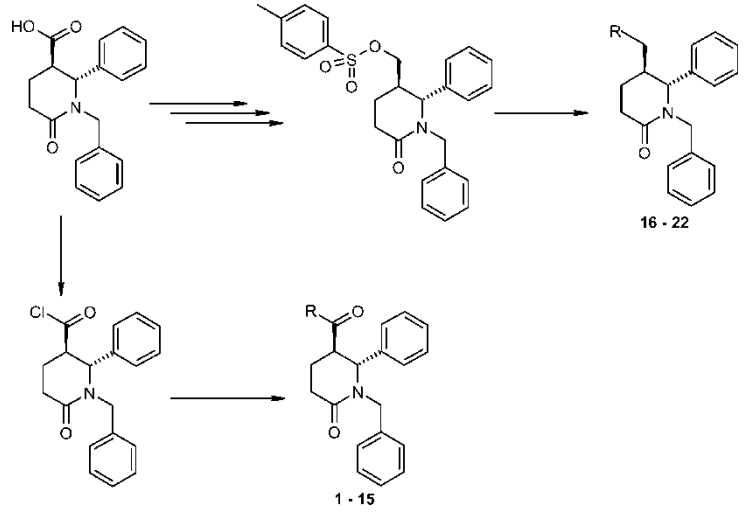
Table 5. Separation log α for compounds **1**–**22** in concrete mobile phases

Compound pair m/n	Developed once	Developed twice	Developed three times
Log α for amidolactams **1**–**15** in mobile phase 7			
8–**10**	0.00	0.00	0.31
10–**9**	0.00	0.31	0.18
9–**1**	0.93	0.86	0.85
1–**7**	0.20	0.25	0.25
7–**5**	0.11	0.07	0.10
5–**14**	0.03	0.05	0.09
14–**4**	0.09	0.15	0.11
4–**12**	0.05	0.02	0.02
12–**11**	0.05	0.02	0.02
11–**15**	0.00	0.02	0.05
15–**13**	0.02	0.06	0.03
13–**6**	0.05	0.04	0.05
6–**2**	0.35	0.43	0.48
2–**3**	0.34	0.45	0.65
log α	0.16	0.19	0.23
Log α for aminolactams **16**–**22** in mobile phase 8			
16–**17**	0.50	0.51	0.47
17–**21**	0.29	0.24	0.22
21–**18**	0.08	0.05	0.07
18–**19**	0.04	0.07	0.06
19–**20**	0.07	0.02	0.08
20–**22**	0.06	0.05	0.04
log α	0.17	0.16	0.16

the mode of LSChrom, where $\varepsilon_{recommended}$ was calculated for the first library. The software suggested numerous mobile phases having these values of ε. We arbitrarily selected thirteen of them (see Table 2) for experimental validation. These mobile phases have the recommended values of ε and different values of m and P'. Mobile phases 1–13 are composed of two to four solvents having different localization m being weak (in the case of hexane, dichloromethane, tetrachloromethane, 1,2-dichloroethane, and toluene) or strong (in the case of ethyl acetate, acetone, tert.-butylmethyl ether, tetrahydrofuran, dioxane, and isopropanol).

TLC with the Automatically Selected Mobile Phases: Retention and Separation of the Adjacent Zones

To check the theoretical prediction of $\varepsilon_{recommended}$ for silica and the specific mobile phases selected, we performed TLC of both libraries of compounds (**1**–**15** and **16**–**22**). The most important result from the experimental values



Scheme 1.

of R_F (Table 3 and Table 4) is the achievement of proper retention above the origin and below the solvent front ($0.01 < R_F < 0.91$), within about 190 measurements. This unequivocally shows, for the sixth time, as in the previous five times,[1–5] the proper theoretical predictions made by the Snyder theory and LSChrom for TLC analysis of compounds **1**–**22** with complex structures and expected pharmacological activities.

The proper retention established in both libraries of piperidinones was not our unique goal. The analysis of any of the libraries required adequate separation of all adjacent zones. The experimental data of Table 3 and Table 4, for single development of the chromatograms, show that this is not the case with the majority of the mobile phases, except for mobile phases 3, 8, and 10. To improve the separation, we applied two or three times development with some of the theoretically recommended mobile phases. As seen from Table 5, complete separation was successfully obtained after three developments with mobile phase 7 for the library of compounds **1**–**15**, where the mean value of $\log \alpha$ increased to 0.23 *vs.* 0.16 (single development) and 0.19 (development two times). Within the second library of compounds **16**–**22**, this approach did not give the expected increase in the separation efficiency. The values of $\log \alpha$ were practically constant (0.17 and 0.16) for any type of development. Table 5 shows that the sequence of the compounds according to their number does not correspond to the sequence of a decrease in their retentions. The reason is that the numbering of the compounds was done on the basis of the variation in their structures. Further improvement of the separation efficiency is possible by application of HPLC. Switching from TLC to HPLC in the LSChrom software is simply done by selection of another adsorbent that is suitable for HPLC.

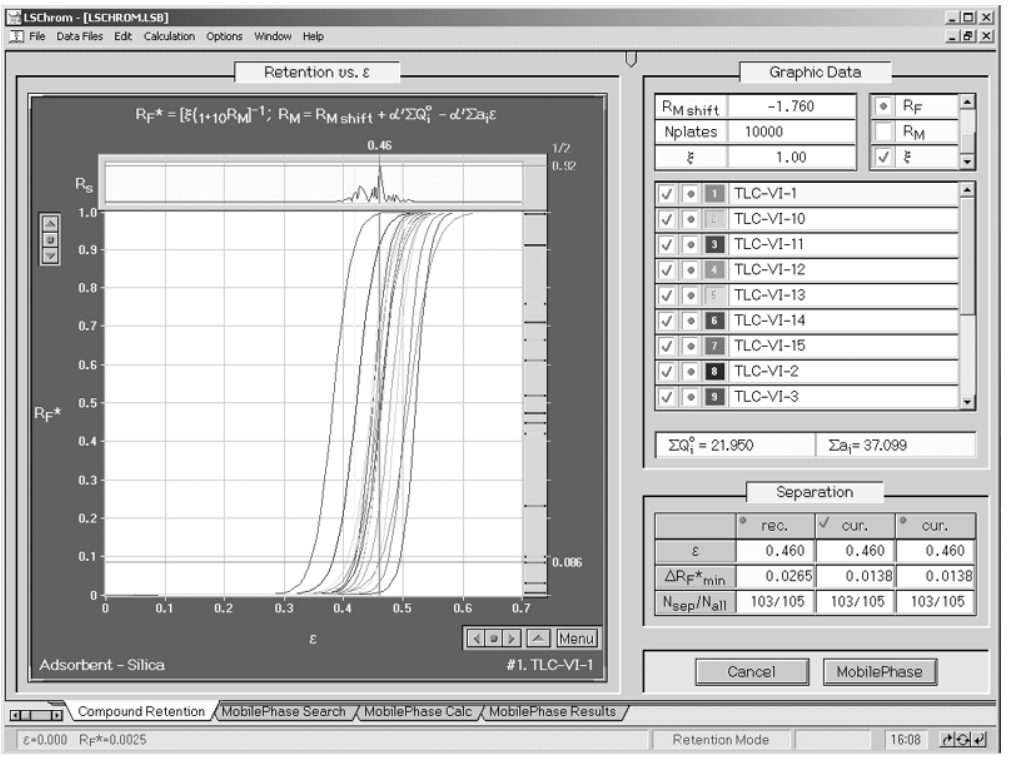


Figure 1. Illustration of the mode of LSChrom, Version 2, for calculation and analysis of retention. The value of the recommended mobile phase strength, $\varepsilon_{recommended}$, was 0.460 for compounds **1**–**15** on silica. Full separation of all compounds is expected.

The proper application of the Snyder theory and the software to HPLC is already demonstrated.[10]

The large experimental database of R_F gives possibility for other conclusions. We would like to point out some of the features.

Although the mobile phases used within any library have equal values of ε, the retention of any individual compound varies significantly from one mobile phase to another mobile phase that is due to the variation, mainly, of the polarity, P'. As expected, a mobile phase with a greater value of P' and, thus, with an increased ability to solve the sample, decreases retention and correspondingly increases the value of R_F. This tendency is seen within mobile phases 1–7, since any of them has a known value of P'. The value of P' is the smallest for mobile phase 1 (1.24) and the greatest for mobile phase 6 (3.87). This accounts for the greater retention of any compound of **1**–**15** in mobile phase 1 and its smaller retention in mobile phase 6.

The variation in the separation efficiencies of the individual mobile phases is attributed[9–11] to variation mainly of their localization, m. Thus, the use of mobile phases with equal ε but different m and P' is a strategy for optimisation of the separation.

CONCLUSIONS

1. The application of the Snyder theory and LSChrom, Version 2, software was successful for the sixth time in the automatic prediction of suitable mobile phases for TLC on silica of two series of twenty two piperidinones forming two libraries: **1**–**15** and **16**–**22**, having complex structures. The predictions are based on the adsorption properties of the adsorbent, mobile phase, and compounds as a function of their structures. The calculations gave a recommended mobile phase strength ε (0.460 for compounds **1**–**15** and 0.371 for compounds **16**–**22**) and specific mobile phases having these values of ε. The experimental TLC with 13 such mobile phases proved the validity of the theoretical predictions in about 190 measurements.
2. Within the theoretically selected mobile phases, complete separation of all adjacent zones was achieved with three mobile phases only when the chromatograms were developed once. Chromatograms developed two or three times showed the expected increased separation efficiency within compounds **1**–**15**. Unexpectedly, this approach did not give such a result for compounds **16**–**22**.
3. The LSChrom, Version 2, software incorporates the Snyder theory and, thus, enables any user, even one not familiar with it, to apply it for automatic selection of mobile phases for TLC and HPLC on silica or alumina of non-ionic compounds, provided their structures are known and can be expressed by the structural fragments available in the software.

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