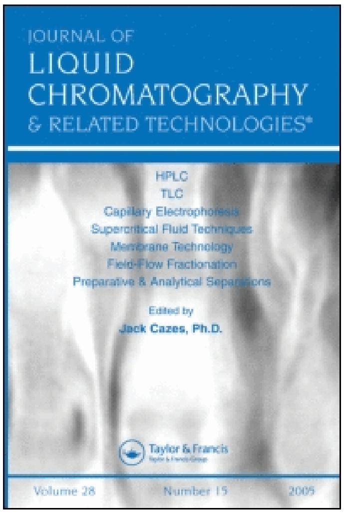

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Lipophilicity of Selected Bile Acids as Determined by TLC. III. Investigations on RP2 Stationary Phase

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Abstract: The following bile acids: cholic acid (C), glycocholic acid (GC), glycodeoxycholic acid (GDC), chenodeoxycholic (CDC), deoxycholic acid (DC), lithocholic acid (LC), and glycolithocholic acid (GLC) were investigated with the use of reversed phase thin-layer chromatography on RP2 plates (E. Merck, # 1.13726) using methanol-water, organic mixture (acetonitrile-methanol 50:50, v/v)-water, acetone-water, dioxane-water in different volume compositions as mobile phases. The chromatographic parameters of lipophilicity (R_{MW} and φ_0) of studied bile acids were determined. Lipophilic parameters (R_{MW} and φ_0) were compared, both with measured partition coefficients ($\log P_{exp}$) and calculated ones ($A\log P_S$, IAlogP, $\log P_{KOWIN}$, xlogP, clogP, $\log P_{Rekker}$). The most significant correlation was found between R_{MW} and φ_0 lipophilic parameters and $\log P_{KOWIN}$ values. IAlogP correlates with the a/m lipophilic parameters slightly more poorly than $\log P_{KOWIN}$ does. The values of R_{MW} and φ_0 lipophilic parameters obtained on both, RP2 and RP18W plates with the use of the a/m mobile phases, indicate that the investigated bile acids may be listed in order of decreasing lipophilicity as follows: LC $>$ DC $\approx$ CDC $\approx$ GLC $>$ C $\approx$ GDC $>$ GC.

Keywords: Bile acids, RP-HPTLC, RP2, Lipophilicity

INTRODUCTION

Lipophilicity of a substance is one of the parameters which influence its biological activity. Partition coefficients, usually expressed as logP values, are used as a measure of lipophilicity. LogP values can be computed or

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determined experimentally. LogP can be determined experimentally by a classical method of measuring partition coefficient of the organic compound between a non polar phase and water.[1] Chromatography, especially reversed phase thin-layer chromatography (RP-TLC) is now widely used to determine the lipophilicity of bioactive compounds.[2–7] The major advantages of RP-TLC are its rapidity, ready availability, and the possibility of simultaneous analysis of a large number of samples, and the compounds applied not needing to be very pure.[8]

Our previous study referred to the determination of lipophilicity parameters (R_{MW}) on RP18W plates using methanol-water, organic mixture-water, dioxane-water and acetone-water as mobile phases.[9,10] It was stated that the a/m mobile phases are suitable for the estimation of the lipophilicity of examined bile acids on RP18W stationary phase. The obtained values of R_{MW} and φ_0 lipophilic parameters indicate that the investigated bile acids may be listed in order of decreasing lipophilicity as follows: LC > DC $\approx$ CDC $\approx$ GLC > C $\approx$ GDC > GC. The most significant correlation was found between lipophilic parameters (R_{MW} and φ_0) and $\log P_{KOWIN}$ calculated from atom/fragmental contribution values. It was found that chromatographic parameter of lipophilicity (R_{MW}) may be an alternative method of lipophilicity determination for examined bile acids.

The aim of the present study was to compare the lipophilic parameters (R_{MW} and φ_0) for the studied bile acids obtained on RP2 plates using different mobile phases with the lipophilicity values estimated by computational methods, and with the previous values of R_{MW} and φ_0 obtained on RP18W plates.[9,10]

EXPERIMENTAL

Chemicals

The following components of a mobile phase: methanol (Merck, Germany; pure p. a), acetonitryle (Merck, Germany pure p. a), acetone (POCh, Gliwice, Poland; pure p. a), dioxane (POCh, Gliwice, Poland; pure p. a), ethanol (POCh, Gliwice, Poland; pure p. a), and distilled water (Department of Analytical Chemistry, Faculty of Pharmacy, Sosnowiec, Poland) were used for TLC analysis. The commercial samples of C, DC, CDC, LC, GLC, GDC, and GC (St. Louis, Sigma Company, USA) were used as test solutes. Methanol (POCh, Gliwice, Poland; pure p. a.) was used for the preparation of bile acids solutions. Phosphomolibdic acid (POCh, Gliwice, Poland) was used to prepare a visualizing reagent.

Sample Preparation

The methanolic solutions of the above mentioned bile acids in 50 mg/10 mL concentrationa for each acid were prepared.

Reversed-Phase Thin-Layer Chromatography

Thin–layer chromatography was done on RP-HPTLC RP2 (E. Merck, #1.13726) glass plates. Solutions of examined bile acids were spotted on chromatographic plates in quantities of 5 μg for each bile acid in 1 μL of methanol. The chromatograms were developed by using the mixture of an organic modifier (methanol, dioxane, acetonitrile, acetone)-water in the following volume compositions: methanol-water, the content of methanol in a mobile phase was gradually varied by 5% [%, v/v] from 35–100 [%, v/v]; organic mixture (methanol-acetonitrile, 50:50, v/v)-water, the content of organic mixture in a mobile phase was gradually varied by 5% [%, v/v] from 35–100 [%,v/v]; acetone-water, the content of acetone in a mobile phase was gradually varied by 5% [%, v/v] from 35–80 [%, v/v]; dioxane-water, the content of acetone in a mobile phase was gradually varied by 5% [%, v/v] from 35–80 [%, v/v].

A mobile phase of 50 mL was placed into a classical chamber. The chamber was saturated with solvent for 20 minutes. The development distance was 8.5 cm. After development and drying the plates, the spots were visualized by dipping them in the 10% ethanol solution of phosphomolibdic acid and then they were heated for 20 minutes at 120°C. The chromatograms were run in triplicate.

Determination of Lipophilicity Parameters

The values of theoretical partition coefficients, i.e., AlogPs, IAlogP, clogP, $\log P_{KOWIN}$, xlogP, and $\log P_{Rekk}$ for the studied bile acids were presented in our previous papers.[9,10] The parameters of lipophilicity, i.e., $\mathbf{R_{MW}}$ and $\boldsymbol{\varphi_0}$, were determined on the base of R_M values extrapolated to zero concentration of organic modifier in eluent, in accordance with respective equations presented in our previous papers.[9,10]

RESULTS AND DISSCUSION

In order to estimate the lipophilicity of examined bile acids, which were obtained using RP2 (#1.13726) plates, the R_M values were extrapolated to zero content of organic modifier in a mobile phase. The correlation Equations (1)–(28) were obtained (Tables 1–4). The high correlation coefficients (r), the values of Fisher test (F), the significance levels (p), and small values of standard errors of the estimates (s) indicated that all the obtained equations were highly significant. The R_{MW} values obtained in this way indicate that LC shows the highest lipophilicity regardless of the applied chromatographic conditions, whereas GC has the lowest lipophilicity. Both, CDC and DC acids have similar lipophilicity, which is lower than the lipophilicity of LC. The C and GDC also have similar lipophilicity, which is higher than the

Table 1. Parameters of linear correlation (±S.D.) between R_M values of bile acids and organic phase content in methanol—water mobile phase (according to Eq.: $R_M = R_{MW} - S \cdot \varphi^a$)

Acid	R_{MW}	S	r	s	F	n	Eq. no.
LC	4.324(±0.153)	5.326(±0.184)	0.9964	0.060	835.5	8	(1)
DC	3.818(±0.201)	4.940(±0.248)	0.9913	0.096	397.8	9	(2)
CDC	3.539(±0.161)	4.690(±0.199)	0.9937	0.077	554.0	9	(3)
GLC	3.137(±0.174)	4.208(±0.215)	0.9910	0.083	383.8	9	(4)
C	3.072(±0.158)	4.288(±0.209)	0.9941	0.055	418.9	7	(5)
GDC	2.784(±0.187)	3.999(±0.231)	0.9885	0.090	299.4	9	(6)
GC	2.163(±0.209)	3.369(±0.276)	0.9837	0.073	149.3	7	(7)

Note: n, number of points used to derive the particular regression Eq.: $R_M = R_{MW} - S \cdot \varphi$; r, correlation coefficients; s, standard error of the estimate; F, value of Fisher test.

[a] For all equations the significance levels $p < 0.0001$.

lipophilicity of GC. Whereas, GLC shows the lipophilicity similar to DC and CDC acids in almost all applied chromatographic systems, except when the mobile phase methanol–water was used, in which case GLC lipophilic properties seem more similar to those of C (Table 1).

It was found that the values of R_{MW} lipophilicity parameters obtained by using RP-HPTLC depend linearly on the slope of regression curve S (Table 5, Eq. (29)–(32). All Equations (29)–(32) have the correlation coefficients higher than 0.9908. Thus, the examined bile acids form a congeneric class and they may be considered as compounds belonging to the same group

Table 2. Parameters of linear correlation (±S.D.) between R_M values of bile acids and organic phase content in methanol–acetonitrile—water mobile phase (according to Eq.: $R_M = R_{MW} - S \cdot \varphi^a$)

Acid	R_{MW}	S	r	s	F	n	Eq. no.
LC	3.871(±0.137)	5.006(±0.169)	0.9960	0.066	874.5	9	(8)
DC	3.346(±0.202)	4.646(±0.249)	0.9900	0.097	346.8	9	(9)
CDC	3.421(±0.214)	4.741(±0.264)	0.9893	0.102	322.5	9	(10)
GLC	3.207(±0.347)	4.530(±0.429)	0.9700	0.166	111.6	9	(11)
C	2.441(±0.130)	3.668(±0.172)	0.9945	0.045	454.3	7	(12)
GDC	2.307(±0.156)	3.514(±0.206)	0.9915	0.054	291.8	7	(13)
GC	1.828(±0.214)	3.140(±0.283)	0.9803	0.075	123.1	7	(14)

Note: n, number of points used to derive the particular regression Eq.: $R_M = R_{MW} - S \cdot \varphi$; r, correlation coefficients; s, standard error of the estimate; F, value of Fisher test.

[a] For all equations the significance levels $p < 0.0001$.

Table 3. Parameters of linear correlation (±S.D.) between R_M values of bile acids and organic phase content in acetone-water mobile phase (according to Eq.: $R_M = R_{MW} - S \cdot \varphi^a$)

Acid	R_{MW}	S	r	s	F	n	Eq. no.
LC	4.637(±0.363)	6.163(±0.552)	0.9805	0.146	124.8	7	(15)
DC	3.374(±0.163)	4.678(±0.248)	0.9930	0.066	355.8	7	(16)
CDC	3.300(±0.151)	4.628(±0.230)	0.9939	0.061	405.2	7	(17)
GLC	3.381(±0.216)	4.729(±0.328)	0.9882	0.087	208.2	7	(18)
C	2.775(±0.122)	4.176(±0.186)	0.9951	0.049	505.8	7	(19)
GDC	2.703(±0.135)	4.041(±0.205)	0.9936	0.054	387.9	7	(20)
GC	2.147(±0.056)	3.619(±0.086)	0.9986	0.023	178.6	7	(21)

Note: n, number of points used to derive the particular regression Eq.: $R_M = R_{MW} - S \cdot \varphi$; r, correlation coefficients; s, standard error of the estimate; F, value of Fisher test.

[a] For all equations the significance levels $p < 0.0001$.

because they show the linear relationship between R_{MW} values and the slope of regression curve S.

The φ_0 values obtained for the group of congeneric derivatives may be used as a standard for comparison of their lipophilicity degree.[11] The values of obtained lipophilicity parameters (φ_0) indicate that the lipophilicity of examined bile acids should decrease in the following order: LC > DC ≈ CDC ≈ GLC > C ≈ GDC > GC (Table 6). Thus, the lipophilic parameter φ_0 may be used as a relative measure of the lipophilicity of studied bile acids.

Table 4. Parameters of linear correlation (±S.D.) between R_M values of bile acids and organic phase content in dioxane—water mobile phase (according to Eq.: $R_M = R_{MW} - S \cdot \varphi^a$)

Acid	R_{MW}	S	r	s	F	n	Eq. no.
LC	4.417(±0.192)	6.155(±0.280)	0.9938	0.091	481.3	8	(22)
DC	3.542(±0.132)	5.222(±0.193)	0.9959	0.062	731.2	8	(23)
CDC	3.654(±0.134)	5.393(±0.203)	0.9951	0.078	707.1	9	(24)
GLC	3.902(±0.179)	5.829(±0.271)	0.9925	0.105	463.8	9	(25)
C	3.362(±0.166)	5.269(±0.260)	0.9904	0.118	412.0	10	(26)
GDC	2.919(±0.161)	4.708(±0.243)	0.9908	0.094	373.8	9	(27)
GC	2.357(±0.128)	4.117(±0.201)	0.9929	0.065	419.2	8	(28)

Note: n, number of points used to derive the particular regression Eq.: $R_M = R_{MW} - S \cdot \varphi$; r, correlation coefficients; s, standard error of the estimate; F, value of Fisher test.

[a] For all equations the significance levels $p < 0.0001$.

Table 5. Parameters of linear correlations (±S.D.) between R_M values of bile acids and slope S for examined mobile phases according to Eq.: $R_{MW} = a \times S + c$

	The parameters of Eq.: $R_{MW} = a \times S + c$		Statistical parameters				
	a	c	r	s	F	p	Eq. no.
$R_{MW\ (m)}$	1.091(±0.039)	−1.540(±0.174)	0.9968	0.062	771.9	<0.0001	(29)
$R_{MW\ (or)}$	1.010(±0.045)	−1.302(±0.189)	0.9952	0.079	512.3	<0.0001	(30)
$R_{MW\ (d)}$	0.976(±0.060)	−1.668(±0.316)	0.9908	0.099	266.6	<0.0001	(31)
$R_{MW\ (a)}$	1.222(±0.198)	−0.964(±0.043)	0.9951	0.085	507.3	<0.0001	(32)

Note: methanol–water (m), organic mixture–water (or), dioxane–water (d), acetone–water (a).

The R_{MW} values for the examined bile acids, obtained by using RP-HPTLC on RP2 plates, were compared with experimental partition coefficients and partition coefficients calculated using different theoretical methods. Both, the values of experimental partition coefficients and those estimated by using computational methods were presented previously.[9,10] Of all the obtained R_{MW} values, the ones obtained by applying RP2 plates and organic mixture–water as a mobile phase are most similar to the absolute experimental values of logP.

Moreover, it was observed that the lipophilic parameter R_{MW}, determined on RP2 plates by using all applied mobile phases, correlates best with the values of partition coefficients calculated by using $\log P_{KOWIN}$ method ($r > 0.9269$) (Table 7). Whereas, the parameter φ_0, obtained by using the same mobile phase, correlates better with both, the experimental partition coefficients and the ones calculated with the use of different databases than R_{MW} does (Table 8). Both a/m lipophilic parameters, i.e., R_{MW} and φ_0,

Table 6. The values of lipophilicity parameters φ_0 obtained for studied bile acids investigated by using various mobile phases according to Eq.: $\varphi_0 = R_{MW}/S$

Acid	$\varphi_{0\ (m)}$	$\varphi_{0\ (or)}$	$\varphi_{0\ (d)}$	$\varphi_{0\ (a)}$
LC	0.812	0.773	0.718	0.752
DC	0.773	0.720	0.678	0.721
CDC	0.754	0.722	0.678	0.713
GLC	0.745	0.708	0.669	0.715
C	0.716	0.665	0.638	0.664
GDC	0.696	0.656	0.620	0.669
GC	0.642	0.582	0.572	0.593

Note: methanol–water (m), organic mixture–water (or), dioxane–water (d), acetone–water (a).

Table 7. The values of correlation coefficients of linear relationship between lipophilicity parameters R_{MW} and partition coefficients

	$\log P_{exp}$[12]	$\log P_{exp}$[13]	$\log P_{exp}$[14]	$AlogP_S$	IAlogP	clogP	$\log P_{KOWIN}$	xlogP	$\log P_{Rekker}$
$R_{MW(m)}$	0.8557	0.9344	0.9312	0.8570	0.8757	0.7906	0.9269	0.8638	0.8638
$R_{MW\ (or)}$	0.9643	0.9452	0.9735	0.9165	0.9508	0.8950	0.9763	0.8911	0.9557
$R_{MW\ (d)}$	0.8120	0.7962	0.8199	0.9280	0.9602	0.8958	0.9403	0.8789	0.9328
$R_{MW\ (a)}$	0.9081	0.9447	0.9552	0.9501	0.9634	0.9041	0.9465	0.9116	0.9062

Note: methanol–water (m), organic mixture–water (or), acetone–water (a), dioxane–water (d).

Table 8. The values of coefficients correlation of linear relationship between lipophilicity parameters φ_0 and partition coefficients

	$\log P_{exp}{}^{[12]}$	$\log P_{exp}{}^{[13]}$	$\log P_{exp}{}^{[14]}$	$AlogP_S$	IAlogP	clogP	$\log P_{KOWIN}$	xlogP	$\log P_{Rekker}$
$\varphi_{0\ (m)}$	0.8584	0.9304	0.9292	0.9134	0.9270	0.8630	0.9657	0.9119	0.9287
$\varphi_{0\ (or)}$	0.8930	0.9072	0.9240	0.9267	0.9524	0.8955	0.9837	0.9178	0.9552
$\varphi_{0\ (d)}$	0.8886	0.9026	0.9193	0.9182	0.9477	0.8817	0.9746	0.9022	0.9470
$\varphi_{0\ (a)}$	0.8701	0.9206	0.9261	0.9380	0.9450	0.9172	0.9864	0.9449	0.9747

Note: methanol–water (m), organic mixture–water (or), dioxane–water (d), acetone–water (a).

Table 9. The values of correlation coefficients of linear relationship between lipophilicity parameters R_{MW} obtained on RP18W and RP2 plates by using various mobile phases[a]

	$RP2_{(m)}$	$RP2_{(or)}$	$RP2_{(d)}$	$RP2_{(a)}$
$RP18W_{(m)}$	0.9883	0.9704	0.9189	0.9627
$RP18W_{(or)}$	0.9884	0.9586	0.8818	0.9272
$RP18W_{(d)}$	0.9146	0.9920	0.9197	0.8940
$RP18W_{(a)}$	0.9607	0.9594	0.9559	0.9913

[a] *Note:* methanol–water (m), organic mixture–water (or), dioxane–water (d), acetone–water (a).

determined by using RP-HPTLC on RP2 plates, correlate the best with $\log P_{KOWIN}$ partition coefficient. However, R_{MW} and φ_0 correlate with IAlogP equally well as with $\log P_{KOWIN}$. Moreover, it was stated that the obtained R_{MW} and φ_0 parameters correlate best with experimental partition coefficients ($\log P_{exp}$) given after Roda and coauthors.[14]

The correlation coefficients of both lipophilic parameters (R_{MW} and φ_0), obtained under all applied chromatographic conditions on RP2 and RP18W plates, were compared. Correlation coefficients values of linear relationships between the parameters of lipophilicity (R_{MW}), which were obtained under different chromatographic conditions, are presented in Table 9. The highest value of correlation coefficient ($r = 0.9920$) was obtained for the relationship between R_{MW} values obtained on RP2 plates by using organic mixture–water as a mobile phase, and R_{MW} values obtained on RP18W plates by using dioxane–water as a mobile phase. The correlation coefficient values for R_{MW} obtained on RP18W with the use of dioxane–water as a mobile phase were lower. A high correlation coefficient ($r = 0.9913$) of linear relationship between R_{MW} values obtained by using acetone–water as a mobile phase was found for both stationary phases, i.e., RP2 and RP18W. Similarly, the R_{MW} values obtained on RP2 plates by using a methanol–water mobile phase correlate well with R_{MW} values obtained on RP18W plates using, respectively, methanol–water, organic mixture–water and acetone–water as mobile phases. In Table 10, the correlation coefficients of linear correlation of relationship between lipophilic parameters φ_0 determined in different chromatographic systems are presented. It was stated that φ_0 values correlate with each other better ($r > 0.98$) than R_{MW} values.

Further investigations are in progress and concern the use of CN stationary phase to evaluate the lipophilicity of studied bile acids.

CONCLUSION

It was stated that the applied stationary phase RP2 (#1.13726), the same as previously used RP18W, can be applied to estimate the lipophilicity of

Table 10. The values of correlation coefficients of linear relationship between lipophilicity parameters φ_0 obtained on RP18W and RP2 plates by using various mobile phases[a]

	RP2 $_{(m)}$	RP2 $_{(or)}$	RP2 $_{(d)}$	RP2 $_{(a)}$
RP18W $_{(m)}$	0.9879	0.9988	0.9952	0.9872
RP18W $_{(or)}$	0.9895	0.9984	0.9981	0.9883
RP18W $_{(d)}$	0.9821	0.9920	0.9928	0.9847
RP18W $_{(a)}$	0.9823	0.9960	0.9921	0.9963

[a] *Note:* methanol–water (m), organic mixture–water (or), dioxane–water (d) acetone–water (a).

examined bile acids. The values of obtained lipophilicity parameters, i.e., φ_0 and R_{MW}, indicate that the lipophilicity of examined bile acids should decrease in the following order: LC > DC ≈ CDC ≈ GLC > C ≈ GDC > GC.

The most significant correlation was found between the values of R_{MW} and φ_0 lipophilic parameters and $\log P_{KOWIN}$. IAlogP correlates with the a/m lipophilic parameters slightly worse than $\log P_{KOWIN}$ does.

The R_{MW} and φ_0 lipophilic parameter values obtained on both, RP2 and RP18W plates with the use of a/m mobile phases, indicate that the investigated bile acids may be listed in order of decreasing lipophilicity as follows: LC > DC ≈ CDC ≈ GLC > C ≈ GDC > GC.

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