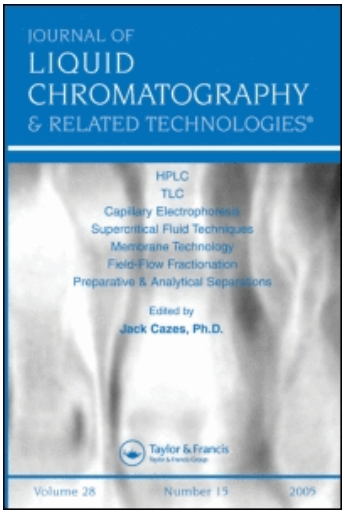

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Lipophilicity of Selected Bile Acids, as Determined by TLC. IV. Investigations on CNF_{254} Stationary Phase

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Abstract: The aim of our study was to determine the lipophilicity of selected bile acids, i.e., cholic acid (C), glycocholic acid (GC), glycodeoxycholic acid (GDC), chenodeoxycholic (CDC), deoxycholic acid (DC), lithocholic acid (LC), and glycolithocholic acid (GLC) with the use of reversed phase thin-layer chromatography on CNF_{254} plates (E. Merck, #1.12571) and methanol-water, organic mixture (acetonitrile–methanol 50 : 50, v/v)–water, acetone–water, dioxane–water in different volume compositions as mobile phases. Lipophilicities R_{MW} and φ_0 were compared, both with measured partition coefficients ($logP_{exp}$) and the calculated ones ($AlogP_S$, IAlogP, $logP_{KOWIN}$, xlogP, clogP, $logP_{Rekker}$). The most significant correlation was found between R_{MW} and φ_0 lipophilic parameters and $logP_{KOWIN}$ values. Moreover, it was stated that the obtained parameters R_{MW} and φ_0 correlate best with experimental partition coefficients ($logP_{exp}$) given after Roda and coauthors. The values of R_{MW} and φ_0 lipophilic parameters obtained on RP18W, RP2, and CNF_{254} 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 ≈ CDC ≈ GLC > C ≈ GDC > GC.

Keywords: Bile acids, CNF_{254} RP-HPTLC, Lipophilicity

INTRODUCTION

Lipophilicity of a substance is one of the parameters which determine its biological activity.[1] Quantitative structure–activity relationships (QSAR) tech-

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niques are commonly utilized to investigate the relationships between biological activity of chemical substances used as drugs and their chemical structures. QSAR plays a crucial role in designing new drugs. The possibility to predict drugs biological properties due to their lipophilicity allows optimization of new drugs structure designs.

The most frequently applied lipophilicity parameter is logP determined by theoretical methods or chromatographic techniques, of which planar chromatography is mainly used (R_{MW}). A methanol–water system is the mobile phase most often employed to predict lipophilicity using RP-TLC and RP-HPTLC, whereas RP18 is the most recommended stationary phase.[2]

Scientific literature describes a lot of examples utilizing the chromatographic parameter of lipophilicity (R_{MW}) obtained by planar chromatography to estimate biological activity of new drugs.[3–7]

Our previous study referred to the determination of lipophilicity parameters (R_{MW} and φ_0) on RP18W and RP2 plates using methanol–water, methanol–acetonitrile–water, dioxane–water, and acetone–water as mobile phases.[8–10] It was stated that the a/m mobile phases were suitable for the estimation of the lipophilicity of examined bile acids on those stationary phases. 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 ≈ CDC ≈ GLC > C ≈ GDC > GC. The most significant correlation was found between lipophilic parameters (R_{MW} and φ_0) and $logP_{KOWIN}$ calculated from atom/fragmental contribution values. It was found that the chromatographic parameter of lipophilicity (R_{MW}) may be an alternative method of determining lipophilicity of examined bile acids.

The aim of the present study was to determine the lipophilicities R_{MW} and φ_0 for the studied bile acids obtained on CNF_{254} (#1.12571) plates using different mobile phases. The obtained lipophilicity values were compared with those estimated by computational methods, and with the previous values of R_{MW} and φ_0 obtained on both RP18W and RP2 plates.[8–10]

EXPERIMENTAL

Chemicals

The following components of a mobile phase: methanol (Merck, Germany; pure p. a), acetonitrile (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 distillate 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 the concentration of 50 mg/10 mL, for each acid, were prepared.

Reversed-Phase Thin-Layer Chromatography

Thin-layer chromatography was done on RP-HPTLC CNF_{254} (E. Merck, #1.12571) glass plates. Solutions of examined bile acids were spotted on chromatographic plates in quantities of 5 μg of 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:

a) methanol water, the content of methanol in a mobile phase was gradually varied by 5% [%, v/v] from 35–80 [%, v/v];
b) 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 35–80 [%,v/v];
c) acetone–water, the content of acetone in a mobile phase was gradually varied by 5% [%, v/v] from 30–80 [%, v/v];
d) dioxane–water, the content of acetone in a mobile phase was gradually varied by 5% [%, v/v] from 30–80 [%, 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., $AlogP_S$, IAlogP, clogP, $logP_{KOWIN}$, xlogP, and log P_{Rekker} for the studied bile acids were presented in our previous papers.[8–10] The parameters of lipophilicity, i.e., R_{MW} and φ_0, were determined on the basis of R_M values extrapolated to zero concentration of organic modifier in eluent, in accordance with respective equations presented in our previous papers.[8–10]

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	3.634 (±0.127)	4.982 (±0.191)	0.9949	0.074	679.91	9	(1)
DC	2.828 (±0.167)	4.151 (±0.254)	0.9907	0.067	265.95	7	(2)
CDC	3.165 (±0.128)	4.704 (±0.201)	0.9946	0.065	547.76	8	(3)
GLC	2.512 (±0.192)	3.848 (±0.290)	0.9807	0.112	175.98	9	(4)
C	2.266 (±0.163)	3.652 (±0.256)	0.9856	0.083	203.20	8	(5)
GDC	1.702 (±0.133)	2.854 (±0.201)	0.9831	0.078	202.18	9	(5)
GC	1.282 (±0.161)	2.559 (±0.253)	0.9719	0.082	102.31	8	(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 $p < 0.0001$.

RESULTS AND DISCUSSION

In order to estimate the lipophilicity of seven examined bile acids, the R_M values obtained with the use of CNF_{254} (#1.12571) plates were extrapolated to zero content of organic modifier in a mobile phase. Correlation equations (1)–(28) were obtained (Tables 1–4). The high correlation coefficients (r),

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.: $R_M = R_{MW} - S(\varphi^a)$

Acid	R_{MW}	S	r	s	F	n	Eq. no.
LC	3.152 (±0.083)	4.750 (±0.125)	0.9976	0.048	1445.23	9	(8)
DC	2.594 (±0.121)	4.247 (±0.182)	0.9936	0.071	542.25	9	(9)
CDC	2.406 (±0.106)	3.997 (±0.160)	0.9944	0.062	625.63	9	(10)
GLC	2.393 (±0.258)	4.166 (±0.390)	0.9777	0.151	114.17	9	(11)
C	2.195 (±0.197)	4.000 (±0.300)	0.9811	0.115	180.17	9	(12)
GDC	1.545 (±0.200)	3.041 (±0.315)	0.9693	0.102	93.36	8	(13)
GC	1.356 (±0.265)	3.058 (±0.418)	0.9784	0.086	95.63	8	(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 $p < 0.0005$.

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	2.545 (±0.130)	3.635 (±0.198)	0.9926	0.052	336.21	7	(15)
DC	1.923 (±0.092)	3.006 (±0.140)	0.9946	0.037	458.62	7	(16)
CDC	1.957 (±0.126)	3.111 (±0.192)	0.9906	0.051	263.22	7	(17)
GLC	1.656 (±0.168)	2.616 (±0.256)	0.9859	0.040	103.99	5	(18)
C	1.532 (±0.074)	2.746 (±0.118)	0.9982	0.013	544.36	4	(19)
GDC	1.520 (±0.159)	2.800 (±0.253)	0.9919	0.028	122.42	4	(20)
GC	0.801 (±0.218)	1.926 (±0.321)	0.9787	0.026	86.04	6	(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 $p < 0.01$.

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 had similar lipophilicity in almost all applied mobile phases, except when the mobile phase methanol–water was used, since CDC lipophilic properties were

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	3.006 (±0.159)	4.735 (±0.240)	0.9911	0.093	387.47	8	(22)
DC	2.338 (±0.080)	3.961 (±0.120)	0.9968	0.047	1079.64	8	(23)
CDC	2.346 (±0.088)	4.039 (±0.134)	0.9962	0.052	913.13	8	(24)
GLC	2.393 (±0.110)	4.009 (±0.167)	0.9940	0.064	577.22	8	(25)
C	1.690 (±0.081)	3.196 (±0.128)	0.9952	0.041	625.94	7	(26)
GDC	1.639 (±0.093)	3.164 (±0.147)	0.9936	0.048	464.57	7	(27)
GC	1.551 (±0.170)	3.204 (±0.258)	0.9841	0.068	153.78	7	(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 $p < 0.0005$.

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.
$R_{MW\ (m)}$	0.910 (±0.042)	−0.992 (±0.164)	0.9947	0.092	469.3	<0.0001	(29)
$R_{MW\ (or)}$	0.963 (±0.076)	−1.515 (±0.076)	0.9850	0.116	162.6	<0.0005	(30)
$R_{MW\ (d)}$	0.850 (±0.018)	−1.036 (±0.070)	0.9988	0.028	2122.2	<0.0001	(31)
$R_{MW\ (a)}$	1.003 (±0.088)	−1.137 (±0.252)	0.9813	0.112	130.3	<0.0005	(32)

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

similar to those of LC. The R_{MW} obtained for C and GDC were similar when the dioxane–water and acetone–water were used as mobile phases. Whereas, by using methanol–water and organic mixture–water as mobile phases, the R_{MW} for C was similar to GLC (Tables 1 and 2).

Under the remaining chromatographic conditions, i.e., by using acetone–water and dioxane–water as mobile phases, C showed similar lipophilicity properties to GDC (Tables 3 and 4). GLC showed lipophilicity similar to the lipophilicity of acids C and GDC, or DC and CDC, depending on applied mobile phase (Tables 1–4).

It was found that the values of R_{MW} lipophilicity parameters obtained by using CNF_{254} depended linearly on the slope of regression curve S (Table 5, Eqs. (29)–(32)). All Equations (29)–(32) have the correlation coefficients higher than 0.9813. Thus, the examined bile acids form a congeneric class and they may be considered as compounds belonging to the same group 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.[2] The values of obtained lipophilicity parameters φ_0 (Table 6) indicate that the lipophilicity of bile acids examined on CNF_{254} plates should decrease in the following order: LC > DC ≈ CDC ≈ GLC > C ≈ GDC > GC. Thus, the lipophilic parameter φ_0 may be used as a relative measure of the lipophilicity of studied bile acids.

The R_{MW} and φ_0 values for the examined bile acids, obtained by using RP-HPTLC on CNF_{254} 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.[8–10] Of all the obtained R_{MW} values, the ones obtained by applying CNF_{254}

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	0.729	0.664	0.635	0.700
DC	0.681	0.611	0.590	0.640
CDC	0.673	0.602	0.581	0.629
GLC	0.653	0.574	0.597	0.633
C	0.620	0.548	0.529	0.558
GDC	0.596	0.508	0.518	0.543
GC	0.501	0.443	0.484	0.416

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

	$logP_{exp}$[11]	$logP_{exp}$[12]	$logP_{exp}$[13]	$AlogP_S$	IAlogP	clogP	$logP_{KOWIN}$	xlogP	$logP_{Rekker}$
$R_{MW\ (m)}$	0.9228	0.8510	0.9840	0.8368	0.9030	0.7958	0.9247	0.7988	0.8761
$R_{MW\ (or)}$	0.7866	0.8373	0.8408	0.8667	0.8962	0.8010	0.9050	0.8324	0.8678
$R_{MW\ (d)}$	0.9676	0.9463	0.9753	0.9398	0.9627	0.9145	0.9454	0.8862	0.9255
$R_{MW\ (a)}$	0.8603	0.8772	0.8924	0.8906	0.9183	0.8443	0.9521	0.8890	0.8945

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

	$logP_{exp}$[11]	$logP_{exp}$[12]	$logP_{exp}$[13]	$AlogP_S$	IAlogP	clogP	$logP_{KOWIN}$	xlogP	$logP_{Rekker}$
$\varphi_{0\ (m)}$	0.8488	0.8885	0.8967	0.8945	0.9179	0.8541	0.9631	0.8978	0.9309
$\varphi_{0\ (or)}$	0.8712	0.9019	0.9133	0.8830	0.9143	0.8329	0.9525	0.8737	0.9112
$\varphi_{0\ (d)}$	0.9292	0.9626	0.9745	0.9602	0.9725	0.9360	0.9778	0.9297	0.9731
$\varphi_{0\ (a)}$	0.8522	0.8965	0.9034	0.9270	0.9409	0.8996	0.9772	0.9273	0.9635

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, RP2 and CNF_{254} plates by using various mobile phases

	$RP18W_{(or)}$	$RP18W_{(d)}$	$RP18W_{(a)}$	$RP2_{(m)}$	$RP2_{(or)}$	$RP2_{(d)}$	$RP2_{(a)}$	$CNF_{254(m)}$	$CNF_{54(or)}$	$CNF_{254(d)}$	$CNF_{254(a)}$
$RP18W_{(m)}$	0.994	0.940	0.982	0.988	0.970	0.919	0.963	0.975	0.953	0.944	0.982
$RP18W_{(or)}$	1	0.928	0.957	0.988	0.959	0.882	0.927	0.974	0.934	0.911	0.975
$RP18W_{(d)}$		1	0.923	0.915	0.992	0.920	0.894	0.938	0.917	0.941	0.903
$RP18W_{(a)}$			1	0.961	0.959	0.956	0.991	0.962	0.969	0.970	0.962
$RP2_{(m)}$				1	0.944	0.900	0.935	0.961	0.959	0.899	0.976
$RP2_{(or)}$					1	0.938	0.931	0.971	0.946	0.963	0.935
$RP2_{(d)}$						1	0.944	0.930	0.856	0.921	0.921
$RP2_{(a)}$							1	0.920	0.938	0.964	0.952
$CNF_{254\ (m)}$								1	0.962	0.924	0.950
$CNF_{254\ (or)}$									1	0.928	0.922
$CNF_{254\ (d)}$										1	0.891

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

Table 10. The values of correlation coefficients of linear relationship between lipophilicity parameters φ_0 obtained on RP18W, RP2 and CNF_{254} plates by using various mobile phases.*

	$RP18W_{(or)}$	$RP18W_{(d)}$	$RP18W_{(a)}$	$RP2_{(m)}$	$RP2_{(or)}$	$RP2_{(d)}$	$RP2_{(a)}$	$CNF_{254(m)}$	$CNF_{254(or)}$	$CNF_{254(d)}$	$CNF_{254(a)}$
$RP18W_{(m)}$	0.995	0.985	0.996	0.988	0.999	0.995	0.987	0.996	0.989	0.957	0.990
$RP18W_{(or)}$	1	0.996	0.994	0.990	0.998	0.998	0.988	0.992	0.987	0.975	0.994
$RP18W_{(d)}$		1	0.986	0.982	0.992	0.993	0.985	0.979	0.976	0.989	0.988
$RP18W_{(a)}$			1	0.982	0.996	0.992	0.996	0.995	0.980	0.962	0.998
$RP2_{(m)}$				1	0.990	0.993	0.976	0.991	0.996	0.967	0.981
$RP2_{(or)}$					1	0.997	0.990	0.994	0.988	0.969	0.993
$RP2_{(d)}$						1	0.986	0.993	0.994	0.975	0.990
$RP2_{(a)}$							1	0.986	0.966	0.964	0.997
$CNF_{254\ (m)}$								1	0.991	0.950	0.993
$CNF_{254\ (or)}$									1	0.957	0.976
$CNF_{254\ (d)}$										1	0.965

[a]Methanol–water (m), organic mixture–water (or), dioxane–water (d), acetone–water (a).

plates and methanol–water as a mobile phase are most similar to the absolute experimental values of logP. In addition, for seven bile acids the R_{MW} values, obtained by using and methanol–water as a mobile phase, were most similar to the partition coefficients calculated by $AlogP_S$. Moreover, it was observed that the lipophilicity parameter R_{MW} obtained on CNF_{254} plates correlates best with partition coefficient values $logP_{KOWIN}$ ($r > 0.9050$) in all applied mobile phases (Table 7).

The lipophilic parameter φ_0 correlates best with partition coefficients calculated by using $logP_{KOWIN}$ and $logP_{Rekker}$ methods ($r > 0.9112$) (Table 8).

Moreover, both a/m lipophilic parameters (R_{MW} and φ_0) obtained by using RP-HPTLC and CNF_{254} plates also correlates well with the IAlogP values. It was stated that the obtained R_{MW} and φ_0 values correlate best with experimental partition coefficients ($logP_{exp}$) given after Roda and coauthors.[13]

The correlation coefficients of both lipophilic parameters (R_{MW} and φ_0), obtained on RP18W, RP2, and CNF_{254} plates under all applied chromatographic conditions were compared. Table 9 presents the correlation coefficients values of linear relationships between the parameters of lipophilicity (R_{MW}) obtained under 12 chromatographic conditions.

Excellent correlation between R_{MW} values obtained on RP18W (#1.14296), RP2 (#1.13726), and CNF254 (#1.12571) plates was observed when methanol–water ($0.961 < r < 0.988$) and acetone–water ($0.952 < r < 0.991$) were applied as mobile phases.

Table 10 presents the linear correlation coefficients of relationships between lipophilic parameters φ_0 determined in different chromatographic systems. It was stated that φ_0 values correlate with each other better ($r > 0.950$) than R_{MW} values.

CONCLUSION

It was stated that both, chromatographic plates CNF_{254} (#1.12571) and previously used RP18W and RP2, can be applied to estimate the lipophilicity of examined bile acids.

The values of R_{MW} and φ_0 lipophilic parameters obtained on all applied plates, i.e., RP18W, RP2, and CNF_{254} plates and methanol–water, organic mixture–water, dioxane–water and acetone–water used as mobile phases, indicate that the investigated bile acids may be listed in the order of decreasing lipophilicity as follows: $LC > DC \approx CDC \approx GLC > C \approx GDC > GC$.

The most significant correlation was found between R_{MW} and φ_0 lipophilic parameters and $logP_{KOWIN}$ values. Moreover, it was stated that the obtained parameters R_{MW} and φ_0 correlate best with experimental partition coefficients ($logP_{exp}$) given after Roda and coauthors.[13]

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