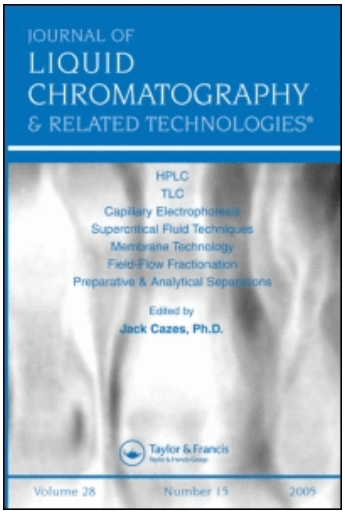

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HPLC Investigation of a Set of Local Anesthetic Aminoether Derivatives

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HPLC INVESTIGATION OF A SET OF LOCAL ANESTHETIC AMINOETHER DERIVATIVES

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ABSTRACT

A series of amino-alkylaryl-ether and thioether derivatives with local anesthetic activity was investigated in an IP-RP HPLC system. Good correlation was found between the retention (log k') and octanol-water partition coefficient (log P). The values of the correlation coefficients gradually increased with the increasing concentration of the ion-pairing agent, sodium dodecyl sulfate (NaDS). This experience is interpreted by the similar interactions in the partition and chromatographic systems. The Δlog k' and $\widetilde{\pi}$ values generated from the log k' and log P values of the compounds having basic nucleus, showed also a good correlation.

INTRODUCTION

HPLC investigation of local anesthetic aminoethers and amino-thioethers have been synthetized by Oelschläger and coworkers[1] is reported in this work. One of the compounds

synthetized earlier the N-γ-(4-phenoxy-methyl-phenyl)--propyl-morpholine, Fomocaine is commercially available.*

The topical local anesthetic efficacy and metabolism of the compounds was previously described[1].

It is known, that octanol-water partition coefficient (log P) representing the lipophilicity is a parameter outstandingly characteristic for local anesthetics. The log P and pK values of the investigated compounds was already reported[2].

This paper deals with the drug-design-related HPLC behaviour of the compounds.

Materials

The model substances (see in Table 1) have been synthetized via different routes which were developed by Oelschläger and coworkers[1]. The quality of model substances was characterized by chromatography and melting point determination.

Methanol (analytical grade) was obtained from Reanal, Budapest.

Dodecyl sulfate sodium (NaDS) 98%, Aldrich.

Citrate buffer, pH = 2.7. Preparation: to 40.30 ml of citrate solution (21.008 g of citric acid monohydrate dissolved in water and after mixing with 2.00 ml of 1 M sodium hydroxyde diluted with water to 1 L.) was added 59.70 ml of 0.1 M hydrochloric acid.

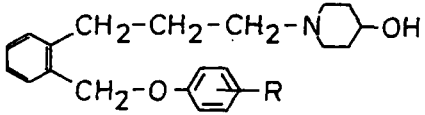
Chromatography

The HPLC apparatus was comprised of an ISCO pump Model 2350 (USA) and an ISCO V ^{4R} variable wavelength detector. The column effluent was monitored at 275 nm. The chromatogr-

*Accepted by Deutscher Arzneimittel-Codex and enlisted there since 1979.

Table 1

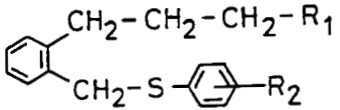
log k' and log P values of the model substances

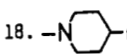
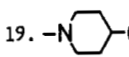
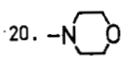
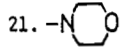
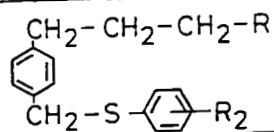
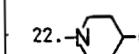


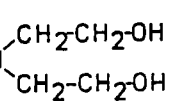
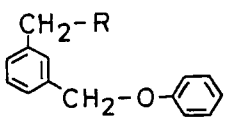
Compound R	log k' MeOH-citrate buffer (pH = 3) 80:20 Dodecyl sulfate sodium concentration M						log P* Octanol/ phosphate buffer (pH= 4)
	0	0.005	0.01	0.02	0.04	0.05	
1. m-OCH_3	-0.456	-0.046	0.114	0.332	0.354	-	-0.762
2. o-OCH_3	-0.398	-0.051	0.021	0.176	0.296	-	-1.194
3. p-OCH_3	-0.456	-0.125	0.061	0.267	0.290	-	-0.899
4. m-OC_2H_5	-0.347	0.124	0.243	0.467	0.447	-	-0.376
5. o-OC_2H_5	-0.328	0.000	0.185	0.413	0.334	-	-0.814
6. p-OC_2H_5	-0.377	0.020	0.217	0.389	0.428	-	-0.547
7. o-CH_2-CH=CH_2	-0.076	0.290	0.462	0.633	0.661	-	0.315
8. p-CH_2-CH=CH_2	-0.167	0.29	0.422	0.628	0.630	-	0.152
9. p-CH_3	-0.301	0.230	0.243	0.470	0.470	-	-0.413
10. p-C_2H_5	-0.076	0.314	0.389	0.642	0.614	-	0.045
11. p-CH_2-C_6H_5	0.045	4.423	0.597	0.767	0.732	-	0.942
12. p-F	-0.523	-0.155	0.097	0.332	0.354	-	-0.669
13. p-Cl	-0.214	0.114	0.301	0.565	0.538	-	-0.031
14. p-Br	-0.142	0.215	0.352	0.544	0.618	-	0.103
15. o-I	-0.097	0.276	0.423	0.685	0.650	-	0.375
16. 3,4,5-$(OCH_3)_3$	-0.553	-0.222	-0.070	0.161	0.176	-	-1.561
17. -H	-0.377	-0.063	0.176	0.332	0.371	-	-0.793

(Table 1 contnd.)

(Table 1 contnd.)

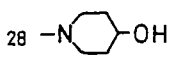
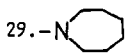
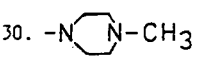
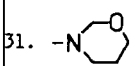
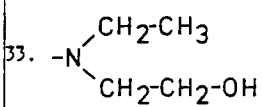


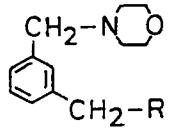
Compound		log k' MeOH–citrate buffer (pH = 3) 80:20 Dodecyl sulfate sodium concentration M						log P* Octanol/ phosphate buffer (pH = 4)
R_1	R_2	0	0.005	0.01	0.02	0.04	0.05	
18. 	o-OCH_3	-0.252	0.021	0.152	0.279	0.366	0.301	-0.515
19. 	H	-0.301	0.125	0.176	0.337	0.463	0.423	-0-232
20. 	p-F	-0.201	0.161	0.230	0.383	0.544	0.544	1.164
21. 	H	-0.260	0.146	0.243	0.371	0.508	0.46	1.212
								
22. 	H	-0.260	0.106	0.190	0.322	0.455	0.42	-0.037

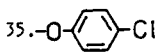
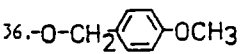
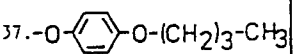
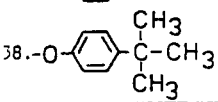
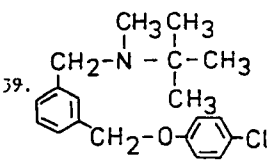
Compound R_1	R_2	log k' MeOH-citrate buffer (pH = 3) 80:20 Dodecyl sulfate sodium concentration M: 0	0.005	0.01	0.02	0.04	0.05	log P* Octanol/phosphate buffer (pH = 4)
23. 	p-F	-0.070	0.230	0.273	0.393	0.525	0.484	1.054
24. 	H	0.021	0.243	0.322	0.420	0.541	0.484	0.995
25. 	H	-0.050	0.224	0.322	0.450	0.589	0.505	1.663
26. 	H	-0.301	0.031	0.114	0.252	0.385	0.317	-0.310
 R								
27. 		-0.125	0.124	0.176	0.365	0.332	-	-0.73

(Table 1 contnd.)

(Table 1 contnd.)

Compound R	log k' MeOH-citrate buffer (pH = 3) 80:20 Dodecyl sulfate sodium concentration M						log P* Octanol/ phosphate buffer (pH = 4)
	0	0.005	0.01	0.02	0.04	0.05	
28 	-0.553	-0.187	0.071	0.213	0.217	-	-0.85
29. 	-0.097	0.130	0.324	0.407	0.407	-	-0.06
30. 	0.217	0.267	0.371	0.470	0.484	-	-0.62
31. 	-0.409	-0.187	-0.022	0.146	0.212	-	-1.10
32. $-N-(CH_2-CH_2-OH)_2$	-0.602	-0.259	-0.097	0.097	0.114	-	-0.82
33. 	-0.456	-0.125	0.00	0.190	0.241	-	-0.92
34. $-N(CH_2CH_2O-CH_2CH_3)_2$	0.137	0.392	0.430	0.550	0.538	-	1.22



Compound R	log k' MeOH-citrate buffer (pH = 3) 80:20 Dodecyl sulfate sodium concentration M						log P* Octanol/ phosphate buffer (pH = 4)
	0	0.005	0.01	0.02	0.04	0.05	
35. 	-0.125	0.146	0.314	0.431	0.484	-	1.25
36. 	-0.237	-0.097	0.061	0.253	0.243	-	0.34
37. 	0.161	0.371	0.512	0.728	0.695	-	1.88
38. 	0.217	0.415	0.550	0.740	0.763	-	2.06
39. 	-0.027	0.176	0.336	0.500	0.484	-	0.04

aphic system included as stationary phase LiChrosorb (5-RP-18) C_{18} with particle size of 5 μm (BST, Budapest) packed in a stainless steel column (250 x 4.6 mm i.d.). As mobile phase methanol-aqueous citrate buffer (pH = 3) 80:20 mixture containing different concentration of NaDS was used. Flow rate 0.8 ml/min. The chromatographic system was connected to an integrator HP 5396 Series II.

All measurements of log k' were made in triplicate.

RESULTS AND DISCUSSION

The log k' values of the compounds for a study of relationships between the structure and chromatographic behaviour, as well as the chromatographic retention vs. partition coefficient were determined in systems containing ion-pairing agent (NaDS) in concentration up to 0.05 M.

Ion-pair formation

Log k' and log P values of the stubstances are shown in Table 1.

Since the pK_a values of the compounds fall between 8-9[2] they were completely protonated at the pH values of HPLC investigation, as well as in the partition systems (pH = 3 and pH = 4).

The log k' values increase gradually with the increase of NaDS concentration in the eluent (see Table 1 and Fig. 1) is characteristic for the ion-pairing machanism in reversed phase systems.

Correlations

The results of correlation log k' vs. log P are summarized in Table 2.

The correlation is quite good for the hydroxy-piperidino-alkyl-aryl ethers as well as for the amino-thio--ethers with different basic nucleus. The points of the

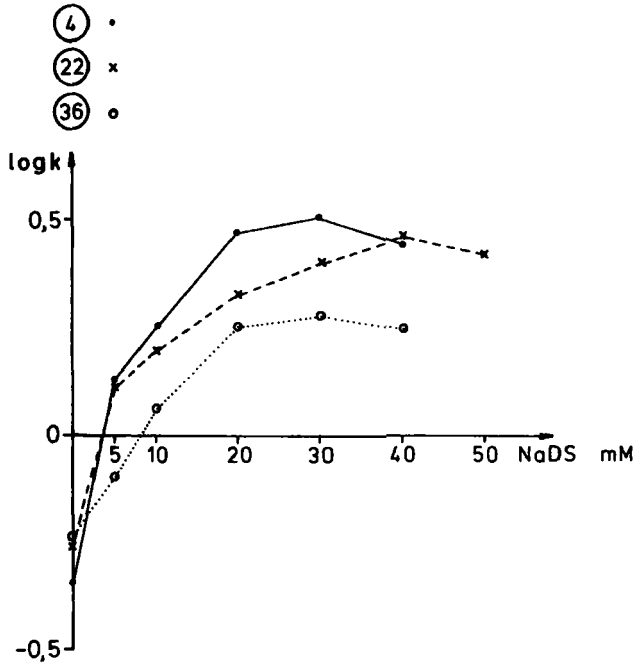


Fig. 1

Relationship between retention and NaDS concentration. Chromatographic system: C_{18}/MeOH - citrate buffer (pH = 3) 80:20 + 0.005 - 0.05 M NaDS

compounds of the two structural types do not fit to a common regression line, a consequence of the selective lipophilicity increase caused by the replacement of etheric oxygen by sulfur (c.f. the values of the slopes in Table 2). The increments of lipophilicity calculated from the log P values from the aminoethers and thioethers are much higher than the increments calculated from the correspond-

Table 2

Correlation between the retention and partition values

$\log P = a \log k' + b$

	Compds. (1-17)	0	0.005	0.01	0.02	0.04	0.05
	a	3.52	3.07	3.35	3.47	3.89	-
n = 17	b	-0.66	-0.656	-1.244	-1.95	-2.18	-
	r	0.914	0.923	0.9813	0.984	0.982	-
						r^2=0.964	
						F =348	
						P 99.9	
	(18-26)						
	a	4.679	8.465	9.881	11.47	10.21	10.97
n = 9	b	1.426	-0.656	-1.665	-3.53	-4.408	-5.449
	r	0.691	0.848	0.884	0.909	0.938	0.919
						r^2=0.88	
						F =110	
						P = 99.9	

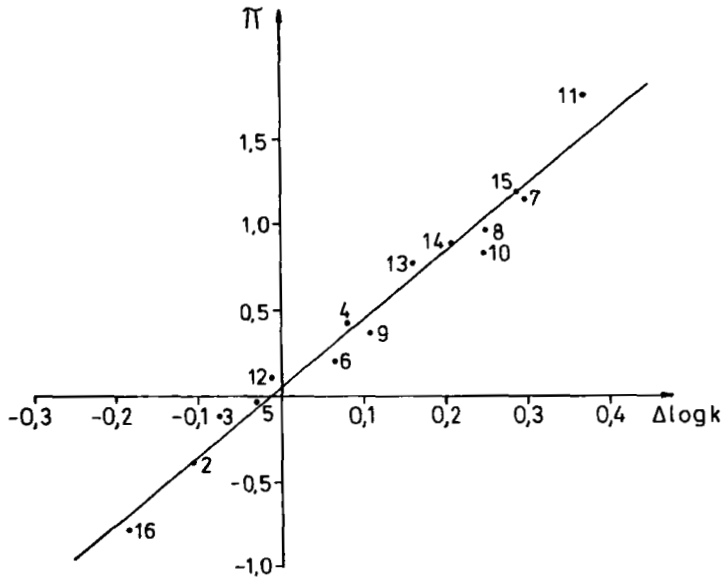


Fig. 2

Relationship between Δlog k' and π values. Chromatographic system: C_{18}/MeOH - citrate buffer (pH = 3) 80:20 + + 0.04 M NaDS

ing log k' values:

$$\log P_{\text{compd.No 19}} - \log P_{\text{compd.No 17}} = 0.561$$

$$\log k'_{\text{compd.No 19}} - \log k'_{\text{compd.No 17}} = 0.098$$

$$\log k'_{\text{compd.No 18}} - \log k'_{\text{compd.No 2}} = 0.113$$

Worthy of note is the observation that the correlation coefficients increase with an increase of NaDS concentration of the eluents. This parallelism may indicate similar interactions in the partition and chromatographic systems (ion--pair formation between the solute and phosphate or dodecyl

sulfate ions resply). While, in the case of aminoethers, the points of the correlation coefficients follow the shape of a saturation curve, the corresponding values for the aminothioethers form a maximum curve.

Also, a very good correlation between the Δlog k' and $\mathcal{T}$ values can be observed.

$\tilde{\mathcal{T}} = a.\Delta\log k' + b$ $\quad\quad$ $\mathcal{T}$: log P_{R-X} - log P_{R-H}

Δ log k': log k'_{R-X} - log k'_{R-H}

$\tilde{\mathcal{T}} = 3.91 \cdot \Delta\log k + 0.059$

r = 0.986

n = 15

chromatographic system: C_{18}/MeOH - citrate buffer (pH = 3) 80:20 + 0.04 M NaDS

Quite a good correlation was found when log k's with the true partition coefficients of compounds (log P_t) containing 4-oxy-piperidine as basic nucleus (compds. No 1-17) were related:

log P_t = log P_{app} + log $(1 + 10^{pK_a - pH})$

log P_t = 4.566 . log k' + 3.236

r = 0.912

n = 16 (compds. 2-17)

chromatographic system: C_{18}/MeOH - citrate buffer (pH = 3) 80:20

log P_t = 2.809 . log k' + 3.568

r = 0.959

n = 16 (compds. 2-17)

chromatographic system: C_{18}/MeOH - citrate buffer (pH = 3) 80:20 + 0.01 M NaDS

Subsequently, in a series of structurally analogous compounds the HPLC method may be applied for the prediction of true partition coefficients.

In the case of compounds containing basic nuclei other than 4-oxypiperidine the correlation between retention and true partition coefficient was not significant as a consequence of the great variance in basic nuclei.

ACKNOWLEDGEMENT

The authors are grateful to I. Kovács-Derzsi for her excellent technical assistance.

REFERENCES

1. Oelschläger, H.: Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. 290/62, 587 (1957); Arzneim. Forsch. 8, 532 (1958), and see also the following PhD-theses: Ralf Morunga (1987), Peter Lang (1987) and Markus Zimmer (1991), all at University of Frankfurt am Main.
2. Takács-Novák, K., Oelschläger, H., Budvári-Bárány, Zs. and Szász, Gy.: Partitioning behaviour of local anesthetic fomocaine derivatives. (In press.)