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Reversed-phase thin-layer and gas chromatographic retention behaviour of triphenylmethane derivatives

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ABSTRACT

Reversed-phase thin-layer chromatographic (RP-TLC) R_M values and Kováts retention indices (I) were determined for 26 triphenylmethane derivatives and their analogues (TMDs). The relationship between R_M values and organic phase concentration in the eluent was investigated. A non-linear function having a minimum extreme value at about 60% acetone concentration was obtained. This phenomenon is related to the dual retention mechanism observed in reversed-phase high-performance liquid chromatography. The relationship between R_M values and gas chromatographic retention indices was also studied. No significant linear relationship was obtained. The poor correlation indicates that gas chromatographic retention indices cannot be used for characterizing the lipophilicity of the TMDs, and RP-TLC is suggested for this purpose.

INTRODUCTION

Lipophilicity (hydrophilicity) is a structural feature of some compounds that has important effects on their biological activity. The determination of the lipophilicity of biologically active compounds is often required in order to predict their biological activity. Lipophilicity can be measured in several ways, the classical way being the measurement of partition coefficients by the "shake-flask" method [1,2]. More convenient and reliable are chromatographic methods, which have the advantages that they are rapid and suitable for substances containing impurities, requiring no quantitative determination, they are highly reproducible and they can be applied over a wide hydrophobicity range. Both reversed-phase thin-layer chromatography (RP-TLC) [3,4] and reversed-phase high-performance liquid chromatography (RP-HLC) [5,6] are simple and readily applicable to the determination of lipophilicity. In many instances good correlations was found between the log P values (the logarithm of the partition coefficient in 1-octanol–water) and the lipophilicity values determined by various chromatographic techniques [7]. However, especially for polar compounds, the correlation sometimes was not significant [8]. Several attempts have been made to determine lipophilicity by gas chromatography (GC), but the results are contradictory. In some instances a significant correlation was found between the lipophilicity

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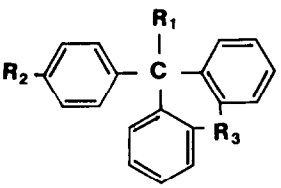
values and the GC retention data [9–11], but other workers did not find any significant correlation between lipophilicity and GC retention parameters [12–14]. To assess the applicability of GC to lipophilicity determination, we investigated the RP-TLC and GC retention parameters of 26 triphenylmethane (trityl) derivatives [some of them (compounds VII, XXIII, XXIV, XXV and XXVI in Table I) are marketed as antifungal compounds]. Relationships between RP-TLC R_M values and GC retention indices were calculated in order to investigate the applicability of these chromatographic methods for measuring lipophilicity.

We are well aware that our results only offer a conclusion regarding the relationship between GC and TLC retention indices and the relationship of these to

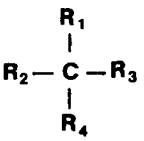
TABLE I

STRUCTURES OF THE COMPOUNDS INVESTIGATED

Structures for compounds X–XV:



Structures for other compounds:



Compound	R_1	R_2	R_3	R_4
I	H	Phenyl	Phenyl	Phenyl
II	OH	Phenyl	Phenyl	Phenyl
III	OH	Phenyl	2-Chlorophenyl	Phenyl
IV	OH	Phenyl	4-Chlorophenyl	Phenyl
V	OH	Phenyl	2,4-Dichlorophenyl	Phenyl
VI	Imidazole	Phenyl	Phenyl	Phenyl
VII	N-Imidazole	Phenyl	2-Chlorophenyl	Phenyl
VIII	N-Imidazole	Phenyl	4-Chlorophenyl	Phenyl
IX	1-Triazole	Phenyl	Phenyl	Phenyl
X	OH	H	$-CH_2-CH_2-$	
XI	OH	Cl	$-CH_2-CH_2-$	
XII	OH	4-Methoxy	$-CH_2-CH_2-$	
XIII	OH	H	$-O-CH_2-$	
XIV	OH	Cl	$-O-CH_2-$	
XV	OH	4-Methoxy	$-O-CH_2-$	
XVI	OH	3-Pyridine	Phenyl	Phenyl
XVII	OH	3-Pyridine	4-Chlorophenyl	Phenyl
XVIII	OH	3-Pyridine	4-Hydroxyphenyl	Phenyl
XIX	OH	3-Pyridine	4-Methoxyphenyl	Phenyl
XX	OH	3-Pyridine	4-Methoxyphenyl	4-Methoxyphenyl
XXI	OH	2-Pyridine	Phenyl	Phenyl
XXII	OH	2-Pyridine	4-Chlorophenyl	Phenyl
XXIII	OH	5-Pyrimidine	2,4-Dichlorophenyl	Phenyl
XXIV	OH	5-Pyrimidine	4-Chlorophenyl	2-Chlorophenyl
XXV	OH	5-Pyrimidine	4-Fluorophenyl	2-Chlorophenyl
XXVI	Triphenyltin hydroxide			

lipophilicity is only hypothetical. We assume that the R_M values determined at low concentrations of organic mobile phase in the eluent characterize the lipophilicity.

EXPERIMENTAL

The investigated trityl derivatives and analogues are listed in Table I. R_M values were measured on silica gel plates (Kieselgel 60 F_{254}; Merck, Darmstadt, F.R.G.) impregnated with 5% paraffin oil in *n*-hexane. The plates were developed in a Chrompres 10 chamber (Labor-MIM, Estergom, Hungary) with the following eluent systems: (1) acetone–water (40:60) (AC40); (2) acetone–water (50:50) (AC50) (3) acetone–water (60:40) (AC60); and (4) acetone–water (70:30) (AC70).

The GC Kováts retention indices (*I*) were determined using a Packard 7400 gas chromatograph with 120 cm × 2 mm I.D. glass columns equipped with a flame ionization detector. The stationary phases were (1) 3.0% Carbowax 20M (CW), (2) 3.0% OV-1, (3) 3.0% OV-210, and (4) no stationary phase (NO) on Chromosorb G (80–100 mesh) chemically bonded Carbowax 20M. The carrier gas was nitrogen at a flow-rate of 50 ml/min.

The R_M values measured on paraffin oil-coated silica were plotted against the composition of the acetone–water eluent. Multiple correlation analysis was applied to evaluate the relationships between R_M and I values [15].

RESULTS AND DISCUSSION

The R_M values measured by RP-TLC are given in Table II. The dependence of the R_M values on the acetone concentration in the eluent shows a peculiar character (Fig. 1), with a minimum at *ca.* 60% acetone. In numerous other instances the R_M values decrease linearly with increase in the water content of binary aqueous–organic eluents [16], making possible the calculation of the R_{M0} value by linear approximation. The "irregular" retention behaviour of the TMDs may be analogous to the dual retention mechanism of crown ethers and certain peptides with unprotected amino groups observed by Horváth and co-workers [17,18] in RP-HPLC. According to their interpretation, in similar instances the retention is caused not only by the usual solvophobic interaction but also by "silanophilic" interactions between the eluite and the accessible silanol groups at the surface of the reversed (paraffin-coated) phase. Considering the dependence of the R_M values of TMDs on the acetone concentration in the eluent in RP-TLC we conclude that the retention must be governed by the dual retention model. This means that the retention is governed by silanophilic interactions (free silanol groups under the imperfect paraffin coating) at low water concentrations, whereas water "masks" silanolic sites at higher water concentrations, when the retention is governed by solvophobic (hydrophobic) interactions. This phenomenon is supported by the special characteristic of the TMDs, namely that they can bind to surfaces with extreme polarities. Both the benzene and the heterocyclic rings are bonded to the central carbon atom to form a propeller-like structure, so one side of the molecule is non-polar whereas the other, as a consequence of a polar substituent (hydroxyl group, imidazole or triazole rings) could be strongly polar. The acetone concentration in the mobile phase influences the binding of the molecule to the stationary phase, because of the possibilities of various interactions of acetone with the two sides of the molecule.

TABLE II

MEASURED R_M AND I VALUES

For meaning of symbols, see Experimental.

Compound	R_M				I			
	AC40	AC50	AC60	AC70	CW	OV-1	OV-210	NO
I	1.597	1.009	−0.577	−0.313	2752	1975	2448	2142
II	0.903	0.319	−0.865	−0.554	3187	2127	2859	2439
III	1.067	0.413	−0.488	−0.301	3120	2239	2800	2415
IV	1.230	0.625	−0.540	−0.317	3383	2335	3075	2638
V	1.497	0.866	−0.485	−0.317	3325	2402	3000	2603
VI	1.119	0.356	−0.506	−0.309	3581	2500	3200	2790
VII	1.143	0.446	−0.883	−0.522	3236	2239	2864	2243
VIII	1.626	0.562	−0.488	−0.470	3374	2347	3060	2659
IX	0.854	0.141	−0.609	−0.357	2850	2145	3151	2451
X	1.050	0.410	−0.606	−0.313	3507	2415	3127	2714
XI	1.439	0.683	−0.499	−0.243	3822	2605	3400	2932
XII	1.023	0.322	−0.602	−0.354	3906	2661	3496	3039
XIII	0.687	0.094	−0.615	−0.416	3548	2400	3200	2762
XIV	1.050	0.356	−0.556	−0.329	3923	2598	3495	3006
XV	0.678	0.072	−0.756	−0.449	3649	2653	3613	3082
XVI	0.350	−0.126	−1.092	−0.729	3507	2254	3144	2663
XVII	−0.061	−0.241	−0.760	−0.769	4102	2610	3400	3015
XVIII	−0.059	−0.436	−1.456	−0.775	3959	2556	3454	2972
XIX	0.325	−0.143	−1.016	−0.712	3832	2516	3531	2998
XX	0.293	0.152	−1.240	−0.732	3800	2669	3403	3032
XXI	0.576	0.084	−0.810	−0.541	3114	2161	2818	2425
XXII	0.960	0.400	−0.675	−0.466	3357	2349	3036	2628
XXIII	0.661	0.113	−0.839	−0.532	3800	2890	3397	2891
XXIV	0.612	0.005	−0.719	−0.477	3822	2561	3368	2938
XXV	0.366	−0.123	−0.705	−0.509	3574	2358	3147	2715
XXVI	1.805	1.301	0.203	0.359	3679	2682	3288	2839

[a] See Table I.

We conclude that the dual retention mechanism observed by Horváth and co-workers [17,18] in RP-HPLC can also be observed in RP-TLC as a result of the interactions of the eluite molecules and the free silanol groups of the silica gel layer. A similar phenomenon was observed for quaternary ammonium steroids and morphine derivatives [19].

The retention indices are also listed in Table II. Multiple correlation analysis was carried out on our data set to find relationships between the RP-TLC R_M values and the GC I values determined on stationary phases of various polarities. The correlation matrix is shown in Table III. Highly significant linear relationships were found between R_M values measured in various eluent systems (r = 0.916–0.977), indicating that the influence of the stationary phase dominates over the structural effects in the interaction, *i.e.*, compounds with similar structures give almost parallel parabolic curves.

The relationship between I values determined on different stationary phases was also significantly linear (r = 0.861–0.957), but no significant correlation was

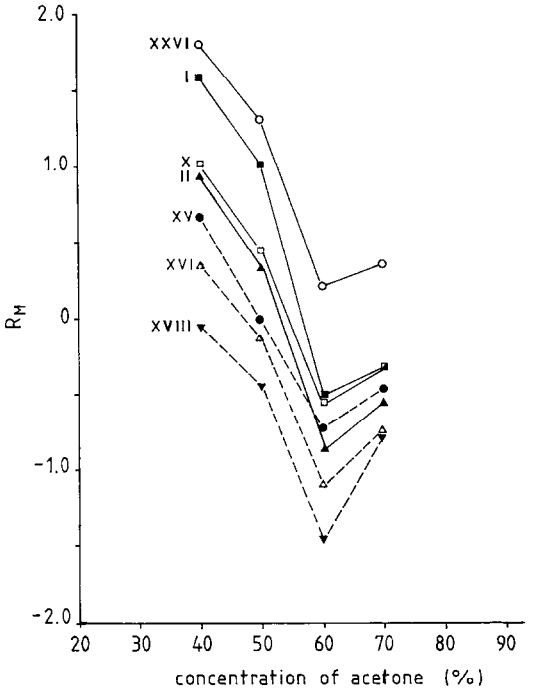


Fig. 1. Plots of R_M values measured on paraffin oil-coated silica against the composition of the acetone–water eluent. For compound numbers, see Table I.

found between RP-TLC and GC retention data ($r = -0.493$ to 0.023). This poor correlation indicates that the GC retention indices of TMDS cannot be used for characterizing lipophilicity. Various papers have demonstrated that the R_M values are in good agreement with the partition coefficients (log P) [20], characterizing lipophilicity, but opinions differ about the applicability of GC retention parameters in lipophilicity investigations [9,12,13].

TABLE III

CORRELATION MATRIX OF THE VARIABLES

For meaning of symbols, see Experimental. ($r_{p=0.1\%} = 0.597$)

	AC40	AC50	AC60	AC70	CW	OV-1	OV-210	NO
AC40	1.000	0.945	0.786	0.807	−0.493	−0.244	−0.422	−0.431
AC50		1.000	0.773	0.825	−0.448	−0.197	−0.434	0.407
AC60			1.000	0.916	−0.238	−0.023	−0.183	−0.167
AC70				1.000	−0.232	−0.028	−0.147	−0.151
CW					1.000	0.872	0.870	0.924
OV-1						1.000	0.861	0.889
OV-210							1.000	0.957
NO								1.000

In an earlier study, highly significant linear relationships were obtained between RP-TLC R_M and I values for triazine derivatives [21], but poor correlations similarly to this present work were obtained for carboxamide [22] and aniline derivatives [14]. Two-parameter equations have been given for the relationship between lipophilic parameters and GC retention indices in several papers [23,24]. Summarizing our earlier and present investigations and the results of other workers on chromatographic retention parameters, we conclude that the RP-TLC R_M values characterize lipophilicity, whereas the GC retention indices can be used only in certain instances as lipophilicity parameters. One must be careful about using I values as a measure of lipophilicity: the type of the solute, the polarity of the stationary phase used and the temperature of the determination may influence the applicability of I values. Among the chromatographic methods we suggest RP-TLC and RP-HPLC rather than GC for the determination of lipophilicity.

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