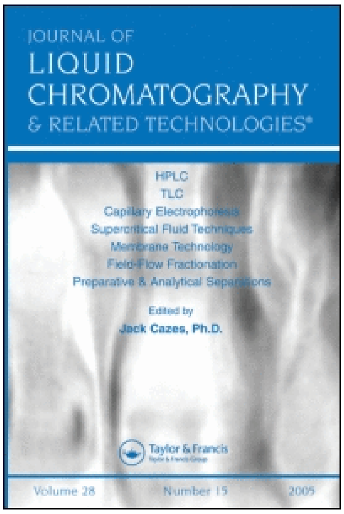

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

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To cite this Article Palamareva, M. D. , Stoyanova, M. P. and Kozekov, I. D.(2003) 'Automatic Selection of Mobile Phases. III. TLC on Silica of 2,3,4-Trisubstituted Tetrahydroisoquinolinones', Journal of Liquid Chromatography & Related Technologies, 26: 8, 1255 — 1266

To link to this Article: DOI: 10.1081/JLC-120020108

URL: http://dx.doi.org/10.1081/JLC-120020108

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JOURNAL OF LIQUID CHROMATOGRAPHY & RELATED TECHNOLOGIES®
Vol. 26, No. 8, pp. 1255–1266, 2003

Automatic Selection of Mobile Phases. III. TLC on Silica of 2,3,4-Trisubstituted Tetrahydroisoquinolinones

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ABSTRACT

New, successful application of the LSChrom software, incorporating the Snyder theory to complex organic compounds is performed. This permitted an automatic selection, without any preliminary attempts, of suitable mobile phases for thin-layer chromatography (TLC), on silica, of *trans*-2-phenethyl-3-(1-methyl-1H-pyrrol-2-yl)-4-substituted-1,2,3,4-tetrahydroisoquinolin-1-ones. The automatic selection of the mobile phases is based on the structure of any compound, literature data for the adsorption properties of the relevant structural fragments (groups) available in the structure and a many calculations.

Key Words: Normal-phase liquid-solid chromatography; Silica; Nitrogen heterocycles; Mobile-phase selection; Snyder theory in LSChrom software.

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DOI: 10.1081/JLC-120020108 1082-6076 (Print); 1520-572X (Online)

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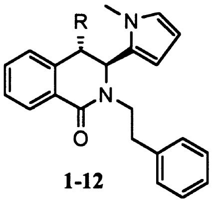
INTRODUCTION

Day after day, organic chemists struggle to isolate and purify a great deal of organic compounds. Liquid chromatography (TLC or HPLC) is an indispensable method in this respect. The art of separation passes through preliminary experiments with specific mobile phases, treatment of the resulting data with a suitable numerical method, and chromatography with the recommended mobile phase.[1–4] Organic chemists often do not have the time needed to optimize separations. They are interested in achieving, as fast as possible, favorable retention of the compounds being in the range from the starting point and to below the solvent front ($0 < R_F < 1$) in the case of TLC. If the spot of a compound is in that range, its purity can be deduced. To solve this problem, one has to find a suitable mobile phase(s) since the adsorbent is mainly silica or alumina and the preference is usually in favor of silica. The selection of a suitable mobile phase for a given separation is done, generally, by the Edisonian trial-and-error method, requiring a lot of work.

Research goes sometimes in unexpected directions. We will outline, briefly, some of our studies contributing to the solution of easier selection of mobile phases for normal-phase liquid chromatography. Synthesising vast numbers of diastereomers, we have established the interesting fact that, within a given group of acyclic compounds, the *erythro* isomer has always a higher R_F value than the corresponding *threo* isomer.[5] Thus, TLC has been proposed as a method for configurational determination of diastereomers of a given class.[5–11] As a consequence of going into the depth of this phenomenon, we have become familiar with the Snyder theory.[12–14] It is the generally accepted theory in normal-phase liquid chromatography, where the adsorbent is silica or alumina. This theory has been used to predict which are the adsorbing groups[15–19] and, thus, to explain the relationships between configuration and R_F. The quantitative application of the Snyder theory requires appropriate software to perform extensive calculations. We have been induced to develop, with the participation of an experienced programmer, such a software, called LSChrom.[20] This first version of the software enables the characterisation of two- to multi-component mobile phases by a parameter, measuring their energy of adsorption. This version of LSChrom permits[16–19,21,22] the selection of mobile phases for a given set of compounds by an easier and more effective procedure than that of trial and error.

Recently, the LSChrom software has been developed[23,24] by incorporating into it another part of the Snyder theory. Thus, prediction of retention is possible on the basis of the adsorption properties of the individual structural fragments or functional groups participating in the sample structure. The corresponding modes give the possibility for an automatic selection of mobile phases without any preliminary experiments, as already shown[23] for HPLC of compounds having relatively simple structures. Successful applications of the last version of LSChrom has been done in the TLC of complex compounds.[25,26]

Scientific software requires extensive applications to outline its use. The present paper reports fully automatic selection of mobile phases for TLC, on silica, of tetrahydroisoquinolinones **1–12** by means of the LSChrom software.



1-12

We have synthesised[27] these compounds by the important reaction between homophthalic anhydride and imines,[28,29] leading to the corresponding *trans* acid and its subsequent stereospecific transformations. The paper avoids any equations, trying to attract, mainly, the attention of organic chemists to whom the studies of this series are dedicated.

THEORY

Parameter R_F, measuring the mobility of a compound in the chromatographic system, is transformed to parameter R_M, measuring the retention of the compound by a well-known equation.[12,25]

We recommend that a reader who would like to treat the LSChrom software as a black box, to skip the following text. We recommend, also, such a reader to imagine that various parameters characterising the adsorption properties of the stationary phase (adsorbent), of mobile phase, and of the compound chromatographed can be calculated by the Snyder theory[12–14] along with the retention itself of the compound.

We will define, in an accessible way, the parameters from the Snyder theory that characterise the adsorption properties of the three components of the chromatographic system.

Parameters Characterising the Adsorption Properties of Stationary Phase (Adsorbent)

These parameters are selectivity α' and a complex parameter denoted as $R_{M(\text{shift})}$. Parameter α' is related to the number of silanol hydroxyl groups per unit adsorbent area and parameter $R_{M(\text{shift})}$ is related to the size of the adsorbent particles and the volume of their pores.

Parameters Characterising the Adsorption Properties of Mobile Phase

Mobile-phase strength ε measures the energy of adsorption of an adsorbent per unit area. The greater the value of ε, the greater will be the adsorption of the mobile phase and this results in lower R_F values. A nomogram[30] can help to find ε values of some mobile phases. Parameters that tune the adsorption properties of the mobile phase are localization m and polarity P'. Mobile phases having a given value of ε and different values of m have different selectivities, i.e., different possibility to separate compounds. In general, a mobile phase having a higher value of P' dissolves, better, the compound chromatographed and, thus, increases its R_F.

Parameters Characterising the Adsorption Properties of the Compound Being Chromatographed

These parameters are energy of adsorption S_X and area of adsorption A_X of the compound being chromatographed. They are additive parameters and are calculated by summation of the relevant contributions of the individual structural fragments or functional groups, i, available in the structure. A group, i, is characterised by its energy of adsorption Q_i^o and area under adsorption a_i. There are literature data[12] about Q_i^o and a_i of the usual groups participating in the structures of organic compounds. On the basis of these data, S_X and A_X of a given compound become known.

Parameters R_M, α', $R_{M(\text{shift})}$, S_X, A_X and ε are related by the Snyder theory in an equation.[12–14] The LSChrom software obtains, in different modes, data about all parameters except ε and R_M. Giving successive values with a given step to ε, the software calculates, approximately, by this equation, retention R_M of a compound. The software makes a detailed analysis of the retentions of all compounds that are selected to participate in a separation. Thus, LSChrom predicts, in a first approximation, and recommends ε ($\varepsilon_{\text{recommended}}$) of mobile phases that are suitable for this separation. The software offers, in another mode, a list of mobile phases that have such values of ε. Details in this respect are available in Refs.[23,25,26]

EXPERIMENTAL

Compounds **1–12** were synthesised in analogy to the procedure in Ref.[31] Their structures and configuration were elucidated by ^{1}H-NMR at 400 MHz and mass spectra. The elemental analysis of each compound was within ±0.40% for the individual elements.

TLC was performed on pre-coated TLC silica 60 GF_{254} (Merck, Germany) using a procedure similar to that in Ref.[19]

The computer program used was LSChrom Ver. 2.1 for Windows.[24]

The mobile phases automatically selected by LSChrom are shown in Table 1. The experimental values of R_F using these mobile phases are summarised in Table 2. The latter shows also the structure of compounds **1–12**.

RESULTS AND DISCUSSION

The present discussion does not include any equations from liquid chromatography or the Snyder theory.

Automatic Selection of Mobile Phases

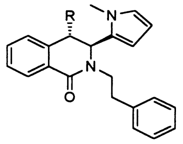
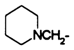
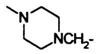
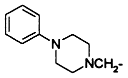
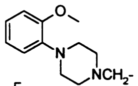
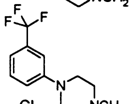
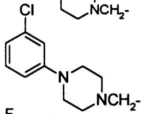
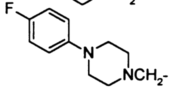
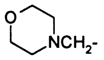
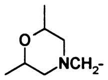
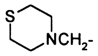
The automatic selection of mobile phases for tetrahydroisoquinolinones **1–12** was done within minutes by different modes of the LSChrom software.

All silicas for TLC have closely related properties and, consequently, they can be characterised by given values of both characterising parameters. Similarly to Refs.[25,26] silica ($R_{M(\text{shift})} = -1.76$ and $\alpha' = 0.57$) was selected from a list offered by the software. If necessary, any individual adsorbent can be charac-

Table 1. Mobile phases recommended by LSChrom for TLC on silica of all compounds studied.

No.	Mobile phase	Composition	ε	m	P'
1	Heptane–ethyl acetate	56.7 : 43.3	0.394	0.59	2.02
2	Heptane–ethyl acetate–ammonia	56.7 : 43.0 : 0.3	~0.394	—	—
3	Heptane–acetone	73.7 : 26.3	0.394	0.93	1.49
4	Heptane–isopropanol	83.4 : 16.6	0.394	—	0.81
5	Heptane–isopropanol–ammonia	83.4 : 16.3 : 0.3	~0.394	—	—
6	Toluene–acetonitrile	83.3 : 16.7	0.394	1.13	2.97
7	Heptane–methylene choride–tetrahydrofuran	63.8 : 20.0 : 16.2	0.394	0.91	1.40

Table 2. Experimental R_F values of compounds **1–12** from their TLC on silica with computer selected mobile phases 1–7.

Compound		R_F for a given mobile phase						
R	No.	1	2	3	4	5	6	7
								
CH_3OOC-	**1**	0.45	0.49	0.21	0.39	0.44	0.53	0.33
HO H_2C-	**2**	0.25	0.27	0.15	0.32	0.39	0.40	0.17
	**3**	0.59	0.67	0.35	0.52	0.54	0.59	0.36
	**4**	0.02	0.03	0.06	0.04	0.06	0.03	0.00
	**5**	0.58	0.62	0.28	0.51	0.50	0.60	0.35
	**6**	0.50	0.54	0.27	0.49	0.48	0.55	0.30
	**7**	0.59	0.62	0.28	0.51	0.50	0.63	0.35
	**8**	0.59	0.63	0.28	0.51	0.50	0.63	0.35
	**9**	0.56	0.59	0.26	0.50	0.48	0.58	0.32
	**10**	0.40	0.44	0.24	0.44	0.42	0.46	0.14
	**11**	0.52	0.58	0.29	0.52	0.49	0.53	0.53
	**12**	0.58	0.62	0.27	0.52	0.49	0.61	0.18

terised by its own values of these two parameters.[23] Proper characterisation of the adsorbent that will be used is of importance for a better prediction of retention.

LSChrom calculates the adsorption properties S_X and A_X of any compound studied on the basis of Q_i^o and a_i taking, automatically, data from corresponding files incorporated in the software. The user has only to input data about the type and number of structural fragments (functional groups) participating in its structure. For instance, the following structural fragments and groups express the structure of compound **6**:

22 olefinic carbon atoms (C=)

2 aliphatic methyl group (Al—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 are no data for Q_i^o and a_i for a CH-group and the presence of two such groups in compound **6** was approximated by two methylene groups. Thus, the total number of the methylene groups became 9.

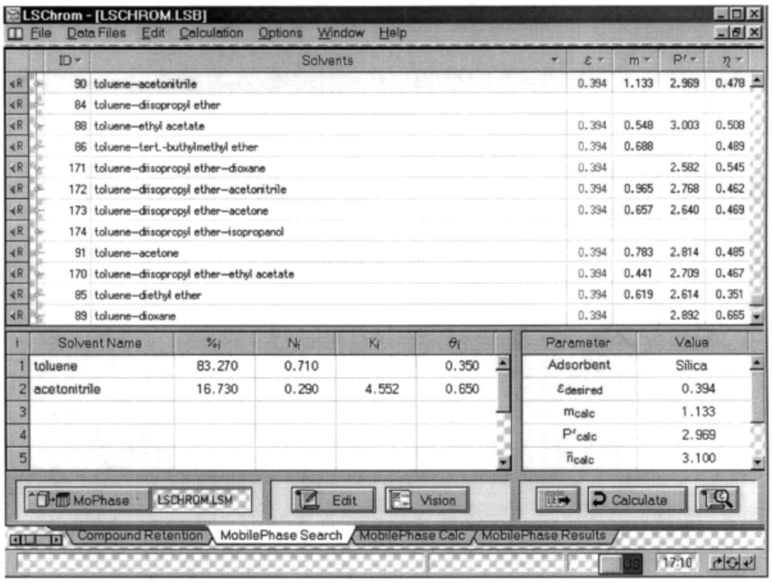
The computer calculated values of S_X and A_X of compound **6** were 34.02 and 79.70, respectively.

In another mode, LSChrom calculated R_M of any compound using the values of $R_{M(\text{shift})}$, α', S_X and A_X mentioned above. For instance, the retention predicted for compound **6** was $R_M = -0.29$ and $R_F = 0.66$ when $\varepsilon = 0.394$.

The software recommended value of ε ($\varepsilon_{\text{recommended}}$) of the mobile phases suitable to separate compounds **1–12** by TLC on silica being 0.394. We selected, arbitrarily, from a list offered by LSChrom (see Fig. 1), seven mobile phases having the recommended value of ε. These automatically selected mobile phases are summarised in Table 1 together with their values of ε, localization m and polarity P'. The last two parameters tune the mobile phase strength ε.[15,19]

Thin-Layer Chromatography of Compounds 1–12 with the Automatically Selected Mobile Phases of Table 1

Table 2 shows the experimental R_F values of compounds **1–12** obtained by their TLC on silica with the automatically selected mobile phases given in Table 1. The R_F value of the strongly basic *N*-methyl derivative **4**, is zero with mobile phase 7. It is known that strong bases require a small quantity of



ID	Solvents	ε	m	P′	η
90	toluene–acetonitrile	0.394	1.133	2.969	0.478
84	toluene–diisopropyl ether				
88	toluene–ethyl acetate	0.394	0.548	3.003	0.508
86	toluene–tert.-buthylmethyl ether	0.394	0.688		0.489
171	toluene–diisopropyl ether–dioxane	0.394		2.582	0.545
172	toluene–diisopropyl ether–acetonitrile	0.394	0.965	2.768	0.462
173	toluene–diisopropyl ether–acetone	0.394	0.657	2.640	0.469
174	toluene–diisopropyl ether–isopropanol				
91	toluene–acetone	0.394	0.783	2.814	0.485
170	toluene–diisopropyl ether–ethyl acetate	0.394	0.441	2.709	0.467
85	toluene–diethyl ether	0.394	0.619	2.614	0.351
89	toluene–dioxane	0.394		2.892	0.665

i	Solvent Name	$\%_i$	N_i	K_i	θ_i
1	toluene	83.270	0.710		0.350
2	acetonitrile	16.730	0.290	4.552	0.650
3					
4					
5					

Parameter	Value
Adsorbent	Silica
$\varepsilon_{desired}$	0.394
m_{calc}	1.133
P'_{calc}	2.969
$\bar{n}_{calc}$	3.100

Figure 1. Illustration of the list of mobile phases having $\varepsilon_{\text{recommended}}$ (0.394). Composition and properties of mobile phase 6 are visualised by having the cursor on its name.

ammonia in the mobile phase to overcome the chemisorption.[25] The presence of ammonia in mobile phases 2 and 5 increases R_F of compound **4**. In the remaining 83 measurements, R_F is in the favorable range of 0.02–0.67. This result shows, unequivocally, that the Snyder theory and LSChrom satisfactorily predicted the mobile phases that are suitable for TLC of the compounds studied, on the basis of their structures.

We did not make a comparison between calculated and experimental values of R_F since a good agreement is not expected, owing to the rough prediction of retention.

It is worth noting that there is a variation in R_F of a given compound. For instance, R_F of compound **6** varied from 0.27 to 0.55 with mobile phases 1–7 having $\varepsilon = 0.394$, but different m and P'. This tuning effect of m and P' is of importance to find an optimum mobile phase for separation of given compounds.[19,25] In fact, we were not interested in finding an optimum mobile phase for separation of the compounds studied, since they are not contained in a common reaction mixture. Our main goal was to find only suitable mobile phases, i.e., mobile phases ensuring retention in the favorable range of $0 < R_F < 1$.

CONCLUSIONS

The present application of the Snyder theory and software LSChrom[24] is successful in automatic prediction of seven mobile phases suitable for TLC of the complex heterocyclic compounds **1–12** on silica $60F_{254}$ (Merck, Germany). This conclusion is based on the fact that the experimental values of R_F with the selected mobile phases were practically in the favorable range of $0 < R_F < 1$. This is the fourth[23,25,26] and, consequently, not trivial, successful application of both theory and software.

The predictions made by LSChrom involve: (a) prediction of a 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 $\varepsilon = \varepsilon_{\text{recommended}}$.

All compounds studied have a *trans* configuration. The selected mobile phases can apply to TLC of the corresponding *cis* isomers or mixtures of both diastereomers.[5–11] If separation of both isomers is not obtained, other mobile phases having the recommended value of ε and different values of m and P' should be used.

The LSChrom software enables any user, even one not familiar with the Snyder theory, to apply it for an automatic selection of mobile phases for normal-phase TLC and HPLC of non-ionic compounds if their structures can be expressed by the structural fragments and functional groups available in the software.

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Received December 20, 2002
Accepted January 24, 2003
Manuscript 6040