STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, LIV, Sp.Iss. 2, 2009

CHEMICAL STRUCTURE DEPENDENCE OF SEPARATION METHODS' PARAMETERS*

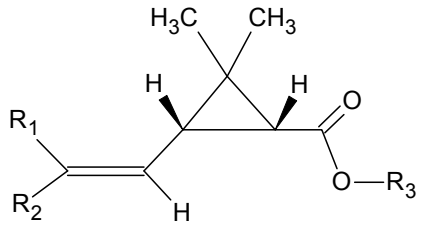
BÉLA TŐKÉS[a,], ZOLTÁN JUVANCZ[b], ROBERT IVÁNYI[c], GABRIELLA DONÁTH-NAGY[a], SZENDE VANCEA[a], VOLKER SCHURIG[d], ANCA-GABRIELA CÂRJE[a]**

ABSTRACT. Chromatographic research of pyrethroidic acids' isomerism offers an excellent possibility for a profound study of the structure dependence of separation parameters. In these compounds appears cumulated (geometrical and chiral) isomerism. Quantitative relations between separation parameters, chemical structure, partition coefficients and steric energy of isomers were established.

Keywords: Separation methods, pyrethroids, isomerism, structural effect relations

INTRODUCTION

In our earlier papers [1-3] we have demonstrated that the separation of steric isomers is decisively structure dependent. This dependence particularly manifests in the pyrethroid series [4] where both the geometric and chiral isomerisms are simoultaneously present:



In their structure there are two chiral centers (1, 3), and the cis(Z) and trans(E) isomerisms mean the steric arrangement of groups introduced in positions 1 and 3 correlate to the cyclopropane plane. Of course, both the

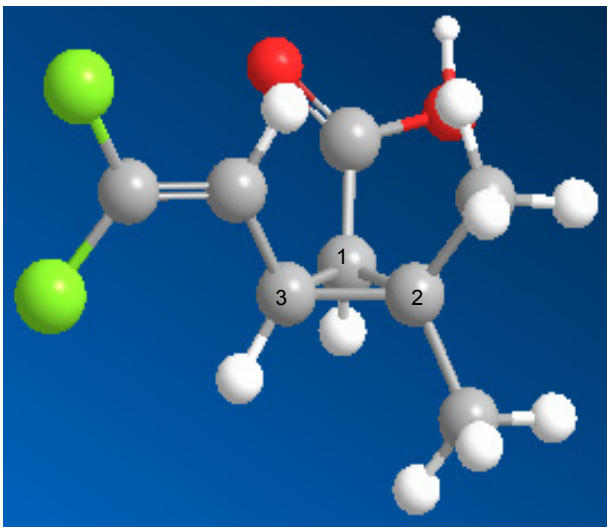
---

* *This paper was presented at the 15th International Conference on Chemistry, EMT, Tg. Mures, November 12-15, 2009*

[a] *University of Medicine and Pharmacy, Tg. Mureş, Physical Chemistry Laboratory, Romania, ** belatokes@yahoo.com*
[b] *Dep. of Environmental Engineering, Tech. Polytechnical Institution, Budapest, Hungary*
[c] *Cyclolab Cyclodextrin R & D. Laboratory Ltd., Budapest, Hungary*
[d] *University of Tübingen, Institute of Organic Chemistry, Germany*

chiral centers can adopt R or S configuration. As illustration are presented two examples (Figures 1a and 1b).

Hereinafter we will examine especially some gas chromatographic parameters of in ester form derivatized pyrethyroid acids.



Figue 1 a. Configuration of (1S,3R)-3-(2,2-((E)-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid

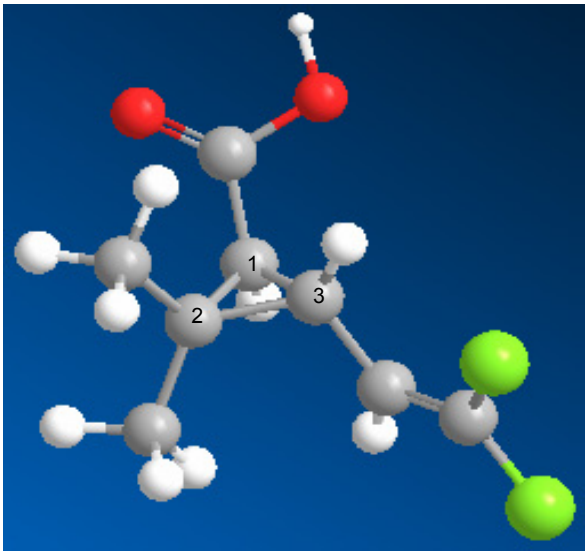


Figure 1 b. Configuration (1R,3R)-3-(2,2-((Z)-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid

RESULTS AND DISCUSSION

The selectivities of gas chromatografic separation of the compounds studied and introduced as guest molecules in inclusion complexes formed with Chirasil-Dex CSP as chiral selector are summed up in the Table 1 [2]. For interpretation of the structural effects this table also contains the inductive (σ^*) and the steric (E_S) Taft- constants of the ester forming alcohols' alchil groups [5].

Table 1. The gas chromatographic selectivities (α) of pyrethroid acids' esters measured in the presence of the Chirasil-Dex CSP as chiral selector in function of the chain length (n), at 100^{O}C

isomer	R1=R2	R3	α	n	σ*	E_S^O
cis	Me	H	1.275	0	0.490	0.25
trans	Me	H	1.153		0.490	0.25
cis	Me	Me	1.013	1	0.000	0.00
trans	Me	Me	<1.010		0.000	0.00
cis	Me	Et	<1.010	2	-0.100	-0.27
trans	Me	Et	<1.010		-0.100	-0.27
cis	Br	Me	1.046b		0.000	0.00
trans	Br	Me	1.040b		0.000	0.00
cis	Cal	H	1.284	0	0.490	0.25
trans	Cal	H	1.194b		0.490	0.25
cis	Cal	Me	1.043	1	0.000	0.00
trans	Cal	Me	1.010		0.000	0.00
cis	Cal	Et	1.023	2	-0.100	-0.27
cis	Cal	Pr	1.019	3	-0.115	-0.56
cis	Cal	Bu	1.014	4	-0.130	-0.59
cis	Cal	sub	1.034		-0.125	-1.13
cis	Cal	pier	<1.010		-0.190	-0.85
cis	Cal	tub	<1.010		-0.300	-2.14

One but not exclusive aim of derivatization (esterification) is to facilitate the gas chromatograpic operations, namely in this way the transfere of the studied compounds in gas phase becomes easier, their volatility get better, the polarity decreases, it can extend the measuring interval, increases the thermal stability, amplifies the detector sign, furthermore at inclusion complex formation can be favourably drive the interactions with the chiral selector.

Comparisons referring to the structural effects in the first steps were performed with esters of cis(Z)-permethrinic acid and right-chain alcohols, including as a limiting case acid itself. Separately, we are interpreted the selectivity of the ramificated-chain alcohols' esters, too [2]. To examine esters of the right- and the ramificated-chain alcohols offers a standing-ground the cross-checks of the Taft's substitution constants. From this it is evident, that according to their structural peculiarity the cis(Z)- and trans(E)-series must enlist in separate groups. Studying the selectivity of cis-permethrinic acid series it is visible that with the increasing of the chain-length (n) of ester-forming alcohol the α values decease (Table 1, Figure 2). Always, the separation of the underivatized acids is the better. That is often the negative side of the derivatization, and we try to explain it.

In the case of esters formed from right-chain alcohols the (α, n) values are distributed on an exponential curve written by the following equation:

$$y=y_0+A_1e^{x/t1}$$

Namely:

$$\alpha = 1{,}0175 + 0{,}2664 \exp(-2{,}326\ n)$$

$$N = 5 \qquad R = -0{,}9996$$

It is visible, that the exponential character with the elimination of the underivatized acid practically breake off.

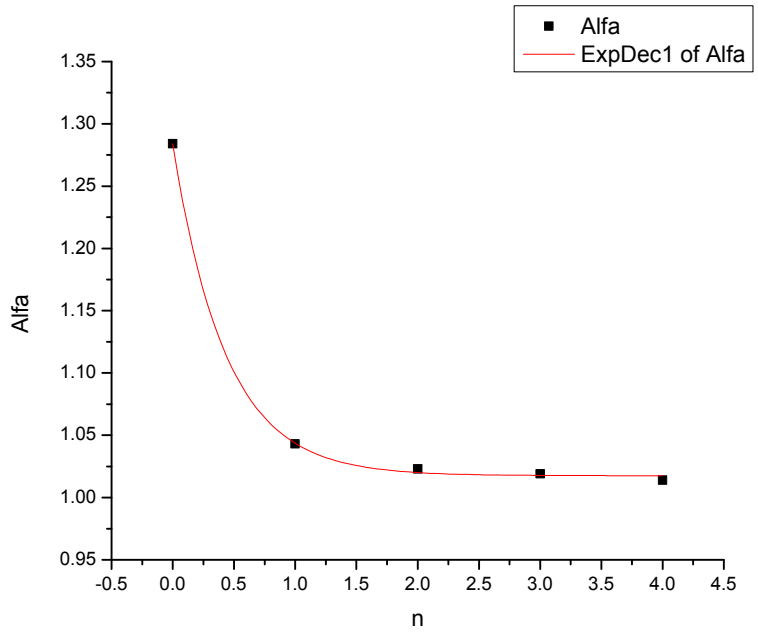


Figure 2. The (α,n) curve of cis-permethrin acid's esters: $R_1 = R_2$= Cal, R_3 = H (0), CH_3 (1), C_2H_5 (2), C_3H_7 (3), C_4H_9 (4)

Oppositely, the (lg α, lg n) correlation is significantly linear (Figure 3):

$$\log \alpha = - (0{,}0201 \pm 0{,}0030) \log n + (0{,}0175 \pm 0{,}0012)$$
$$N = 4 \qquad R = - 0{,}968$$

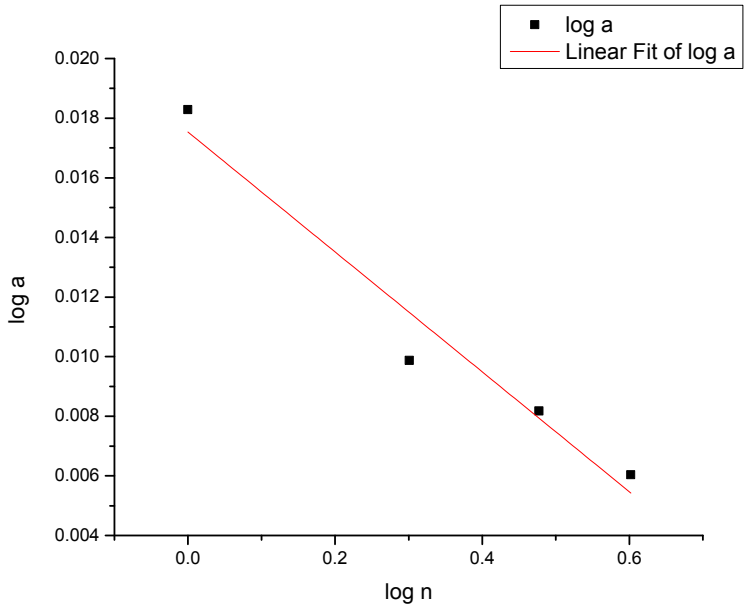


Figure 3. The (lg α, lg n) correlation of cis-.permethrin acid's esters

Since this equation may be written as

$$\lg (K_2/K_1) = - 0{,}020 \lg n + 0{,}0175$$

obviously we got to a special form of the linear free energy relations (Hammett, Taft, Hansch) as

$$\lg (K_2/K_1) = \rho\sigma + k,$$

or

$$\ln \alpha = \ln (K_B/K_A) = - \Delta(\Delta\mu_{BA}^{o})/RT = - \Delta_{BA}\Delta G^{o}/RT$$
$$= - (\Delta_{BA}\Delta H^{o}/R)\ 1/T + \Delta_{BA}\Delta S^{o}/R$$

Formally, the lg n terms, that is the logarithms of 1, 2, 3, 4 (0,00; 0,30; 0,48 and 0,60) acceptabily correspond with Taft's E_S values (0,00; 0,27; 0,56 and 0,59).

Perceptibly, the selectivity of ramificated alcohols' esters drop out of this normal distribution. As follows, since the structural parameters and physical data of esters are not available, we will assume that the changes in the properties of esters of basic pyrethroid (permethrin) acids are decisively produced by alcohols, and comparisons may be done between these

compounds and the corresponsive alchil-groups. After all, approximately monotonous change is observed if we follow the (α, σ*), respectively the (α, E_S) series. The more greater the negative numerical values of these substituent constants the more the chains are apolar. Significantly linear correlation was obtained only for the (lg α, σ*) values:

$$\lg \alpha = \lg(K_2/K_1) = 0{,}144\ \sigma^* + 0{,}030$$
$$N = 8,\ R = 0{,}965$$

That corroborates our earlier conclusion. The free term includes the steric effects.

To configure a mohr complet image on the studied phenomenon, we will use our model [6] proposed for describing the working mechanism of chiral selectors (cyclodextrins). After this point of view the formation of inclusion complexes and their stability may be described by the help of the repartition constants of a microequlibrium between the cavity of cyclodextrin, as an apolar phase, and its exterior polar surroundings (water). That is, between lg K_{st} and lg K_{OW} (log P) it requires a proportionality. The reparation constant is measured conventionally in 1-octanol/water system. At the same time, the measure of the polar-apolar character is given by the (relative) dielectric constant (ε) of the medium. Accordingly to expectation we obtained an excelent correlation between lg K_{OW} and ε (Table 2):

$$\lg K_{OW} = 50{,}76\ 1/\varepsilon - 2{,}14$$
$$N = 12 \quad R = 0{,}997$$

The more apolar is the dissolved compound the greater is the lg K_{OW} since it dissolves better in the apolar phase. If the apolar phase is considered the inside of cyclodextrin (regarded approximately as homogeneous), in the case of a given homologous series with increasing chain (i.e. with the decrease of the polar character) increases the inclusion complex stability (lg K_{st}) and inherently the lg K_{OW}, too. According to literature sources the dielectric constant of the cavity varies between 2 and 20. In the case of gas chromatographic measurements using a cyclic chiral selector to separate enantiomers it is necessary that these isomers be joint distinctly to the inner structure of selector. Both the very veak and the exceedingly strong bonding (complex stability) diminish the separation efficienty (selectivity). The longer the apolar chain the better the solubility of boh isomers in the apolar phase (in the cavity of the host molecule), more strongly are bound to the chiral selector, and the smaller will be the selectivity α. This interpretation agrees to the experimental data (Table 2).

For comparison, will be highlighted some data alluding to the complexity of phenomena (Table 3). It is apparent that although in the selected group the t-butyl alcohol's polarity is the smallest its miscibility is unlimited as long as the solubility of the more polar 1-butanol is relatively small [8]. The role of solvation particularities is obvious.

Table 2. Structure, dielectric constants and repartition coefficients of alcohols.

Name	Formula	n	ε	1/ε	lgK_{ow}
methanol	$H(CH_2)OH$	1	34.05	0.029	-0.66
ethnanol	$H(CH_2)_2OH$	2	25.2	0.040	-0.16
propanol	$H(CH_2)_3OH$	3	19.7	0.051	0.34
i-propanol	$H(CH_2CHCH_3)OH$	3	18.3	0,055	0.36*
n-butanol	$H(CH_2)_4OH$	4	17.7	0.056	0.88
sec.-butyl alcohol	$H(CH_3)_2(CH_2CH)OH$	4	16.4	0.061	0.805*
terc-butyl alcohol	$H(CH_3)_2CH_2COH$	4	12.3	0.081	0.806*
1-pentanol	$H(CH_2)_5OH$	5	14.4	0.069	1.40
2-pentanol	$H(CH_2)_3CH_3CHOH$	5	14.2	0,070	1.25*
3-pentanol	$H(CH_2)_3CH_3CHOH$	5	14.0	0,071	1.25*
hexanol	$H(CH_2)_6OH$	6	12.5	0.080	2.03
heptanol	$H(CH_2)_7OH$	7	11.1	0.090	2.53
octanol	$H(CH_2)_8OH$	8	9.8	0.102	3.03
decyl alcohol	$H(CH_2)_{10}OH$	10	8.1	0.123	4.03
i-amyl alcohol	$H(CH_3)_2C(CH_2)_2OH$	5	14.7	0.068	1.16
terc-amyl alcohol	$H(CH_3)_2(CH_2)_2COH$	5	5.70	0,175	1.25*
i-butyl alcohol	$H(CH_2)_2CH_3CHOH$	4	17.7	0.056	0.65

*The missing repartition coefficients were calculated by the Buchwald and Bodor's [7] additivity method: **H**: 0,086; **›C‹**: 0,182; **-CH‹:** 0,314; **-CH2-**: 0,446; **-CH3**: 0,579; **-OH:** -1,113.

Table 3. Physical parameters of some alcohols

Solvent	Boiling point (°C)	Fusion s-point (°C)	density (g/mL)	Solubility in water (g/100g)	Relatíve polarity
t-butyl alcohol	82.2	25.5	0.786	M	0.389
2-propanol	82.4	-88.5	0.785	M	0.546
1-butanol	117.6	-89.5	0.81	7.7	0.602
1-propanol	97	-126	0.803	M	0.617
ethanol	78.5	-114.1	0.789	M	0.654
methanol	64.6	-98	0.791	M	0.762
water	100.00	0.00	0.998	M	1.000

One from the purposes of esterification is the enhancement of the volatility, an important standing-point at gas chromatographic measurements. However the esters' selectivity is smaller like of acids. Consequently, the possible gain realized by the polarity's diminution is lost in separation selectivity. At the same time, the rate of evaporation [9-11] exponentially drops as a function of chain length (Figure 4):

$$V_p = -0.073+12.11\ e^{-0,026\ t_f}$$

N = 17 R = - 0,984

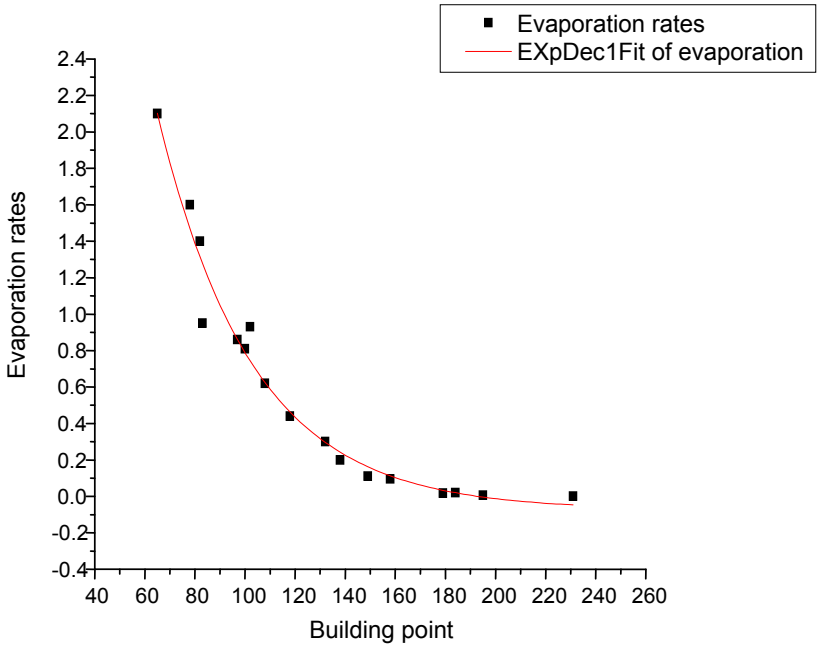


Figure 4. Relation between boiling points and evaporation rates of alcohols

It is a phenomenon frequently observed [2], that at gas chromatographic separation from geometrical isomers first pass through the Z(cis) form and its resolution is greater than of the E(trans) isomer. In our sight its explanation partially may be done by the drawn image. Since cis-isomers are in general more polar as against trans forms, these latters are stronger retained by selector, furthermore that is concomitant with a weaker separation of isomers Table 4, Figure 5).

Table 4. R_s and lg K_{OW} values of some pyrethyroid acids at pH = 6.5 using β-PMMACD as chiral selector

Nr	Trivial name	$R_1 = R_2$	R_S	lg K_{OW}
1	c-chrysanthemic acid	CH_3	8.5	3.18
2	tr.-chrysanthemic acid	CH_3	1.5	3.18
3	c-permethrinic acid	Cal	17.2	3.36
4	tr.-permethrinic acid	Cal	6.6	3.36
5	c-deltamethrinic acid	Br	20.0	3.54
6	tr.-deltamethrinic acid	Br	11.6	3.54

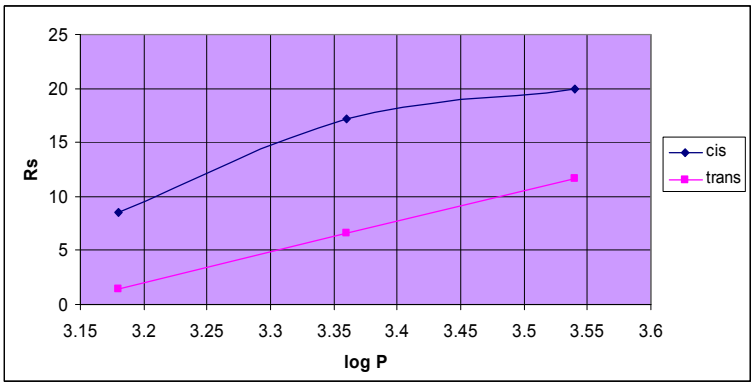


Figure 5. Relation between R_s and lg K_{OW} at some cis-trans isomers of pyrethroid acids

CONCLUSIONS

The gaschromatographic separation of derivatized (esterified) pyrethroid acids' enantiomers using Chirasil-Dex CSP as chiral selector is significantly dependent on the alcohols 'structure. This dependence is quantitatively represented by correlation of different parameters, as well. The authors have elaborated models to explaine the experimentally observed modifications.

The structure dependence of the selectivity represents a new form of the linear free energy relations.

EXPERIMENTAL SECTION

The separation of enantiomers of the studied chiral compounds (esters of pyretroid acids) was performed by gaschromatographic method [11-13], in the laboratory of CIB-Geigy Corporation (Basel, Switzerland). The conditions of the GC measurements: quartz capillary (10 m x 0.1 mm) with a Chirasil-Dex stationary phase (15 % chemically bound wetted permetril-β-cyclodextrin, in 0.15 μm thickness) The syntheses of pyrethroid esters and their parameters were described in earlier papers by one of authors [11-13].

Molecular modeling was performed with Chembio 3D from ChemBioOffice 2008 Ultra® 11.0 (Cambridgesoft, Cambridge, MA, USA) using the MM2 Molecular Mechanics algorithms running on a Windows platform. Host structures were built from the corresponding 2D drawings transferred in Chembio 3D and then fully optimized by help of the MM2 algorithm with a maximum iteration number of 1000. They were then inserted in the corresponding CD cavities and fully optimized. Data were processed using an Originlab Corp. Origin 7.0 program.

ACKNOWLEDGMENTS

This work has been supported in part by the research projects OTKA K72861 and NKTH OTKA 68863.

REFERENCES

1. L. Ferencz, B. Tőkés, F. Kilár, „Selector effects in the case of simultaneous presence of geometrical and optical isomerisms", 11th International Conference of Chemistry, Cluj, nov. 11-13, **2005**, Vol. Conf. 206.
2. Z. Juvancz, "Enantiomer elválasztások kapilláris kromatográfia módszerével", Akadémiai doktori értekezés, Vízgazdálkodási Tudományos Kutató Részvénytársaság, Vízminőségvédelmi Intézet, Budapest, **2001**.
3. B. Tőkés, L. Ferencz., P. Buchwald, G. Donáth-Nagy, Sz. Vancea, N. Sánta, E-L. Kis, *J. Biochem. Biophys. Methods*, **2008**, *70*, 1276.
4. L.Ferencz, "Pesticides" University Press, Tg. Mureş, **2006**.
5. B.P. Nikolsky (Ed.), "Spravochnik khimika", Vol. III, "Khimiya", Moskva, **1964**, *956*, 958.
6. B. Tőkés, G. Donáth-Nagy, Sz. Vancea, Cs. Kun, "Microequlibria at inclusion complexes. I. Theoretical bases", 14th International Conference on Chemistry. Hungarian Technical Scientific Society of Transsylvania, Cluj, November 13-15, **2008**, 146-150.
7. P. Buchwald, *J. Phys. Chem*., **2003**, *106*: 6864.
8. L.H. Hall, L.B. Kier, J. Wallace, W.J. Murray. *J Pharm Sci*, **1975**, *64*, 1974.
9. M. Kompany-Zareh, *Acta chimica slovenica*, **2003**, *50*, 259.
10. L. Qianfeng, Ch. Xingguo, H. Zhide, *Chemometrics and Intelligent Laboratory Systems*, **2004**, *72*, 93. References and further reading may be available for this article. To view references and further reading you must purchase this article.
11. Z. Juvancz, K. Grolimund, E. Francotte, *Chirality,* **1992**, *4*, 459.
12. E. Francotte, K. Grolimund, Z. Juvancz, *Chirality*, **1993**, *5*, 232.
13. Z.Z. Juvancz, K. Grolimund, V. Schurig, *J. Microcol. Separation*, **1993**, *5*, 459.