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Note

Relationship between retention parameters (log *k'*) and octanol–water partition coefficients (log *P*) of a series of phenyl carbamates and phenylureas. Part III

B. RITTICH*
Research Institute of Animal Nutrition, 69123 Pohořelice (Czechoslovakia)
J. ŠTOHANDL
Research Institute of Macromolecular Chemistry, Chemopetrol, Tkalcovská 2, 65649 Brno (Czechoslovakia)
R. ŽALUDOVÁ
Research Institute of Animal Nutrition, 69123 Pohořelice (Czechoslovakia)
and
H. DUBSKÝ
Department of Forensic Medicine, Faculty of Medicine, J. E. Purkyně University, Tvrdého 2a, 66299 Brno (Czechoslovakia)
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The hydrophobicity of biologically active compounds is known to affect their biological responses[1]. In studies on quantitative structure–activity relationships, Hansch's π parameters have been calculated from the logarithms of the partition coefficients (log *P*), which were determined between 1-octanol and water[2]. However, the values determined in this way do not always account for electronic or steric effects caused by the introduction of a substituent group. Therefore, it is safer to determine the partition coefficient directly by an experimental procedure. The shake-flask method, generally adopted as a standard method for the determination of partition coefficients, is time consuming[3] and difficult to apply to compounds that are poorly soluble in either water or 1-octanol, or which cannot be detected by conventional methods. Instead of measuring log *P* values by equilibration methods, partition chromatographic data can be used.

Recently, reversed-phase high-performance liquid chromatography (RP-HPLC) has been applied for the determination of hydrophobic parameters (*e.g.*, refs. 4–9).

The aim of this study was to investigate the relationships between the log *k'* values of carbamates (measured by RP-HPLC) and the corresponding partition coefficients or Hansch's parameters for different groups of compounds.

EXPERIMENTAL

Chemicals and equipment

Carbamates (see Table I) were prepared according to literature procedures[10]. Their identities were confirmed by elemental analysis, melting points and UV spectro-

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TABLE I

SOME PHYSICO-CHEMICAL CONSTANTS OF THE PHENYL N-METHYLCARBAMATES TESTED

Substituent	*M. p. (°C)*	*λ_{max} (nm)*	
		*A**	*B**
H	111.0–112.0	208, 260, 265	241, 290
3-CH_3	56.0– 57.0	209, 265, 270	243, 293
4-CH_3	93.5– 95.0	211, 267, 272	243, 244, 301
4-OCH_3	94.0– 96.0	223, 279, 286	239, 319
3-Cl	78.5– 79.5	212, 268, 273	244, 296
4-Cl	114.0–115.0	220, 264, 270, 274	246, 303
3-NO_2	157.0	208, 262	231, 270, 293, 400
4-CN	118.0–120.0	230, 265, 274	273
4-CH_3CO	111.0–112.0	205, 253	238, 332

* A, Measured in ethanol; B, measured in a 0.2 mol l^{-1} solution of potassium hydroxide in ethanol.

photometry (see Table I). UV spectra were measured on a Specord UV–visible spectrophotometer (Carl Zeiss, Jena, G.D.R.).

Chromatography was performed on a Varian LC 8500 liquid chromatograph with a UV-50 variable-wavelength detector (200–900 nm). A Micro Pak CH-10 column (250 × 2.2 mm I.D.) pre-packed with 10-μm silica gel and with an octadecyl

TABLE II

HYDROPHOBIC PARAMETERS OF THE PHENYL N-METHYLCARBAMATES TESTED

P_1 = Partition coefficient for phenols determined in the 1-octanol–water system[2]; P_2 = partition coefficient for phenoxyacetic acids determined in the 1-octanol–water system[2]; ΔR_{M1} and ΔR_{M2} = chromatographic parameters for O-alkyl-O-arylphenylphosphonothioates measured by RP-TLC [mineral oil/acetone–water (6:4)] or by polyamide TLC/acetone–water (6:4)[12]; P_3 = partition coefficient determined in the 1-octanol–water system[11].

No.	*Substituent*	*Log P_1*	*Log P_2*	*ΔR_{M1}*	*ΔR_{M2}*	*Log P_3*	*Log k'*	
							*A**	*B***
I	4-F	2.15	1.36	0.044	0.019	–	–	–
II	4-Br	2.59	2.23	0.247	0.327	–	–	–
III	4-I	2.91	2.47	0.317	0.417	–	–	–
IV	4-C_2H_5	–	2.18	0.235	0.227	–	–	–
V	H	1.46	1.21	0.000	0.000	1.16	0.276	0.293
VI	4-OCH_3	1.34	1.17	−0.040	−0.028	1.20	0.417	0.336
VII	4-CH_3	1.94	1.73	0.096	0.181	1.66	0.537	0.530
VIII	4-Cl	2.39	1.91	0.201	0.232	2.01	0.602	0.753
IX	3-CH_3	2.02	1.72	0.092	0.066	1.70	0.485	0.530
X	3-Cl	2.50	1.97	0.214	0.195	2.03	0.625	0.679
XI	3-NO_2	2.00	1.32	0.039	0.060	1.39	0.508	0.452
XII	3-CH_3CO	1.39	0.93	–	–	0.90	0.347	0.046
XIII	4-CH_3CO	1.35	0.84	–	–	1.01	0.426	0.276
XIV	4-CN	1.32	0.89	−0.099	0.034	0.95	0.417	–

* Micro Pak CH-10 column, methanol–water (1:4) mobile phase, flow-rate 60 ml h^{-1}.

** Micro Pak CH-10 column, dioxan–water (1:4) mobile phase, flow-rate 60 ml h^{-1}.

chemically bonded non-polar stationary phase was obtained from E. Merck (Darmstadt, F.R.G.). The samples were injected using a Hamilton 705 syringe.

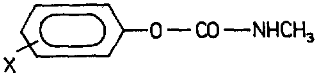
Conditions

Separation of carbamates on the Micro Pak CH-10 column was carried out with methanol–water and dioxan–water mixtures of varying composition as mobile phases. The flow-rate was 60 cm^3h^{-1}. Samples were dissolved in the mobile phase at a concentration of about 1 mg ml^{-1} and applied to the column in 5–10-μm volumes.

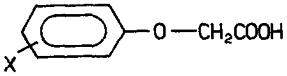
Log P values determined in 1-octanol–water were taken from literature[2,11]. ΔR_{M1} values measured by reversed-phase TLC [mineral oil/aceton–water (6:4)] for O-alkyl-O-arylphenylphosphonothioates[12] and ΔR_{M2} values measured by polyamide TLC using acetone–water (6:4) for the same compounds[12] were used. Spectra of the carbamates were measured in ethanol and in a 0.2 mol l^{-1} solution of potassium hydroxide in ethanol.

RESULTS AND DISCUSSION

The elution volumes of the phenyl N-methylcarbamates (I) using methanol–water (1:4) and dioxan–water (1:4) as mobile phases were measured and log k' values were calculated (Table II). Experimental log k' values were correlated with the logarithms of partition coefficients for different groups of compounds, log P_1 for phenols and log P_2 for phenoxyacetic acids (II), with ΔR_{M1} and ΔR_{M2} values for O-alkyl-O-arylphenylphosphonothioates (III) and with log P_3 values for phenyl N-methylcarbamates. The relationships obtained are presented in eqns. 1–10 (Table III). The log k' value of phenyl N-methylcarbamate was excluded from the set of compounds in eqns. 1–5, because this compound was found to be more hydrophobic than an outlier from the observed relationships.



I



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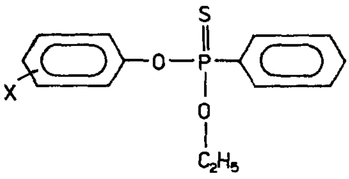

III

TABLE III

EQUATIONS DERIVED PHENYL N-METHYLCARBAMATES

n = Number of compounds in the set; r = correlation coefficient; s = standard deviation; t_b = Student's characteristic for the coefficient b of the regression equation $Y = bX + a$ (the coefficient was tested on the hypothesis $b = 0$).

Mobile phase	*Compounds*	*Equation*	*n*	*r*	*s*	t_b	*No.*
Methanol–water (1:4)	VI–XIV	$\log P_1 = 4.773 \log k'_A - 0.509$	9	0.941	0.170	7.331*	(1)
	VI–XIV	$\log P_2 = 4.437 \log k'_A - 0.765$	9	0.903	0.209	5.561*	(2)
	VI–XI, XIV	$\Delta R_{M1} = 1.359 \log k'_A - 0.625$	7	0.960	0.035	7.693*	(3)
	VI–XI, XIV	$\Delta R_{M2} = 1.095 \log k'_A - 0.465$	7	0.926	0.040	5.501*	(4)
	VI–XIV	$\log P_3 = 4.526 \log k'_A - 0.767$	9	0.946	0.154	7.695*	(5)
Dioxan–water (1:4)	V–XIII	$\log P_1 = 1.871 \log k'_B + 1.011$	9	0.907	0.204	5.704*	(6)
	V–XIII	$\log P_2 = 1.773 \log k'_B + 0.655$	9	0.924	0.173	6.370*	(7)
	V–XI	$\Delta R_{M1} = 0.551 \log k'_B - 0.195$	7	0.964	0.028	8.157*	(8)
	V–XI	$\Delta R_{M2} = 0.564 \log k'_B - 0.187$	7	0.930	0.041	5.664*	(9)
	V–XIII	$\log P_3 = 1.847 \log k'_B + 0.652$	9	0.968	0.112	10.264*	(10)

* Statistically highly significant difference ($P < 0.01$).

For the mutual correlations of physico-chemical parameters the limit of the allowable precision of a correlation was taken to be a value of the correlation coefficient[13] $|r| \geqslant 0.90$. It is therefore possible to use Hansch's π parameters for phenoxyacetic acids in the correlations of biological activity with physico-chemical parameters from ref. 14, although the value of the correlation coefficient is just the allowable limit.

Structurally, phenyl derivatives of urea are similar to phenylcarbamates. Therefore, for phenylureas we correlated the logarithms of the capacity factors[7] log

TABLE IV

HYDROPHOBIC PARAMETERS OF THE PHENYLUREAS TESTED

C = Micro Pak CH-10 column, methanol–water (3:7) mobile phase, flow-rate 60 ml h^{-1}; taken from Rittich and Dubský[7]. D = Micro Pak CH-10 column, dioxan–water (1:4) mobile phase, flow-rate 60 ml h^{-1}; taken from Rittich and Dubský[7]. E = Obtained by extrapolation to pure water in methanol–water mobile phase, Lichrosorb RP-18 column, fow-rate 102 ml h^{-1}; taken from Braumann *et al.*[15]. F = Obtained by extrapolation to pure water in acetonitrile–water mobile phase, Lichrosorb RP-18 column, flow-rate 102 ml h^{-1}; taken from Braumann *et al.*[15]. P_4 = Partition coefficient determined in the 1-octanol–water system[11].

No.	*Substituent*				$\log k'_C$	$\log k'_D$	$\log k'_E$	$\log k'_F$	$\log P_4$
	R_1	R_2	R_3	R_4					
XV	CH_3	CH_3	H	Cl	0.501	0.367	2.239	3.086	1.91
XVI	CH_3	CH_3	Cl	Cl	0.983	0.794	2.816	2.929	2.68
XVII	CH_3	OCH_3	H	Cl	0.666	0.535	2.453	3.035	1.99
XVIII	CH_3	OCH_3	H	Br	0.760	0.628	2.603	3.024	2.37
XIX	CH_3	CH_3	Cl	OCH_3	0.412	0.235	2.185	3.518	1.98
XX	CH_3	OCH_3	Cl	Cl	1.135	0.982	3.072	3.064	2.76
XXI	CH_3	CH_3	Cl	CH_3	–	–	2.640	2.837	2.55
XXII	CH_3	CH_3	H	H	–	–	1.838	2.902	1.18

TABLE V

EQUATIONS DERIVED FOR UREA DERIVATIVES

Mobile phase	*Compounds*	*Equation*	*n*	*r*	*s*	t_b	*No.*
Methanol-water (3:7)	XV–XX	$\log k'_E = 1.650 \log k'_C + 1.226$	6	0.996	0.034	22.399*	(11)
		$\log P_4 = 1.324 \log k'_C + 1.289$	6	0.950	0.132	6.080*	(12)
Dioxan–water (1:4)	XV–XX	$\log k'_E = 1.830 \log k'_D + 1.239$	6	0.993	0.046	16.540*	(13)
		$\log P_4 = 1.530 \log k'_D + 1.273$	6	0.926	0.159	4.919*	(14)

* Statistically highly significant difference ($P < 0.01$).

k'_C [mobile phase: methanol–water (3:7)) and log k'_D [mobile phase: dioxan–water (1:4)] with the log k' values published by Braumann *et al.*[15] and log P_4[11] (Table IV). The values of log k' were obtained by extrapolation to pure water in methanol–water (log k'_E and acetonitrile–water (log k'_F). The results are given in equations 11–14 (Table V). The regression equations calculated for log k'_F were statistically non-significant ($r = 0.647$ and $r = 0.681$). Even the correlation between log k'_E and log k'_F was taken as log k' with pure water as the mobile phase and should therefore be independent of the nature of the organic modifier. However, from the results presented here it follows that this assumption is incorrect. This conclusion is in accordance with the results in ref. 15 and shows that it is better to use directly measured capacity factors.

It follows from the results presented here that for the expression of the hydrophobic parameters of phenyl carbamates it is possible to use the log k' values measured directly by RP-HPLC with methanol–water (1:4) and dioxan–water (1:4) as the mobile phases. The R_M values measured for structurally related compounds may be also used. For the expression of the hydrophobic parameters of phenylureas it is also possible to use the log k' values measured by RP-HPLC with methanol–water (3:7) as the mobile phase.

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