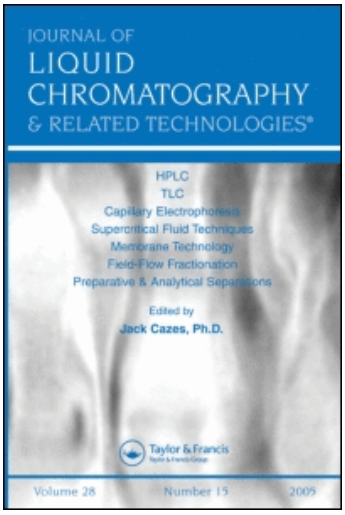

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AUTOMATIC SELECTION OF MOBILE PHASES. II. TLC ON SILICA OF *TRANS*- AND *CIS*-2-PHENETHYL-3-(9-METHYLCARBAZOL-3-YL)-4-SUBSTITUTED ISOQUINOLINES

R. I. Koleva[a]; M. D. Palamareva[b]
[a] Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, ME, U.S.A. [b] Department of Chemistry, University of Sofia, Sofia, Bulgaria

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AUTOMATIC SELECTION OF MOBILE PHASES. II. TLC ON SILICA OF *TRANS*- AND *CIS*-2-PHENETHYL-3-(9-METHYLCARBAZOL-3-YL)-4-SUBSTITUTED ISOQUINOLINES

R. I. Koleva* and M. D. Palamareva†

University of Sofia, Department of Chemistry, 1 James Bouchier Avenue, Sofia 1164, Bulgaria

ABSTRACT

Thin-layer chromatography (TLC) on silica of the title compounds was done. The automatic selection of mobile phase strength, ε was performed by the LSChrom software, incorporating the Snyder theory and data about the adsorption properties of usual structural elements or functional groups. This data enabled us to describe any sample structure necessary to do further calculations. The values of ε recommended were small ranges around 0.338 for compounds **1–12** and 0.379 for tetrahydroisoquinolines **13–25**. Using the same software, twelve mobile phases having such values of ε were selected. The experimental R_F values were, in general, in the favorable range of 0.01–0.95, showing proper automatic prediction both of ε and the concrete mobile phases for TLC of compounds **1–25**, most of them having three heterocyclic rings in their structure.

*Present address: Center for Molecular Medicine, Maine Medical Center Research Institute, 81 Research Drive, Scarborough, ME 04074, USA.
†Corresponding author. E-mail: mpalamareva@chem.uni.sofia.bg

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INTRODUCTION

Precise prediction of retention R_M or k as a function of sample structure in normal-phase liquid–solid chromatography (TLC or HPLC), is not yet obtained. The Snyder theory[1–3] gives a first-level approximation of this relationship:

$$R_M = \log k = R_{M(\text{shift})} + \alpha'(S_X - \varepsilon A_X) \tag{1}$$

or

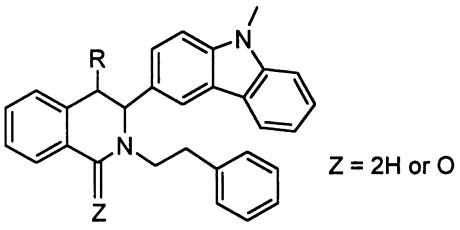
$$R_M = \log k = R_{M(\text{shift})} + \alpha'\left(\sum Q_i^o - \varepsilon \sum a_i\right) \tag{1a}$$

where $R_{M(\text{shift})}$ and α' characterize the adsorption properties of the stationary phase, S_X and A_X are respective adsorption energy and molecular area under adsorption of the sample compound, and ε is the adsorption energy of mobile phase per unit of its area under adsorption. S_X and A_X are found by summation of adsorption energy Q_i^o and area under adsorption a_i of any structural element, i, respectively.

Equation (1a) and the corresponding data for Q_i^o and a_i were incorporated in the last version[4] of the LSChrom software. Originally,[5] this software offered a possibility to find, by the Snyder theory, ε of a given mobile phase, or to select a mobile phase with a given value of ε on the basis of iterative procedures.

The last version of LSChrom has been recently applied[6] to find automatically, without any preliminary experiments, suitable mobile phases for TLC on silica of compounds with complex structure. One can argue that this successful application of both the Snyder theory and LSChrom is occasional. The present paper reports another case of their application for automatic selection, first of ε and then of concrete mobile phases for TLC of compounds **1–25**, most of them containing three heterocyclic rings in their structure.

EXPERIMENTAL



1-25

Compounds **1–25** were synthesized in analogy to Ref. [7]. Their structure (see Tables 2 and 3) and configuration were elucidated by NMR and mass spectra.

Thin-layer chromatography was performed on pre-coated TLC silica 60 GF_{254} (Merck, Germany) plates similarly to Ref. [6].

The computer program used was LSChrom Ver. 2.1 for Windows.[4]

RESULTS AND DISCUSSION

The compounds studied were the diastereoisomers **1** (cis) and **2** (trans) being chromatographed both with *trans*-tetrahydroisoquinolines **3–12** and *trans*-dihydroisoquinolinones **13–25**. The trans-isomer **2** was a parent compound for preparation of compounds **3–25**.

Automatic Selection of Mobile Phases

The automatic selection of mobile phases was done in minutes by different modes of the LSChrom software.

Similarly to Ref. [6], silica [$R_{M(\text{shift})} = -1.76$ and $\alpha' = 0.57$] was selected from a list offered by the software. The proper characterization of the adsorbent that will be used is of importance in order to receive good results.

The adsorption properties of any compound studied were found by calculation of S_X and A_X inputting data about the type and number of structural elements (functional groups) participating in its structure. For instance, the following groups expressed the structure of compound 18:

30 olefinic carbon atoms (C=)
1 aromatic methyl group (Ar−CH_3)
9 aliphatic methylene groups (Al−CH_2−Al)
3 tertiary aliphatic nitrogen atoms [Al−N (tert)]
1 aliphatic amide group (Al−$CONH_2$) and
1 aromatic methoxy group (Ar−OCH_3).

It is worth noting that there is no data about Q_i^o and a_i for a CH-group, and the presence of two such groups in compound **18** was taken into account, approximately by two methylene groups. Thus, the total number of the methylene groups became 9. The data for all other compounds are available on request.

The computer calculated values of S_X and A_X of compound **18** were 35.99 and 85.30, respectively.

In another mode, LSChrom calculated R_M of any compound by Eq. (1a), using the values of $R_{M(\text{shift})}$, α', S_X, and A_X mentioned above, and ascribing to ε successive values with a given step. The interconversion of R_F and R_M is done by

a well-known equation (see Ref. [6]). In the same mode, LSChrom made an analysis of the retention of the compounds studied and predicted a recommended value of ε ($\varepsilon_{\text{recommended}}$) of the suitable mobile phases for their TLC separation on silica selected. This value is found on the basis of best separation, i.e., maximum value of resolution R_s, and favourable retention ($0 < R_F < 1$) of the compounds. The value of $\varepsilon_{\text{recommended}}$ was 0.338 for compounds **1–12** and 0.379 for dihydroisoquinolinones **13–25**. Small ranges around these values of ε belong to the recommended range of ε comprising the relevant greater values of R_s, including the maximum value. Figure 1 illustrates the retention analysis and prediction of $\varepsilon_{\text{recommended}}$ for compounds **1–12**. For instance, the retention predicted for compound **18** was $R_M = 0.31$ and $R_F = 0.33$ when $\varepsilon = 0.379$.

Selection of concrete mobile phases having $\varepsilon_{\text{recommended}}$, or ε in the recommended range, was performed in another mode where the desired value of ε was input. After relevant calculations, LSChrom showed a list of mobile phases with this value of ε. We selected from such lists (see Fig. 2), 12 mobile phases that are summarized in Table 1 together with their values of ε, localization m, and polarity P'. The last two parameters tune the mobile phase strength ε (see Refs. [6, 8]).

Thin-Layer Chromatography of Compounds 1–25 with the Automatically Selected Mobile Phases of Table 1

Tables 2 and 3 show the experimental R_F values of compounds **1–25**, obtained by their TLC on silica with the automatically selected mobile phases given in Table 1. The R_F values of the strong base *N*-methyl derivatives **6** and **16** are zero with some mobile phases. It is known that strong bases require a small quantity of ammonia in the mobile phase (see Ref. [6] for instance). In all other cases of 155 measurements, R_F is in the favorable range of 0.01–0.95. That result shows, unequivocally, that the Snyder theory and LSChrom predicted, accurately, the mobile phases that are suitable for TLC of the compounds studied, on the basis of their structure.

We did not make a comparison between calculated and experimental values of R_F, since good agreement is not generally expected when Eq. (1a) is used.

It is worth noting, that there is a variation in R_F when mobile phases with equal ε, but different m and P', are used. For instance, R_F of compound **18** varied from 0.06 to 0.52 with mobile phases 7–10 having $\varepsilon = 0.379$. This tuning effect of m and P' is of importance in order to find an optimum mobile phase for separation of given compounds. The strategy for solving this problem is to use mobile phases with equal or close ε, but with different m and P' (see Refs. [6, 8]). In fact, we were not interested to find an optimum mobile phase for separation of

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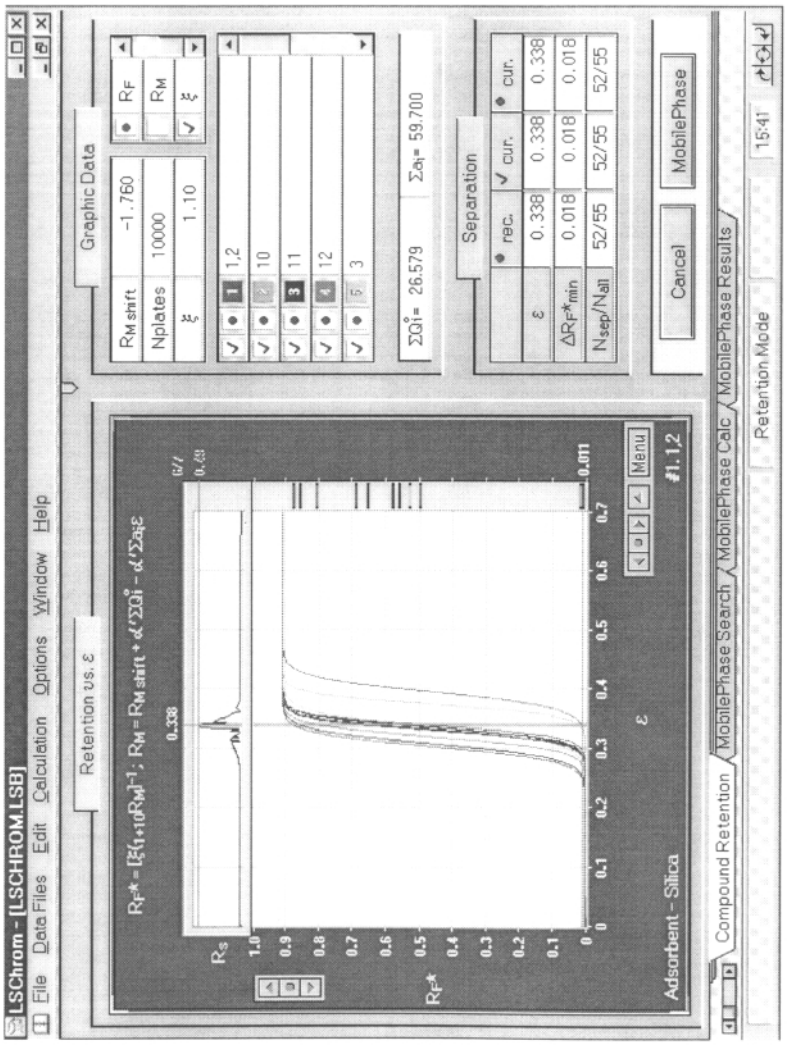

Figure 1. Illustration of the prediction of $\varepsilon_{\text{recommended}} = 0.338$ for compounds **1–12** (see the text).

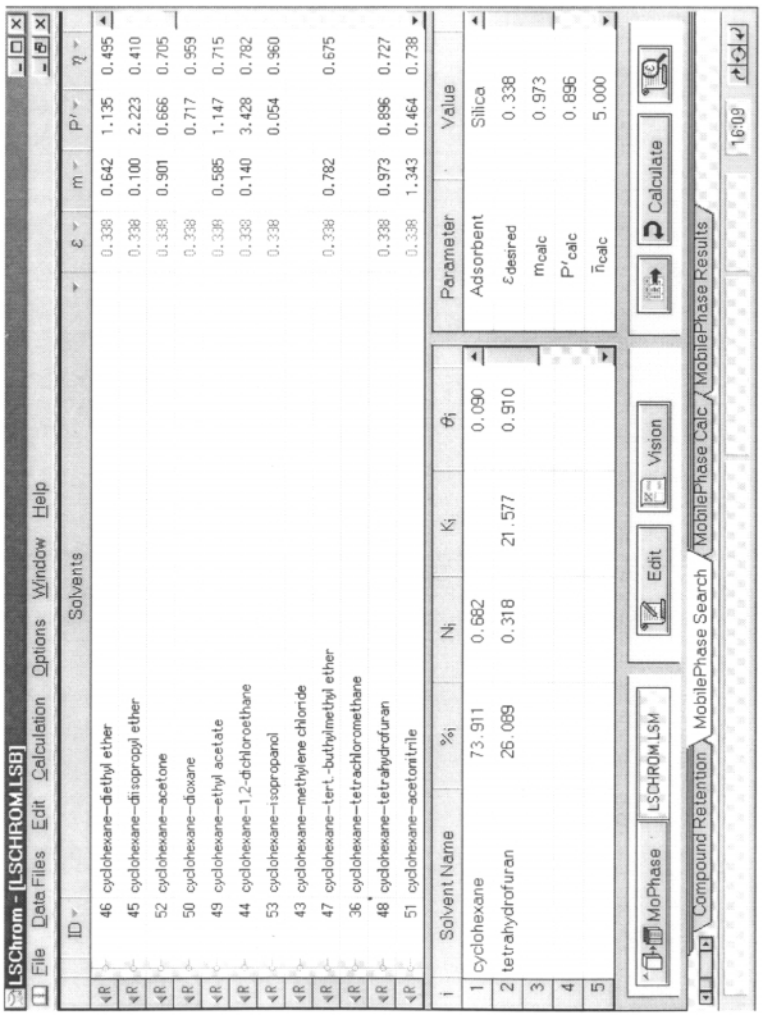

Figure 2. Illustration of the list of mobile phases having $\varepsilon_{\text{recommended}}$ (0.338) for compounds **1–12**. Properties of mobile phase 1 are visualised by having the cursor on its name.

Table 1. Mobile Phases Recommended by LSChrom for TLC on Silica of All Compounds Studied

No.	Mobile Phase	Composition	ε	m	P'
1	Cyclohexane–tetrahydrofuran	73.911 : 26.089	0.338	0.97	0.90
2	Hexane–toluene–tret.-butylmethyl ether	66.829 : 10.000 : 23.171	0.338	0.76	—
3	Diisopropyl ether–dichloromethane	85.590 : 14.410	0.338	0.09	2.50
4	Heptane–ethyl acetate	75.273 : 24.727	0.338	0.59	1.24
5	Hexane–ethyl acetate	76.130 : 23.870	0.326	0.59	1.13
6	Hexane–ethyl acetate	70.539 : 29.461	0.346	0.59	1.37
7	Hexane–acetone	75.117 : 24.883	0.379	0.93	1.34
8	Toluene–acetonitrile	86.538 : 13.462	0.379	1.03	2.86
9	Cyclohexane–isopropanol	87.326 : 12.674	0.379	—	0.32
10	Hexane–ethyl acetate	59.510 : 40.490	0.379	0.59	1.84
11	Hexane–ethyl acetate	62.770 : 37.230	0.370	0.59	1.70
12	Hexane–ethyl acetate	55.231 : 44.769	0.390	0.59	2.03

the compounds studied, since they are not obtained in a common reaction mixture. Our main goal was to find only suitable mobile phases, i.e., mobile phases that result in retention in the favorable range of $0 < R_F < 1$.

CONCLUSIONS

The present application of the Snyder theory and LSChrom software is successful in automatic prediction of 12 mobile phases suitable for TLC of the complex heterocyclic compounds **1–25** on silica $60F_{254}$ (Merck, Germany).

The prediction involves: a) prediction of recommended value of ε ($\varepsilon_{\text{recommended}}$) of mobile phases that are suitable for TLC, of the compounds studied on the basis of their structure and b) prediction of concrete mobile phases having $\varepsilon = \varepsilon_{\text{recommended}}$.

The success of the present application is also due to the proper characterization of the adsorbent used, with the relevant values of $R_{M(\text{shift})}$ (-1.76) and α' (0.57) being previously derived.[6]

The software, LSChrom,[4] enables any user, even though familiar with the Snyder theory, to apply it for an automatic selection of mobile phases for normal-

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Table 2. Experimental R_F Values of Compounds **1–12** with Computer Selected Mobile Phases 1–6

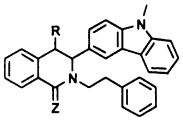
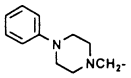
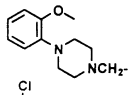
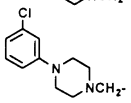
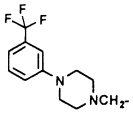
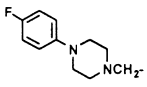
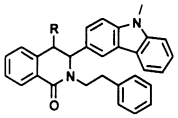
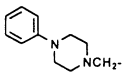
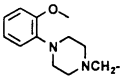
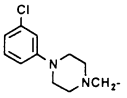
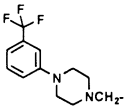
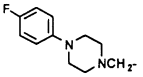
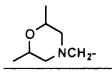
Compound			R_F for a Given Mobile Phase					
R	Z	No.	1	2	3	4	5	6
								
		ε	0.338	0.338	0.338	0.338	0.326	0.346
		m	0.97	0.76	0.09	0.59	0.59	0.59
		P'	0.90	-	2.52	1.24	1.13	1.37
cis CH_3OOC-	(Z=O)	**1**	0.22	0.11	0.67	0.24	0.20	0.35
trans CH_3OOC-	(Z=O)	**2**	0.20	0.09	0.65	0.23	0.19	0.33
trans	(Z=2H)							
HO-CH_2-		**3**	0.24	0.09	0.59	0.23	0.21	0.34
		**4**	0.08	0.02	0.04	0.03	0.03	0.03
		**5**	0.20	0.05	0.09	0.06	0.05	0.09
		**6**	0.02	0	0.02	0.01	0	0.01
		**7**	0.62	0.36	0.92	0.56	0.51	0.68
		**8**	0.47	0.16	0.69	0.33	0.32	0.48
		**9**	0.66	0.43	0.95	0.61	0.55	0.73
		**10**	0.66	0.45	0.95	0.63	0.57	0.75
		**11**	0.61	0.33	0.92	0.54	0.49	0.68
		**12**	0.51	0.21	0.71	0.41	0.38	0.42

Table 3. Experimental R_F Values of Compounds **1**, **2** and **13–25** with Computer Selected Mobile Phases 7–12

Compound		R_F for a Given Mobile Phase					
R	No.	7	8	9	10	11	12
							
	ε	0.379	0.379	0.379	0.379	0.370	0.390
	m	0.93	1.03	-	0.59	0.59	0.59
	P'	1.34	2.86	0.32	1.84	1.70	2.03
cis CH_3OOC-	**1**	0.07	0.40	0.36	0.59	0.53	0.76
trans CH_3OOC-	**2**	0.05	0.38	0.36	0.58	0.50	0.73
HO-CH_2-	**13**	0.02	0.21	0.28	0.27	0.23	0.46
	**14**	0.06	0.10	0.29	0.05	0.05	0.07
	**15**	0.12	0.30	0.41	0.46	0.43	0.63
	**16**	0	0	0.04	0	0	0
	**17**	0.08	0.41	0.42	0.64	0.62	0.84
	**18**	0.06	0.35	0.39	0.52	0.49	0.74
	**19**	0.08	0.47	0.42	0.66	0.64	0.86
	**20**	0.08	0.48	0.42	0.66	0.63	0.91
	**21**	0.07	0.42	0.40	0.61	0.59	0.83
	**22**	0.07	0.30	0.35	0.43	0.42	0.65
	**23**	0.11	0.36	0.40	0.62	0.59	0.86

(continued)

Table 3. Continued

	**24**	0.10	0.46	0.43	0.71	0.67	0.89
	**25**	0.01	0.06	0.15	0.06	0.05	0.13

phase TLC and HPLC of non-ionic compounds whose structure can be expressed by the ones available in the software functional groups.

REFERENCES

1. Snyder, L.R. *Principles of Adsorption Chromatography*; Marcel Dekker, Inc.: New York, 1968.
2. Snyder, L.R.; Kirkland, J.J. *Introduction to Modern Liquid Chromatography*, 2nd Ed.; Wiley-Interscience: New York, 1979.
3. Snyder, L.R. In *High-Performance Liquid Chromatography*; Horváth, C.S., Ed.; Academic Press: New York, 1983; Vol. 3, 157–223.
4. Palamarev, Ch.E.; Palamareva, M.D. *LSChrom, Ver. 2.1, Demo Version*, 1999; http://www.members.tripod.com/lschrom
5. Palamareva, M.D.; Palamarev, H.E. J. Chromatogr. **1989**, *477*, 235–248.
6. Palamareva, M.D.; Koleva, R.I.; Kozekov, I.D. J. Liq. Chromatogr. & Rel. Technol. **2001**, *24*, 1411–1424.
7. Kozekov, I.D.; Koleva, R.I.; Palamareva, M.D. J. Heterocycl. Chem. **2002**, *39*, 229–236.
8. Palamareva, M.D.; Kozekov, I.D. J. Liq. Chromatogr. **1996**, *19*, 1483–1498.

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