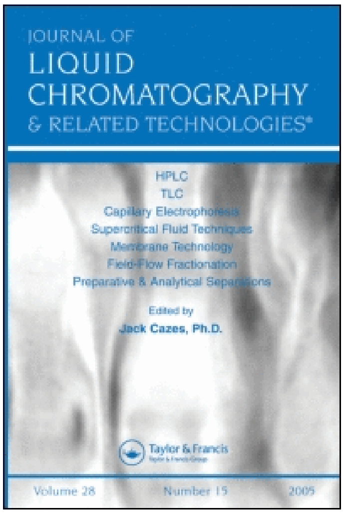

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Automatic Selection of Mobile Phases. V. Thin-Layer Chromatography on Silica vs. Alumina of 3,4-Disubstituted Isochroman-1-Ones Including Spiro Analogues

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Automatic Selection of Mobile Phases. V. Thin-Layer Chromatography on Silica vs. Alumina of 3,4-Disubstituted Isochroman-1-Ones Including Spiro Analogues

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Abstract: Avoiding any 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) of substituted isochromanones 1–8 and the spiro analogues 9–12. The procedure takes into account the adsorption properties of the mobile phase (parameter ε and tuning parameters m and P'), stationary phase and sample structure expressed by relevant groups. The calculations yielded a recommended value of ε and subsequently a list of mobile phases having this value of ε. The approach was applied to TLC on two types of silica and, for the first time, on alumina. Within about 130 measurements using 10 computer selected mobile phases, the retention of any compound fell in a favorable range ($0 < R_F < 1$). The separation, α, of the *cis/trans* isomers **1**–**6** depended on their retention, stationary phase, and values of m and P' of the mobile phase. Silica was more effective and did not cause compound decomposition in contrast to alumina.

Keywords: Normal-phase liquid chromatography, Thin-layer chromatography, Silica, Alumina, O-containing heterocycles, *Cis/trans* isomers, Mobile-phase selection, Snyder theory in LSChrom software

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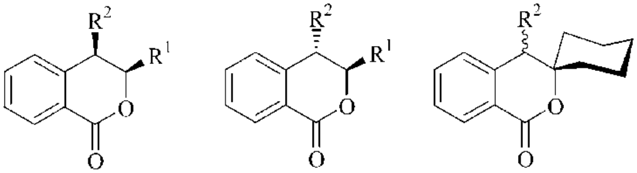
INTRODUCTION

The present series of papers[1–4] tries to specify the scope and limitation of the well-known Snyder theory,[5–7] applied by the software LSChrom[8–10] developed for an 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 frequently in the analysis of organic compounds. The procedure used in LSChrom, Version (Ver) 2[10] for this purpose, includes the approximate calculation of retention by the following equation.

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

where the right-hand parameters are related to the adsorption properties of the stationary phase (adsorbent), compound X, and the mobile phase: $R_{M(shift)}$, α'; $S_X = \sum Q_i^o$, $A_X = \sum a_i$; and ε, respectively. The procedure is free from any trial and error experiments prior to the final analysis.

This paper describes the application of LSLChrom Ver 2 and the Snyder theory to predict suitable mobile phases for TLC on silica or alumina of isochromanones **1–12** from two different groups. Compounds **9–12** are with a spiro coupling in position 3 of the isochromanone ring. Compounds **1–8** have *cis* or *trans* configuration and compounds **1–6** form three diastereomeric pairs. The new aspects of the paper are connected with the study of O-containing heterocycles with complex structures and the use of alumina for the first time in the automatic approach.



cis-1,3,5 **trans**- 2,4,6-8 9-12

R^1= phenyl, 4-NO_2-phenyl, thiophen-2-yl; R^2= $COOCH_3$, cyclic amide groups

THEORY AND EXPERIMENTAL

The dimensionless parameters of Eq. (1) have the following meaning.

$R_{M(shift)}$: Parameter depending on the surface area of the adsorbent, its void volume and mass.

α': Selectivity of the adsorbent that is proportional to the number of the adsorbent active sites.

$S_X = \sum Q_i^o$: The energy of adsorption S_X of a compound X is a sum of the energy of adsorption Q_i^o of any structural fragment *i* from its structure.

$A_X = \sum a_i$: The area under adsorption A_X of a compound X is a sum of the area under adsorption a_i of any structural fragment i from its structure.

ε: Strength of the mobile phase that is proportional to the dimensionless Gibbs energy ($\Delta G^o/RT \ln 10$) of adsorption of the mobile phase per unit of its area under adsorption. Two additional parameters tune ε: localization, m, measuring the mutual geometry of the adsorbent and mobile phase at a molecular level and polarity, P', measuring the mobile phase ability to solve compounds of different polarity. The greater the ε value, the weaker the sample retention. Changes in m modify mobile phase selectivity. Increase in P' decreases retention and vice versa.

Tables 1–4 summarize the data obtained in this study.

Methyl esters **1–4** were prepared from the parent acids[11] and diazomethane. Compounds **5–12** were synthesized by a multi-step transformation[12,13] of the carboxylic group in the parent acids obtained from homophthalic anhydride and an aldehyde[11] or ketone. The structures of all compounds and configuration of compounds **1–8** (see Table 3) were elucidated by ^{1}H-NMR spectra and X-ray analysis.[14] Compounds **1–8** with two stereogenic centers have *cis* or *trans* configuration and compounds **1–6** are diastereomeric pairs. Compounds **9–12** have one stereogenic center only and do not possess *cis-trans* isomerism.

The stationary phases for TLC were two types of silica and an alumina: silica 1 = pre-coated TLC aluminium sheets: silica 60 F_{254} (Merck, Germany), silica 2 = pre-coated TLC plastic sheets: polygram sil G/UV_{254} (Macherey-Nagel, Germany), and alumina = pre-coated TLC aluminium cards: alumina, F_{254} (Fluka, Switzerland). TLC was performed as described in Ref. 1 with a traveling distance of 8 cm.

The computer program used was LSChrom Ver 2.1 for Windows[10] where calculation procedure 3.1 was made active.

Table 1 shows the structure of compounds **1–12** expressed by the composing structural elements and their adsorption properties. The selected mobile phases by LSChrom are shown in Table 2. These mobile phases are composed of two to four solvents. They were prepared from the relevant solvents by use of analytical reagent grades. The experimental values of R_F (a single measurement or arithmetic means of two measurements), using the computer selected mobile phases, are summarized in Table 3. Table 4 gives data for R_F, R_M and separation α of the *cis/trans* pairs within compounds **1–6**. The last two parameters are calculated by Eqs. (2) and (3).

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

$$\log \alpha = R_{M(cis)} - R_{M(trans)} \tag{3}$$

Table 1. Structure description by functional groups and adsorption properties of compounds **1**–**12**

			Number of relevant functional groups in compound											
Group i^a	Q_i°	a_i	1	2	3	4	5	6	7	8	9	10	11	12
Silica 1 and Silica 2: R_M*(shift)* $= -1.76$, $a' = 0.57$														
C=	0.25	1.00	12	12	12	12	10	10	10	10	6	6	12	6
Al-CH_2-Al	−0.05	0.90	2	2	2	2	6	6	7	6	11	12	11	11
Al-CH_3	5.80	10.50	−1	−1	−1	−1	−1	−1	−1	−2	−1	−1	−1	−2
Al-N (tert)	9.60	10.30											1	
Al-$CONH_2$	3.61	9.00					1	1	1	1	1	1	1	1
Al-O-CH_3	0.07	1.60								1				1
Ar-NO_2	2.77	7.50			1	1								
Ar-S-Ar	0.48	3.00					1	1	1	1				
Al-CO_2-CH_3	5.27	10.50	2	2	2	2	1	1	1	1	1	1	1	1
ΣQ_i°			13.37	13.37	16.14	16.14	17. 48	17.48	17.43	17. 43	15.75	15.70	23.05	19.29
$\Sigma\ a_i$			33.20	33.20	40.70	40.70	37.60	37.60	38.50	45.00	35.10	36.00	51.60	42.50
R_F (calc. at $\varepsilon = 0.343$)			0.81	0.81	0.77	0.77	0.13	0.13	0.19	0.04	0.31	0.42	0.05	0.11
Alumina: R_M*(shift)* $= -4.25$, $a' = 0.65$														
ΣQ_i°			13.79	13.79	16.54	16.54	17.91	17.91	17.93	21.44	16.01	16.03	22.63	19.54
Σa_i			18.61	18.61	21.10	21.10	23.10	23.10	24.00	23.60	20.60	21.50	29.80	21.10
R_F (calc. at $\varepsilon = 0.460$)			0.88	0.88	0.39	0.39	0.25	0.25	0.37	0.002	0.50	0.65	0.05	0.01

[a] Al = Alkyl; Ar = Aryl.

Table 2. Computer selected mobile phases 1–10

No.	Composition	Vol.%	ε	m	P'
Silica 1 and silica 2					
1	Hexane-ethyl acetate	71.43 : 28.57	0.343	0.59	1.33
2	Cyclohexane-ethyl acetate	69.08 : 30.92	0.343	0.59	1.22
3	Benzene-acetonitrile	90.63 : 9.37	0.343	0.52	3.00
4	Dichloromethane-1, 2-dichloroethane-ethyl acetate-acetone	81.69 : 10 : 4 : 4.31	0.343	0.14	3.28
5	Chloroform-acetone	92.45 : 7.55	0.343	0.33	4.18
6	Benzene-isopropanol	96.28 : 3.72	0.343	–	2.75
Alumina					
7	Hexane-ethyl acetate	72.90 : 27.10	0.460	0.77	1.27
8	Cyclohexane-ethyl acetate	69.32 : 30.68	0.460	0.76	1.21
9	Benzene-acetonitrile	95.26 : 4.73	0.460	0.67	2.85
10	Benzene-acetonitrile	90.63 : 9.37	0.479	0.87	3.00

RESULTS AND DISCUSSION

Automatic Selection of Mobile Phases

The automatic selection of mobile phases performed by LSChrom requires all of the parameters of Eq.(1), except ε, to be known for the selected adsorbent in advance.

From a list, the user selects an adsorbent with known values of $R_{M\ (shift)}$ and α', including them in the calculations. These parameters should be established preliminarily for any other adsorbent.[9] The user describes the structure of any compound analyzed, selecting from a list corresponding structural fragments, and specifies their number. Thus, the values of S_X and A_X become known.

LSChrom Ver 2 calculates retention R_M by Eq. (1) of the organic compounds as a function of the mobile phase strength ε, and allows one to predict the retention of any compound in the entire range of ε. The software analyzes the retention of all compounds studied in respect of ε, and using an optimization procedure, determines the mobile phase strength ε ($\varepsilon_{recommended}$) for their separation. The latter is established on the basis of 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 having the recommended value of ε is the most difficult calculating problem solved successfully in the software. Many mobile phases are included in a list showing the composing solvents only. Their ratio is calculated for the recommended value of ε. This also makes it possible to calculate the values of m and P' for each mobile phase.

Table 3. Experimental RF values of compounds **1–12** with computer selected mobile phases 1–10

			RF for a given mobile phase									
			Silica 1							Alumina		
Compound No.	R1	R2	1	2	3	4	5	6^a	7	8	9	10
		e	0.343	0.343	0.343	0.343	0.343	0.343	0.460	0.460	0.460	0.479
		m	0.59	0.59	0.52	0.14	0.33	—	0.77	0.76	0.67	0.87
		P′	1.33	1.22	3.00	3.28	4.18	2.75	1.27	1.21	2.85	3.00
cis-1	C6H5	COOCH3	0.44	0.45	0.58	0.90	0.89	0.54 (0.50)	0.57^b	0.63^b	0.73^b	0.84^b
trans-2	C6H5	COOCH3	0.49	0.49	0.60	0.91	0.89	0.59 (0.57)	0.54^b	0.63^b	0.69^b	0.83^b
cis-3	4-O2N-C6H4	COOCH3	0.24	0.28	0.50	0.88	0.89	0.48 (0.48)	—^{c}	—^{c}	—^{c}	—^{c}
trans-4	4-O2N-C6H4	COOCH3	0.29	0.31	0.51	0.89	0.89	0.53 (0.52)	—^{c}	—^{c}	—^{c}	—^{c}
cis-5	Thiophen-2-yl		0.02	0.04	0.03	0.10	0.24	0.08 (0.08)	0.03	0.07	0.02	0.08
trans-6	Thiophen-2-yl		0.06	0.09	0.09	0.41	0.71	0.19 (0.18)	0.09	0.24	0.10	0.25
trans-7	Thiophen-2-yl		0.23	0.16	0.21	0.61	0.84	0.26 (0.26)	0.22	0.38	0.21	0.43
trans-8	Thiophen-2-yl		0.06	0.14	0.09	0.39	0.64	0.19 (0.19)	0.09	0.15	0.13	0.29
9	—		0.04	0.07	0.03	0.23	0.5	0.10 (0.10)	0.08	0.14	0.04	0.14
10	—		0.13	0.19	0.06	0.38	0.73	0.16 (0.17)	0.15	0.31	0.08	0.27
11	—		0.13	0.19	0.05	0.41	0.74	0.19 (0.21)	0.12	0.29	0.08	0.26
12	—		0.03	0.05	0.03	0.19	0.4	0.09 (0.09)	0.05	0.11	0.04	0.17

[a] The value in parentheses are for Silica 2.

[b] Partial decomposition on alumina and appereance of decomposition products at the origin.

[c] Complete decomposition on alumina and all products are at the origin.

Table 4. Experimental R_F values and derived values of R_M and log α for the diastereoisomeric compounds **1–6**[a]

	Silica 1						Alumina				
No.	1	2	3	4	5	6	7	8	9	10	Average
R_F for indicated mobile phase[b]											
1	0.44	0.45	0.58	0.90	0.89	0.54	0.57	0.63	0.73	0.84	0.66
2	0.49	0.49	0.60	0.91	0.89	0.59	0.54	0.63	0.69	0.83	0.67
3	0.24	0.28	0.50	0.88	0.89	0.48	—	—	—	—	0.55
4	0.29	0.31	0.51	0.89	0.89	0.53	—	—	—	—	0.57
5	0.02	0.04	0.03	0.10	0.24	0.08	0.03	0.07	0.02	0.08	0.07
6	0.06	0.09	0.09	0.41	0.71	0.19	0.09	0.24	0.10	0.25	0.22
R_M for indicated mobile phase											
1	0.10	0.09	−0.14	−0.95	−0.91	−0.07	−0.12	−0.23	−0.43	−0.72	−0.34
2	0.02	0.02	−0.18	−1.00	−0.91	−0.16	−0.07	−0.23	−0.35	−0.69	−0.36
3	0.50	0.41	0.00	−0.87	−0.91	0.03	—	—	—	—	−0.14
4	0.39	0.35	−0.02	−0.91	−0.91	−0.05	—	—	—	—	−0.19
5	1.69	1.38	1.51	0.95	0.50	1.06	1.51	1.12	1.69	1.06	1.25
6	1.19	1.00	1.00	0.16	−0.39	0.63	1.00	0.50	0.95	0.48	0.65
Log a for indicated mobile phase											
1–2	0.08	0.07	0.04	0.05	0.00	0.09	−0.05	0.00	−0.08	−0.03	0.06[c]
3–4	0.11	0.06	0.02	0.04	0.00	0.08	—	—	—	—	0.05
5–6	0.50	0.38	0.51	0.79	0.89	0.43	0.51	0.62	0.74	0.58	0.59
Mean absolute log α			Silica 1 0.69					Alumina 0.57			

Performance of TLC of the compounds studied on the selected stationary phase with the theoretically found mobile phases is the final step of the study, since the Snyder theory is semiempirical and is elaborated on the basis of model compounds. It is not clear in advance that the theoretical predictions, especially for compounds with complex structure, will be correct in any case.

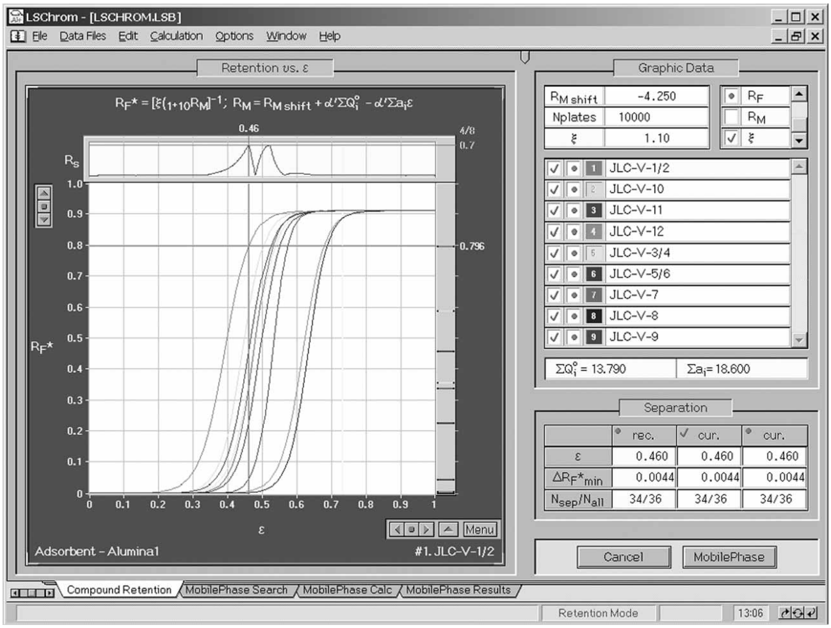
The procedure described was applied to TLC on silica or alumina for the compounds studied.

TLC of compounds **1–12** was theoretically treated and performed experimentally mainly on silica 1 or alumina. Silica 1 has been used in our other studies[1–4] and defined by $R_{M(shift)} = -1.76$ and $\alpha' = 0.57$. The same values were attributed to silica 2 since it is also a TLC silica. Silica 2 was used to verify the validity of the last two values for any TLC silica.

The available information in the software for $R_{M(shift)} = -1.76$ and $\alpha' = 0.65$ for an acidic alumina of Merck did not give good results, in our case, for a neutral alumina. That made us determine its values of both parameters on the basis of TLC of nitrobenzene as a test compound on this adsorbent with hexane-ethyl acetate 97.13:2.87 ($\varepsilon = 0.240$). The test compound includes in its structure 6 aromatic carbon atoms and one nitro group connected with an aryl group (Ar-NO_2) leading to $S_X = 4.60$ and $A_X = 8.50$. The experimental R_F of nitrobenzene was 0.50. Ascribing to alumina used $\alpha' = 0.65$ as it is general in the Snyder theory,[8] we obtained $R_{M(shift)} = -4.25$ on the basis of Eq. (1).

Differentiation of the *cis* and *trans* diasteromers and all other isomeric compounds is not done in the automatic approach for selection of mobile phases, although such a differentiation is possible when experimental corrections for the isomers are included.[9] In the present study, the structure of any isomeric pair was described in the same way. This does not cause any problem since the diastereomers have similar energy of adsorption, and a mobile phase that is suitable for the one isomer is suitable also for the other isomer. Table 1 gives details for description of the structure of all compounds studied by relevant structural fragments or groups, and for the adsorption properties of the compounds. It is worth noting that the lacton fragment OCO from the isochroman ring is expressed by one Alkyl-**$COOCH_3$** group subtracting one Alkyl-**CH_3** group. The values of S_X and A_X for a methine (CH) fragment are not specified. That is why this fragment is replaced by a methylene (CH_2) fragment. Table 1 shows that the adsorption properties (S_X, A_X) and retention of compounds **1–12** depend on the adsorbent type.

In the case of compounds **1–12**, LSChrom calculated $\varepsilon_{recommended}$ of 0.343 for silicas 1, 2, and 0.460 for alumina (see Figure 1). The software suggested several mobile phases having the recommended values of ε. We used nine of them (see Table 1, mobile phases 1–9) for the experimental validation. These mobile phases have the recommended value of ε and different values of m and P'. Mobile phase 10 is equal in composition to mobile phase 3, but both mobile phases have different adsorption properties because they are used with different adsorbents and permit a comparison of



$R_F^* = [\xi(1+10^{R_M}]^{-1}$; $R_M = R_{M\,shift} + \alpha'\Sigma Q_i^o - \alpha'\Sigma a_i\varepsilon$

Adsorbent - Alumina1

#1. JLC-V-1/2

$R_{M\,shift}$	-4.250
Nplates	10000
ξ	1.10

● R_F
☐ R_M
☑ ξ

☑ ● 1 JLC-V-1/2
☑ ● 2 JLC-V-10
☑ ● 3 JLC-V-11
☑ ● 4 JLC-V-12
☑ ● 5 JLC-V-3/4
☑ ● 6 JLC-V-5/6
☑ ● 7 JLC-V-7
☑ ● 8 JLC-V-8
☑ ● 9 JLC-V-9

$\Sigma Q_i^o = 13.790$ $\Sigma a_i = 18.600$

	● rec.	✓ cur.	● cur.
ε	0.460	0.460	0.460
$\Delta R_F{}^*_{min}$	0.0044	0.0044	0.0044
N_{sep}/N_{all}	34/36	34/36	34/36

Figure 1. Illustration of the mode of LSChrom Ver 2 for calculation and analysis of retention. The value of the recommended mobile phase strength, $\varepsilon_{recommended}$, is 0.460 for compounds **1**–**12** on alumina.

the retention on these adsorbents. Mobile phases 1–10 are composed of two to four solvents where hexane, cyclohexane, benzene, dichloromethane, 1,2-dichloroethane, and chloroform are weak localizing solvents. The remaining solvents (ethyl acetate, acetone, acetonitrile, and isopropanol) are strong localizing solvents.

TLC with the Automatically Selected Mobile Phases: Retention and Isomer Separation

The data for R_F (Table 3) obtained on silica or alumina for compounds **1**–**12** and mobile phases 1–9 having $\varepsilon_{recommended}$ showed that retention in all cases was in the favorable range above the origin and below the solvent front, namely $0.02 < R_F < 0.90$. This is the most important result showing the proper theoretical predictions of LSChrom for silica 1 (mobile phases 1–7), silica 2 (mobile phase 6), and alumina (mobile phases 7–9). A similar result ($0.08 < R_F < 0.84$) was obtained on alumina with mobile phase 10 having $\varepsilon = 0.479$, i.e., somehow a greater value than $\varepsilon_{recommended}$ leading to the expected increase of R_F. Retention of any compound on silica 1 and silica 2 with mobile phase 6 is practically the same. Thus, the values of

$R_{M(shift)}$ and α' used in the calculations for both silicas are also proper. The same is valid for alumina.

We would like to point out some other features of the data obtained.

TLC of compounds **1–12** on the same mobile phase (3 and 10) showed that any compound has a smaller retention on alumina. Alumina caused a complete decomposition of esters **cis-3** and **trans-4** and the resulting compounds remained at the origin. This is probably due to the electronegative nitro group that facilitates the hydrolysis of these esters. Along with other products, the parent acids were detected by authentic samples[11] in TLC with hexane-ethyl acetate-formic acid (1 : 1 : 0.02). In the case of esters **cis-1** and **trans-2** without such a substituent the decomposition was partial, making possible the determination of their R_F values. Decomposition was not established for the same compounds on silica 1 or silica 2.

The expected influence of P' is, in general, seen from the following data. TLC of compounds **1–12** on alumina with hexane-acetonitrile-pyridine 97.47 : 1.53 : 1.00 ($\varepsilon = 0.460$, $m = 1.27$, $P' = 0.24$) showed that the majority of the compounds were at the origin, and compounds **2**, **5**, and **6** only had R_F in the region 0.04–0.11. The data were not included in Table 3. The failure of this mobile phase to ensure retention in the favorable range for the majority of the compounds is probably due to the small value of P', while mobile phases 7–9 have considerably greater P' (1.21–2.85). On the contrary, the retention of any compound on silica is smallest, with mobile phase 3 having the greatest value (3.28) of P'.

A discussion of the separation of the *cis/trans* isomers within compounds **1–6** follows: Table 4 shows that silica 1 is more effective than alumina: the mean absolute values of log α are 0.69 and 0.57, respectively. Moreover, amides **cis-5/trans-6** are considerably better separated on both types of adsorbents (log $\alpha = 0.38 - 0.89$) than the diastereomeric esters **1–4** (the absolute values of log $\alpha = 0 - 0.09$), which can be attributed to the greater retention and adsorption of the amides. Best separation (log $\alpha = 0.89$) of **cis-5/trans-6** was obtained on silica 1 with mobile phase 5 having intermediate value of m (0.33). Moreover, **cis-5** is retained stronger than **trans-6** as seen from the positive values of log α and this is related to their mechanism of adsorption. Esters **1–4** show either a better retention of the *cis* isomers on silica or of the *trans* isomers on alumina and negative values of log α. The diastereomers of these compounds are not separated (log $\alpha = 0$) on silica with mobile phases 5 and 7. These data unequivocally indicate that the use of mobile phases with a given favorable value of ε and different values of m and P' is a strategy for optimization of separation.

CONCLUSIONS

The application of the Snyder theory and LSChrom Ver 2 software was successful in the automatic prediction of mobile phases for TLC of isochromanones **1–12** with complex structures on two silicas and an alumina. The predictions are based on the structure of the analytes. The calculations give a suitable mobile phase strength ε (0.343 for silica and 0.460 for alumina) and specific mobile phases having the recommended values of ε. The experimental TLC with 10 mobile phases proves the validity of the theoretical predictions in about 130 measurements. This conclusion is made for the first time for alumina.

The use of alumina instead of silica in the present study, showed a shortcoming of a partial or complete decomposition of esters **1–4**.

The separation of the *cis*/*trans* isomers **1–6** was more successful on silica than on alumina in the cases studied.

The LSChrom Ver 2 software incorporates the Snyder theory and, thus, allows 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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