Chromatographic parameters of dimethylammonioethyl alkoxycarbanilate chlorides

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Conditions were found to separate dimethylammonioethyl alkoxycarbanilate chlorides by thin-layer chromatography on silica gel and cellulose. The R_M values were calculated from the R_f and ΔR_M values for the methylene increment in homologic series of compounds. A linear relationship between the R_M values from partition chromatography and the partition coefficient measured ($\log P'$) or the substitution constant π was ascertained. The R_M values were also employed for correlation with the anaesthetic activity ($\log U$).

Найдены условия для хроматографического разделения диметиламиноэтиловых эфиров алкоксифенилкарбамовых кислот в тонком слое силикагеля и целлюлозы. На основании хроматографических величин R_f были рассчитаны величины R_M, а в гомологических рядах ΔR_M для метиленового звена —CH_2—. Между величинами R_M и измеренным коэффициентом разделения ($\log P'$) или константой замещения π была установлена линейная зависимость. Величины R_M были использованы и при корреляции с биологическим действием — анестетической активностью ($\log U$).

Biologic activity of a compound can be, *inter alia,* expressed in terms of its physicochemical properties of electronic and steric structures [1]. A correlation between the chromatographic and other characteristic data, *e.g.* partition coefficient has also been reported [2]; the R_M values resulting from partition chromatography can be used instead of classic partition coefficients in correlations between physicochemical properties and biologic activity.

Chromatographic behaviour of basic esters of substituted carbamic acids on Silufol and cellulose sheets was investigated [3]. A linear dependence of the R_M upon $\log P'$, or substitution constant π was found when investigating 38 compounds of two various groups differing in the character of both the substituent at the aromatic ring (2-, 3-, 4-propyloxy to octyloxy groups) and the alcohol (2-morpholinoethanol and 2-*N*,*N*-dipropylaminoethanol); the R_M values were also employed for correlation with biologic activity.

We studied [4] the synthesis and properties of piperidinoethyl alkoxyphenylcarbanilates (2-, 3-, 4-methoxy to decyloxy groups) and calculated the R_M and ΔR_M values in homologic series using the R_f values. The R_M values obtained in this way were correlated with the partition coefficient (log P'), surface tension (γ), and biologic effect — the anaesthetic activity (log U).

In this paper, which is a continuation of preceding papers [3, 4], a further series of compounds differing in the number of carbon atoms of the substituent and in the position at the aromatic ring is examined. Preparation of these compounds and their biologic activity (the local anaesthetic effect) have already been published [5].

Experimental

The procedure for chromatographic separation of compounds under study (Table 1) has been published previously [3]. The cellulose sheets for partition chromatography were impregnated with 40 % formamide in ethanol (96 %) containing tris-hydroxymethylaminomethane (TRIS, 1 %), soaked up by filter paper and dried for 120 min in the air. Following mobile phases were employed: S_1 — isopropyl alcohol—diethylamine (9.5 : 0.5), S_2 — light petroleum—diethylamine (8.5 : 1.5), S_3 — light petroleum—diethylamine (8.75 : 1.25), S_4 — 1-propanol. Experimental determination of the partition coefficient (log P') and the procedure for dissociation constant estimation have already been described [3].

Results and discussion

Chromatographic parameters of a series of *N*,*N*-dimethylaminoethyl phenylcarbamates substituted in the respective positions 2-, 3-, and 4- by an alkoxyl group (methoxyl up to decyloxy) and their relationship to physicochemical parameters were investigated by adsorption and partition chromatography. Silica gel (the pre-coated Silufol (Kavalier, Votice) sheets UV 254) was found to be the well suited sorbent for thin-layer chromatography. Nevertheless, we did not succeed in finding a common system for separation of all substances; the most suitable systems for compounds substituted in positions 2-, 3-, and 4- were S_1, S_2, and S_3, respectively. The separation was good, the spots were round-shaped and sharp. Since the compounds under study differ in the homologic alkoxy series by one methylene group it was anticipated that the R_f value would be shifted towards higher values with the increasing number of carbon atoms. This anticipation proved to be correct (Table 1) and an almost linear enhancement of R_f values was ascertained in the 2-substituted homologic series. Compounds substituted in positions 3- or 4- by a group containing one or two carbon atoms displayed an anomalous behaviour. The R_M values (Table 1) and substituents constants $\Delta R_{M(CH_2)}$ were calculated from the R_f values (which are an arithmetic mean of 6 measurements). Fig. 1 shows the relationship of R_M values on the number of carbon atoms in the alkoxyl group chain; the relationship is linear with the exception of the first two members of the homologic series, also differing in the $\Delta R_{M(CH_2)}$ values (0.05—0.10), when compared with those of other members (0.03—0.05).

Cellulose (the ready-made Lucefol Quick sheets) was found to be a suitable sorbent for partition chromatography and the spots were detected with Dragendorf reagent. Good separation of all the investigated compounds was achieved in the elution system 1-propanol. The Lucefol sheets were prior to the separation treated with 40 % formamide containing TRIS (1 %). The R_M (Table 1) and $\Delta R_{M(CH_2)}$ values were calculated from the experimentally determined R_f ones.

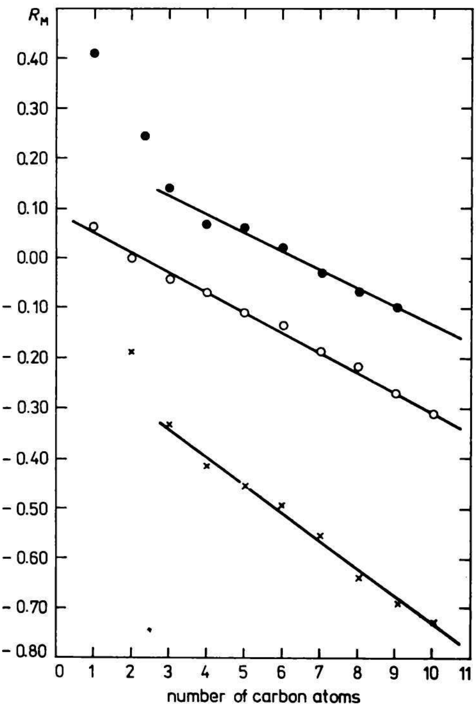
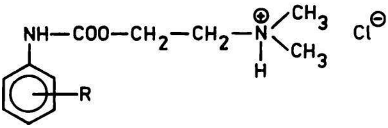


Fig. 1. Dependence of R_M values from adsorption chromatography upon the number of methylene groups in the alkoxyl substituent.
○ 2-Alkoxyl; × 3-alkoxyl; ● 4-alkoxyl.

Table 1

pK_a, R_f, and R_M values of dimethylammonioethyl alkoxycarbanilate chlorides



Compound	R	pK_a[a]	Adsorption chromatography			Partition chromatography		
			$\bar{R}_f$[b]	s	R_M	$\bar{R}_f$[b]	s	R_M
1	2-OCH_3	7.46	0.466		0.0592	0.371		0.230
2	2-OC_2H_5	7.41	0.505		0.0000	0.424		0.133
3	2-OC_3H_7	7.36	0.523		−0.040	0.461		0.070
4	2-OC_4H_9	7.26	0.541		−0.071	0.476		0.041
5	2-OC_5H_{11}	7.17	0.563	0.022	−0.110	0.506	0.022	−0.011
6	2-OC_6H_{13}	7.11	0.576		−0.133	0.518		−0.032
7	2-OC_7H_{15}	7.09	0.605		−0.185	0.535		−0.061
8	2-OC_8H_{17}	7.05	0.624		−0.220	0.543		−0.075
9	2-OC_9H_{19}	6.99	0.652		−0.273	0.557		−0.099
10	2-$OC_{10}H_{21}$	6.99	0.672		−0.312	0.569		−0.121
11	3-OCH_3	—	—		—	—		—
12	3-OC_2H_5	7.09	0.608		−0.191	0.406		−0.165
13	3-OC_3H_7	7.34	0.684		−0.335	0.440		−0.105
14	3-OC_4H_9	7.21	0.725		−0.421	0.463		0.065
15	3-OC_5H_{11}	7.24	0.741	0.042	−0.457	0.472	0.026	0.049
16	3-OC_6H_{13}	7.28	0.757		−0.494	0.497		0.000
17	3-OC_7H_{15}	7.22	0.781		−0.552	0.511		−0.019
18	3-OC_8H_{17}	7.05	0.814		−0.641	0.520		−0.035
19	3-OC_9H_{19}	7.11	0.831		−0.692	0.531		−0.054
20	3-$OC_{10}H_{21}$	—	0.843		−0.730	0.541		−0.072
21	4-OCH_3	7.39	0.281		0.408	0.285		0.400
22	4-OC_2H_5	7.45	0.361		0.248	0.365		0.241
23	4-OC_3H_7	7.44	0.420		0.140	0.460		0.070
24	4-OC_4H_9	7.26	0.462		0.066	0.490		0.017
25	4-OC_5H_{11}	7.32	0.465	0.024	0.061	0.515	0.019	−0.026
26	4-OC_6H_{13}	7.26	0.491		0.016	0.535		−0.061
27	4-OC_7H_{15}	7.27	0.517		−0.030	0.552		−0.091
28	4-OC_8H_{17}	7.17	0.540		−0.070	0.562		−0.108
29	4-OC_9H_{19}	7.04	0.558		−0.101	0.577		−0.135
30	4-$OC_{10}H_{21}$	—	—		—	0.596		−0.169
31	—	—	—		—	0.077		0.229

a) Procedure and calculation published in [3]; *b*) $\bar{R}_f$ — the mean value of six chromatograms.

Lipo-hydrophility is usually characterized by the partition coefficient P'; that of the investigated series was determined by the classical method in a system consisting of polar and nonpolar solvents [3]. Considering the fact that the characteristic chromatographic value R_M was employed for further correlations in this series, the validity of the relationship R_M *vs*. the number of carbon atoms of the alkoxyl substituent had to be verified (Fig. 2). This relationship is linear, the R_M

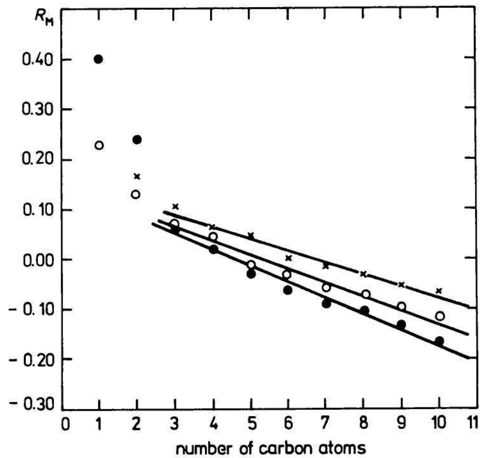


Fig. 2. Dependence of R_M values from partition chromatography upon the number of methylene groups in the alkoxyl substituent.
For symbols see Fig. 1.

values decrease in all series, the methoxyl and ethoxyl groups being the exceptions. These R_M values do not lie on the line and differ in the $\Delta R_{M(CH_2)}$ value by 0.05—0.10 from that (0.03—0.05) of the other members of the series.

Fig. 3 shows the dependence of P' upon R_M on the basis of partition chromatography; this relationship could be considered linear. Mathematical expression of this relationship are the equations

Compound		r_k	s_r	
1—10	$\log P' = -\ 8.0804\ R_M + 2.1625$	0.963	0.102	(*1*)
11—20	$\log P' = -11.4631\ R_M + 2.3242$	0.906	0.173	(*2*)
21—30	$\log P' = -\ 5.3083\ R_M + 2.3842$	0.920	0.183	(*3*)

Introduction of another physicochemical parameter in the correlation equations (*1—3*) was of no influence on the pK_a values, since they minimally differ from each other (Table 1). By introducing the Hansch substitution constants π into correlation with R_M values following equations were deduced

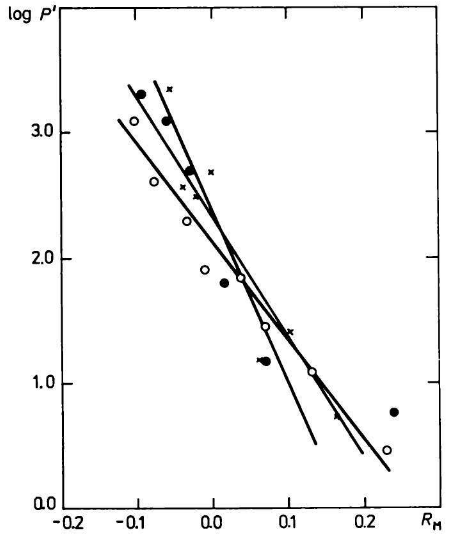


Fig. 3. Dependence of P' upon R_M from partition chromatography.
For symbols see Fig. 1.

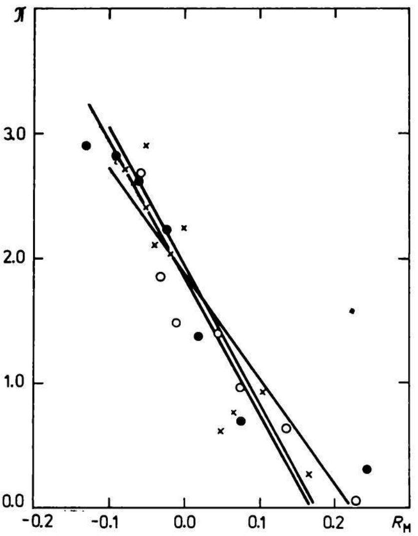


Fig. 4. Dependence of π upon R_M from partition chromatography.
For symbols see Fig. 1.

Compound		r_k	s_r	
1—10	$\pi = -\ 8.0780\ R_M + 1.7166$	0.963	0.102	(*4*)
11—20	$\pi = -11.4631\ R_M + 1.8782$	0.906	0.173	(*5*)
21—30	$\pi = -\ 5.2239\ R_M + 1.9398$	0.921	0.189	(*6*)

The linear course of this relationship is presented in Fig. 4. The relationship between the logarithm of the surface-local anaesthetic activity and R_M values is expressed by the equations

Table 2

log P', π, and log U values of dimethylammonioethyl alkoxycarbanilate chlorides

Compound	log P'	π	log U
1	0.453	0.009	0
2	1.085	0.639	0
3	1.445	0.999	0
4	1.847	1.401	0.167
5	1.892	1.446	1.136
6	2.289	1.843	1.800
7	3.152	2.706	2.004
8	2.619	2.173	2.096
9	3.096	2.650	1.720
10	—	—	0
11	—	—	—
12	0.716	0.270	0
13	1.405	0.950	0.125
14	1.175	0.729	0.153
15	1.048	0.602	1.021
16	2.674	2.228	1.301
17	2.504	2.058	1.408
18	2.562	2.116	0
19	3.346	2.900	0
20	—	—	0
21	0.833	0.045	0
22	0.757	0.311	0
23	1.168	0.722	0
24	1.835	1.389	0
25	2.695	2.249	0
26	3.095	2.649	0
27	3.313	2.867	0
28	—	—	0
29	—	—	0
30	3.341	2.895	0

Compound		r_k	s_r	
1—10	$\log U = -5.1990\, R_M + 0.9313$	0.615	0.279	(*7*)
11—20	$\log U = -0.8911\, R_M + 0.4655$	0.116	0.375	(*8*)

As seen, the correlation between $\log U$ and R_M values was not evidenced. Compounds *21—30* are not included, since they reveal a very low surface-local anaesthetic effect (Table 2). Based upon the experimental data, the R_M values obtained from partition chromatography can directly be applied in the quantitative relationship between the structure and activity for expression of the lipo-hydrophility of the particular compound instead of the classical $\log P'$ or π parameters; the R_M values can also be substituted into correlation equations for compounds the lipo-hydrophility of which has so far not been tabulated.

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