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SOLVENT SELECTIVITY IN THE RESOLUTION OF SOME REGIOISOMERIC AND DIASTEREOMERIC PROSTAGLANDIN INTERMEDIATES ON SILICA

M. LÕHMUS*, I. KIRJANEN, M. LOPP and Ü. LILLE
Institute of Chemistry, Estonian Academy of Sciences, Akadeemia tee 15, 200108 Tallinn (U.S.S.R.)
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SUMMARY

The possibilities of predicting the selectivity in the resolution of regioisomeric and diastereomeric prostaglandin intermediates on silica gel was investigated. A satisfactory correlation between log α and the solvent localization parameters m and m^0 was obtained, confirming the importance of solvent–solute localization in determining α values. The results will be useful in developing further the theory of the selectivity of resolution.

INTRODUCTION

Based on the competition model[1,2], Snyder and co-workers[3–6] pointed out three main physico-chemical factors that determine the selectivity of resolution in normal-phase (including silica gel) adsorption chromatography: (1) solvent strength selectivity; (2) solvent–solute localization (including solvent-specific solvent–solute localization) and (3) solvent–solute hydrogen bonding in stationary and mobile phases.

Nowadays, the solvent strength selectivity is almost impossible to calculate owing to the vertical adsorption of many chemical compounds[7,8]. It is also almost impossible to take into consideration the selectivity of resolution arising from hydrogen bonding[4,6]. Hence the prediction of the selectivity of resolution can be made only on the basis of solvent–solute localization, whereas maximum selectivity in the resolution of certain compounds is attainable using mobile phases with maximum or minimum values of the localization parameter[3,9], which can easily be calculated from other chromatographic data.

So far it has been shown that it is mainly solvent–solute localization that is responsible for the resolution of some relatively nonpolar compounds[3] and many tetrasubstituted ethanes (diastereomers)[7,10,11]. However, it has also been reported that with more polar chromatographic systems the description of solvent selectivity by the localization terms deteriorates (the dependence of log α on the localization parameter of the pure solvent, m^0, was established)[12].

This work was aimed at elucidating the possibilities of predicting the selectivity in the resolution of prostaglandin intermediates on silica gel. It is evident that the

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isomers to be studied are structurally more complicated than those investigated earlier with respect to the localization theory. However, the chromatographic data reported demonstrate a relatively high importance of localization effects in determining the selectivity of resolution.

EXPERIMENTAL

Experiments were performed on a DuPont Model 8843 liquid chromatograph equipped with UV spectrophotometric and refractometric detectors. A Zorbax-SIL

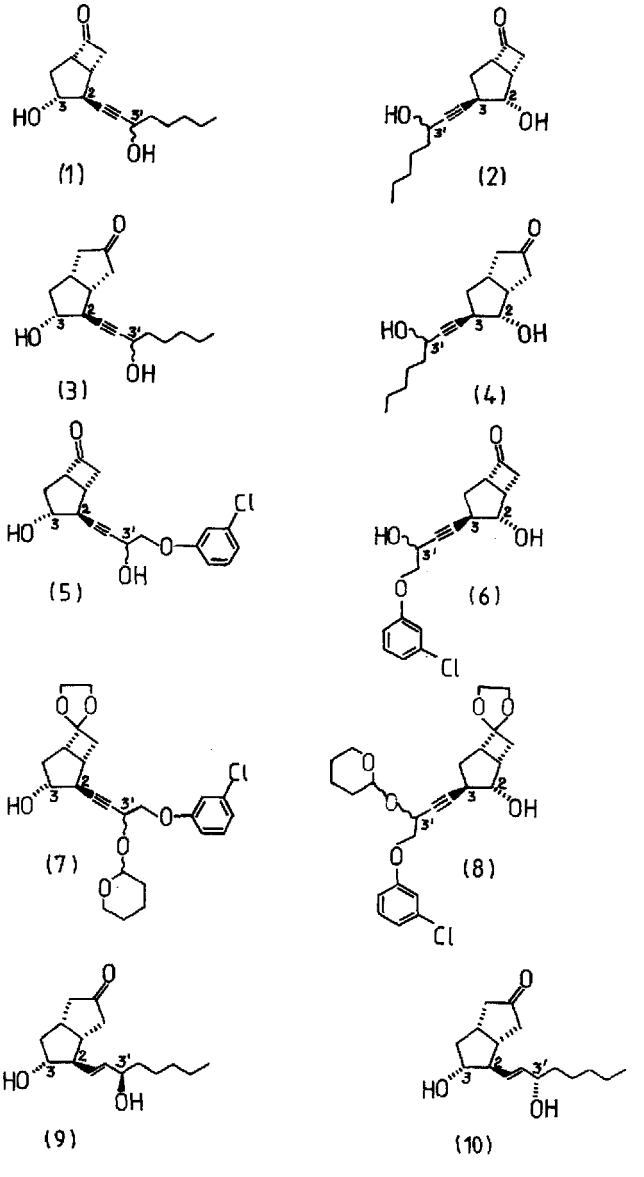


Fig. 1. Formulae of the compounds studied.

column (250 × 4.6 mm I.D.) was used and the mobile phase flow-rate was varied in the range 0.6–1.0 ml/min. The selectivity of resolution was studied in binary mobile phases A–B, where A is *n*-hexane, benzene, chloroform or dichloromethane and B is isopropanol, methanol, acetonitrile, acetone or ethyl acetate. The choice of the solvent was guided by preparative considerations. All the solvents were purchased from Reakhim, USSR. Dichloromethane was distilled before use. The other solvents were prepared as described in ref. 13.

Compounds 1–10, the formulae of which are shown in Fig. 1, were synthesized in the Laboratory of Prostanoids of the Institute of Chemistry, Academy of Sciences of the Estonian S.S.R.[14]. Their structures were verified by ^{13}C NMR spectroscopy.

The capacity factors (k')[15] of compounds 1–10 (Table I) were calculated from the

TABLE I

CAPACITY FACTORS (k') OF COMPOUNDS 1–10 ON A ZORBAX-SIL COLUMN

Temperature, 35°C. Abbreviations: HX = *n*-hexane; BE = benzene; CH = chloroform; IP = isopropanol; ME = methanol; AN = acetonitrile; AC = acetone; EA = ethyl acetate; DCM = dichloromethane.

Mobile phase (v/v)	*Mobile phase No.*	*Compound*									
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
HX–IP:											
80:20	1	–	–	–	–	1.09	1.54 1.63	–	–	–	–
85:15	2	1.33	1.84 1.99	2.52 2.61	1.90	1.75	2.46 2.63	–	–	5.32	4.36
90:10	3	2.90	3.84 4.14	5.69 5.99	4.01 4.16	3.48	4.73 5.08	2.07 2.20	1.75	–	–
93:7	4	–	–	–	–	–	–	3.04 3.24	2.67	–	–
95:5	5	–	–	–	–	–	–	4.32 4.64	4.06	–	–
BE–IP:											
95:5	6	–	–	–	–	1.46	1.79	–	–	–	–
96:4	7	2.46	3.07 3.15	5.17	3.71	–	–	–	–	–	–
97:3	8	4.23	5.23 5.34	9.23	6.63	3.71	4.57	0.79 0.85	1.18 1.29	–	–
98:2	9	–	–	–	–	7.88	9.90	1.52 1.75	2.52 2.71	–	–
99:1	10	–	–	–	–	–	–	3.51 4.68	7.47 7.67 8.96 8.96	–	–
CH–IP:											
95:5	11	–	–	–	–	1.39	1.60	–	–	–	–
96:4	12	1.68	1.88	2.61	2.14	–	–	–	–	3.87	3.87
97:3	13	2.39	2.66	3.32	2.77 2.95	4.90	5.64	0.70 0.80	1.52 1.53	–	–
97.5:2.5	14	–	–	–	–	6.78	7.84	0.95 1.10	2.16 2.45	–	–

(*Continued on p. 80*)

TABLE I (*continued*)

Mobile phase (v/v)	*Mobile phase No.*	*Compound*									
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
98:2	15	–	–	–	–	–	–	1.43 1.68	3.44 3.53 4.05 4.05	–	–
98.5:1.5	16	–	–	–	–	–	–	2.14 2.40	5.30 5.41 6.33 6.33	–	–
BE–ME:											
95:5	17	–	–	–	–	1.09	1.03	–	–	2.68	2.68
97:3	18	4.30	4.39	7.13	5.38	2.27	2.27	–	–	–	–
98:2	19	–	–	–	–	4.31	4.48	0.74 0.82	0.91	–	–
99:1	20	–	–	–	–	–	–	1.92 2.21	3.35 3.56	–	–
99.5:0.5	21	–	–	–	–	–	–	3.05 3.94	6.76 7.00 8.19 8.19	–	–
CH–ME:											
96:4	22	–	–	–	–	0.92	0.86	–	–	–	–
97:3	23	1.97	1.97	2.55	2.10	1.66	1.60	–	–	–	–
98:2	24	3.43	3.75	5.09	4.11	3.58	3.58	0.54	0.78 0.81	–	–
98.3:1.7	25	–	–	–	–	4.82	4.95	–	–	–	–
98.5:1.5	26	–	–	–	–	–	–	0.76 0.86	1.61 1.80	–	–
98.8:1.2	27	–	–	–	–	–	–	1.26 1.48	2.90 2.95 3.34 3.34	–	–
99:1	28	–	–	–	–	–	–	1.41 1.67	3.16 3.26 3.66 3.66	–	–
99.2:0.8	29	–	–	–	–	–	–	1.73 2.07	4.18 4.28 4.99 4.99	–	–
BE–AN:											
0:40	30	–	–	–	–	–	–	–	–	3.18	5.57
70:30	31	–	–	–	–	0.78	1.02	–	–	–	–
75:25	32	–	–	–	–	1.14	1.54	–	–	–	–
80:20	33	2.33	3.31	6.02	4.17	1.69	2.37	–	–	–	–
85:15	34	–	–	–	–	3.17	4.42	1.00 1.26	1.62 1.83	–	–
90:10	35	–	–	–	–	–	–	1.99 2.56	3.66 3.66 4.81 4.93	–	–

TABLE I (*continued*)

Mobile phase (v/v)	*Mobile phase No.*	*Compound*									
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
CH–AN:											
60:40	36	–	–	–	–	–	–	–	–	2.03	3.36
70:30	37	–	–	–	–	0.78	0.98	–	–	3.40	5.96
80:20	38	2.26	3.19	–	–	1.97	2.60	–	–	–	–
85:15	39	3.56	5.03	–	–	3.51	4.64	–	–	–	–
90:10	40	–	–	–	–	8.46	11.3	1.63	4.12	–	–
								2.05	4.12		
									5.41		
									5.54		
93:7	41	–	–	–	–	–	–	2.87	8.32	–	–
								3.86	8.32		
									11.4		
									11.6		
BE–AC:											
80:20	42	0.91	1.33	1.84	1.32	0.89	1.21	–	–	3.13	4.61
90:10	43	3.27	4.76	7.37	5.53	3.30	4.73	0.78	1.11	–	–
								0.85	1.31		
95:5	44	–	–	–	–	–	–	2.24	4.17	–	–
								2.61	5.01		
CH–AC:											
85:15	45	2.25	3.60	–	–	2.07	3.05	–	–	–	–
88:12	46	3.87	6.17	–	–	3.66	5.26	0.75	1.57	–	–
								0.89	1.93	–	–
94:6	47	–	–	–	–	–	–	2.11	5.41	–	–
								2.50	6.97		
96:4	48	–	–	–	–	–	–	3.52	10.4	–	–
								4.43	14.0		
HX–EA:											
20:80	49	–	–	–	–	–	–	–	–	1.14	1.63
30:70	50	–	–	–	–	0.52	1.01	–	–	1.78	2.50
							1.07				
40:60	51	–	–	–	–	0.85	1.73	–	–	2.87	3.88
							1.79				
50:50	52	1.29	2.71	3.17	2.05	1.61	3.17	–	–	–	–
			2.79				3.27				
55:45	53	1.61	3.34	4.40	2.74	–	–	–	–	–	–
			3.48								
60:40	54	2.19	4.60	–	–	3.11	6.29	–	–	–	–
			4.75				6.49				
65:35	55	3.11	6.49	–	–	4.53	9.08	2.36	2.36	–	–
			6.73				9.42	2.69	2.43		
									2.89		
									2.89		
70:30	56	–	–	–	–	–	–	3.35	3.51	–	–
								3.35	3.62		
								3.82	4.31		
								3.86	4.35		

(*Continued on p. 82*)

TABLE I (*continued*)

Mobile phase (v/v)	*Mobile phase No.*	*Compound*									
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
75:25	57	–	–	–	–	–	–	4.96 4.96 5.67 5.78	5.44 5.67 6.71 6.80	–	–
BE–EA:											
40:60	58	–	–	–	–	–	–	–	–	2.00	2.97
50:50	59	–	–	–	–	–	–	–	–	3.18	5.12
60:40	60	–	–	–	–	0.91	1.92	–	–	5.72	9.56
70:30	61	1.78	3.72 3.84	–	–	1.71	3.48	–	–	–	
80:20	62	4.03	8.10 8.27	–	–	4.00	7.76	1.72 2.04	2.41 2.51 3.13 3.13	–	–
90:10	63	–	–	–	–	–	–	5.03 6.43	9.30 9.54 12.5 12.5	–	–
CH–EA:											
50:50	64	–	–	–	–	0.85	1.75 1.80	–	–	2.79	4.48
60:40	65	–	–	–	–	1.39	2.81 2.88	–	–	–	–
65:35	66	1.97	4.15 4.26	3.19	4.30	–	–	–	–	–	–
70:30	67	2.71	5.49 5.65	–	–	2.69 2.73	5.29 5.38	–	–	–	–
75:25	68	–	–	–	–	4.06 4.17	7.77	1.40 1.64	2.61 2.70 3.42 3.42	–	–
80:20	69	–	–	–	–	6.72 6.89	12.4	2.01 2.45	4.37 4.52 5.83 5.83	–	–
85:15	70	–	–	–	–	–	–	2.94 3.79	7.39 7.62 10.2 10.2	–	–
DCM–EA:											
60:40	71	–	–	–	–	0.83	1.52	–	–	–	–
70:10	72	1.87	3.28	–	–	1.44	2.53	–	–	–	–
80:20	73	3.66	6.02	–	–	3.12 3.21	4.97	1.37 1.65	2.56 3.39	–	–

chromatograms plotted on a recorder. To improve the precision of measurements, the chart speed was chosen so that the values of the measured distances exceeded 5 cm. Reproducibility measurements of the given k' values were shown to have a relative standard deviation of less than 1%. The column void volume (V_0) determined as the elution volume of toluene using *n*-hexane–isopropanol (75:25) as the mobile phase, was 3.41 ml.

For regioisomeric pairs 1–2, 3–4, 5–6 and 7–8, the selectivity (α)[15] (Table II) was

TABLE II

α VALUES FOR RESOLUTION OF ISOMER PAIRS 1–10, THE SOLVENT STRENGTH, ε_{AB}, OF THE MOBILE PHASES USED, THE MOLAR FRACTION OF SOLVENT B IN THE ADSORBED MONOLAYER, θ_B, AND THE LOCALIZATION PARAMETER OF MOBILE PHASES, m

Column, Zorbax-SIL.

Mobile phase	*Compound pair*					ε_{AB}	θ_B	m
*No.**	*1–2*	*3–4*	*5–6*	*7–8*	*9–10*			
1	–	–	1.45	–	–	0.421	0.93	0.84
2	1.44	0.74	1.45	–	0.82	0.401	0.92	0.83
3	1.38	0.70	1.41	0.82	–	0.383	0.91	0.83
4	–	–	–	0.85	–	0.368	0.89	0.82
5	–	–	–	0.91	–	0.356	0.88	0.82
6	–	–	1.22	–	–	0.383	0.56	0.50
7	1.26	0.72	–	–	–	0.367	0.51	0.43
8	1.25	0.72	1.23	1.51	–	0.345	0.44	0.32
9	–	–	1.26	1.60	–	0.321	0.35	0.22
10	–	–	–	2.02	–	0.291	0.22	0.11
11	–	–	1.14	–	–	0.364	0.47	0.43
12	1.12	0.82	–	−1.0	0.350	0.42	0.36	
13	1.11	0.86	1.15	2.03	–	0.331	0.35	0.29
14	–	–	1.16	2.25	–	0.322	0.31	0.26
15	–	–	–	2.42	–	0.312	0.26	0.22
16	–	–	–	2.57	–	0.301	0.21	0.19
17	–	–	0.95	–	1.0	–	–	–
18	1.02	0.76	1.0	–	–	–	–	–
19	–	–	1.04	1.17	–	–	–	–
20	–	–	–	1.67	–	–	–	–
21	–	–	–	2.16	–	–	–	–
22	–	–	0.94	–	–	–	–	–
23	1.0	0.82	0.96	–	–	–	–	–
24	1.09	0.81	1.0	1.47	–	–	–	–
25	–	–	1.03	–	–	–	–	–
26	–	–	–	2.10	–	–	–	–
27	–	–	–	2.29	–	–	–	–
28	–	–	–	2.23	–	–	–	–
29	–	–	–	2.42	–	–	–	–

(*Continued on p. 84*)

TABLE II (*continued*)

Mobile phase	*Compound pair*					ε_{AB}	θ_B	m
*No.**	*1–2*	*3–4*	*5–6*	*7–8*	*9–10*			
30	–	–	–	–	1.75	0.455	0.80	0.97
31	–	–	1.31	–	–	0.436	0.73	0.90
32	–	–	1.31	–	–	0.422	0.68	0.85
33	1.42	0.69	1.35	–	–	0.404	0.63	0.76
34	–	–	1.40	1.53	–	0.380	0.55	0.61
35	–	–	–	1.87	–	0.348	0.44	0.39
36	–	–	–	–	1.66	0.448	0.77	0.96
37	–	–	1.26	–	1.75	0.426	0.69	0.88
38	1.41	–	1.32	–	–	0.392	0.58	0.71
39	1.41	–	1.32	–	–	0.369	0.50	0.53
40	–	–	1.34	2.61	–	0.336	0.39	0.39
41	–	–	–	2.95	–	0.314	0.30	0.29
42	1.42	0.72	1.37	–	1.47	0.428	0.71	0.80
43	1.47	0.75	1.43	1.48	–	0.379	0.57	0.57
44	–	–	–	1.89	–	0.331	0.40	0.30
45	1.60	–	1.47	–	–	0.400	0.61	0.70
46	1.59	–	1.44	2.13	–	0.383	0.56	0.60
47	–	–	–	2.9	–	0.336	0.38	0.36
48	–	–	–	3.03	–	0.314	0.29	0.26
49	–	–	–	–	1.43	0.460	0.99	0.60
50	–	–	2.00	–	1.40	0.447	0.99	0.60
51	–	–	2.07	–	1.35	0.429	0.98	0.60
52	2.13	0.65	2.00	–	–	0.406	0.97	0.60
53	2.12	0.62	–	–	–	0.394	0.97	0.60
54	2.13	–	2.05	–	–	0.381	0.96	0.59
55	2.13	–	2.04	1.05	–	0.365	0.95	0.59
56	–	–	–	1.10	–	0.347	0.94	0.59
57	–	–	–	1.15	–	0.332	0.93	0.59
58	–	–	–	–	1.49	0.428	0.87	0.58
59	–	–	–	–	1.61	0.414	0.83	0.56
60	–	–	2.12	–	1.67	0.400	0.78	0.55
61	2.12	–	2.04	–	–	0.380	0.70	0.50
62	2.03	–	1.94	1.49	–	0.352	0.59	0.40
63	–	–	–	1.91	–	0.311	0.40	0.19
64	–	–	2.09	–	1.61	0.411	0.80	0.56
65	–	–	2.05	–	–	0.395	0.74	0.54
66	2.13	0.74	–	–	–	0.385	0.70	0.52
67	2.06	–	1.97	–	–	0.375	0.65	0.48
68	–	–	1.88	2.00	–	0.362	0.59	0.43
69	–	–	1.82	2.30	–	0.347	0.53	0.37
70	–	–	–	2.63	–	0.330	0.44	0.29
71	–	–	1.83	–	–	0.380	0.60	0.44
72	1.75	–	1.76	–	–	0.362	0.49	0.33
73	1.64	–	1.57	1.97	–	0.343	0.36	0.23

* See Table I.

calculated as the ratio of the k' value of 3-alkynyl-substituted isomers to that of 2-alkynyl-substituted isomers. In some instances the resolution of diastereomers at C-3′ took place. With compounds 7 and 8, diastereomers at a carbon atom in the masking tetrahydropyranyl group were also resolved (see Table I). Therefore, the values were calculated using the mean values of the capacity factors given in Table I (it is evident that regioisomers are more easily resolvable than the respective diastereomers).

For diastereomers 9 and 10, α was calculated as the ratio of k' of isomer 10 to that of isomer 9 (Table II).

CALCULATIONS

The solvent strength (ε_{AB}) of the mobile phases (Table II) was determined using the equation[4,6]

$$\varepsilon_{AB} = \varepsilon_A + \frac{\log(N_B \cdot K + 1 - N_B)}{\alpha' n_B} \tag{1}$$

where

$$K = 10^{\alpha' n_B(\varepsilon_B - \varepsilon_A)} \tag{2}$$

N_B = molar fraction of solvent B in the mobile phase; α' = adsorbent activity function ($\alpha' = 0.57$)[10,12]; n_B = molecular area of solvent B (isopropanol, 4.4; acetonitrile, 3:1; acetone, 4.2; ethyl acetate, 5.2)[6,16]; ε_A and ε_B = solvent strengths for pure solvents A and B, respectively (for solvents A, the following ε_A values were used: *n*-hexane, 0.0; benzene, 0.25; chloroform, 0.26; dichloromethane, 0.30)[6,17].

As the solvent strength of the localizing solvent B is different for the localized (ε_B') and delocalized (ε_B'') molecules, then ε_B depends also on the localization function $\%_{lc}$[4,6,16,18]:

$$\varepsilon_B = \%_{lc}(\varepsilon_B' - \varepsilon_B'') + \varepsilon_B'' \tag{3}$$

The localization function depends on the molar fraction of solvent B in the adsorbed monolayer θ_B[4,6,16,18]:

$$\%_{lc} = (1 - \theta_B)[1/(1 - 0.94\theta_B) - 14.5\theta_B^9] \tag{4}$$

The value of θ_B depends on K and N_B[12,18]:

$$\theta_B = \frac{KN_B}{N_A + KN_B} \tag{5}$$

where N_A is the molar fraction of solvent A in the mobile phase.

The ε_B values were calculated from eqns. 2–5 using the iterative method. From these equations the θ_B values were also found (Table II). ε_B' and ε_B'' were taken from refs. 6 and 16 or calculated using eqn. 15 and Table I in ref. 6. For methanol-containing

TABLE III

VALUES OF ε'_B AND ε''_B FOR THE SOLVENT SYSTEMS STUDIED

*Solvent system**	ε'_B	ε''_B
HX–IP	1.83	0.60
BE–IP	0.80	0.60
CH–IP	0.76	0.60
BE–AN	0.60	0.52
CH–AN	0.58	0.52
BE–AC	0.68	0.53
CH–AC	0.66	0.53
HX–EA	0.94	0.48
BE–EA	0.53	0.48
CH–EA	0.52	0.48
DCM–EA	0.48	0.48

* Abbreviations as in Table I.

mobile phases it was impossible to calculate ε_B. For clarity these values are given in Table III.

The localization parameters (m) of the mobile phases (Table II) were calculated using the equation[3]

$$m = m^0 f(\theta_B) + m_A^0 f(\theta_A + \theta_B) - f(\theta_B) \quad (6)$$

where $f(\theta_A)$ = solvent-localization function, which varies with θ_B [the $f(\theta_B)$ values were found by means of the θ_B values by interpolating the data in Table 3 in ref. 3]; $f(\theta_A + \theta_B) = 1$; m_A^0 = solvent-localization parameter for pure solvent A (for chloroform and dichloromethane, $m_A^0 = 0.10$; for benzene and *n*-hexane, $m_A^0 = 0.0$)[6]; m^0 = solvent-localization parameter for pure solvent B.

The m^0 values were taken from ref. 12 (isopropanol, 0.85; acetonitrile, 1.05; acetone, 0.96; ethyl acetate, 0.60). For methanol m^0 was not available in the literature.

RESULTS AND DISCUSSION

The dependence of the log α values on the localization parameters m and m^0 using eleven solvent systems was studied as an example on compound pairs 1–2, 5–6 and 7–8, for which a significant amount of experimental data was obtained. The methanol-containing mobile phases were not studied in this respect owing to the lack of m^0 and ε' values for methanol in the literature.

Solutes with hydroxyl, carbonyl and ether functionalities compete with polar solvent molecules for active silanol OH groups on the silica surface, and this solvent–solute localization to some extent influences the selectivity of separation. However, Fig. 2 demonstrates the absence of a linear log α–m correlation for the resolution of the regioisomeric pairs of ketonediols 1–2 and 5–6 (the correlation coefficient $r = 0.06$). This is not surprising because polar solvents with proton acceptor and donor properties (see Table I in ref. 19) participate in solvent–solute interactions,

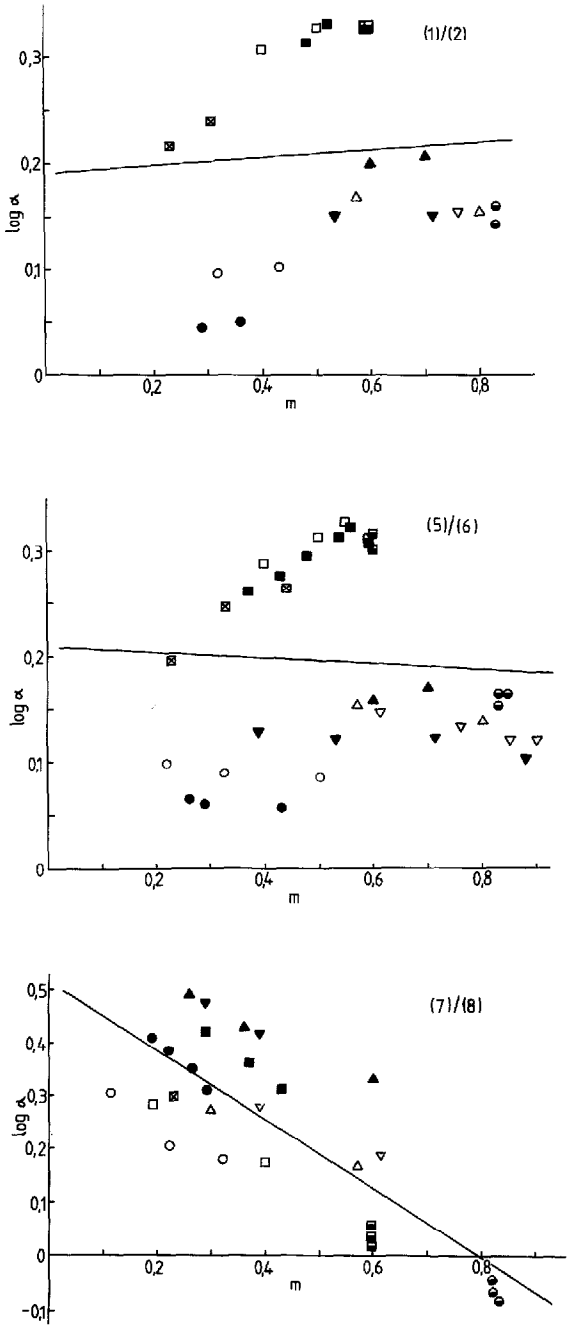


Fig. 2. Dependence of log α on the mobile phase localization parameter *m* for the resolution of compounds 1–2, 5–6 and 7–8 (r = 0.06, 0.06 and 0.79, respectively). Solvent systems: ◒, *n*-hexane–isopropanol; ○, benzene–isopropanol; ●, chloroform–isopropanol; ▽, benzene–acetonitrile; ▼, chloroform–acetonitrile; △, benzene–acetone; ▲, chloroform–acetone; ⬓, *n*-hexane–ethyl acetate; □, benzene–ethyl acetate; ■, chloroform–ethyl acetate; ⊠, dichloromethane–ethyl acetate.

particularly hydrogen bonds, which effect the selectivity in a different way to the localization effects. As a result, the log α–m correlation is absent.

The protection of one hydroxyl and carbonyl function in two ketonediols, 5 → 7 and 6 → 8, results in a much better log α–m correlation ($r = 0.79$). It is evident that the hydrogen bonds with the hydroxyl groups in the 2/3-position and ether oxygen (including ketal oxygen) influence the selectivity of separation in a similar manner to the localization effects.

It is also worth mentioning the intramolecular hydrogen bond between the C-3 hydroxyl group and the ketal oxygen atom of the carbonyl-protecting group at C-6 for compound 7 demonstrated in ref. 20. In compound 8 such a hydrogen bond is absent.

An increase in the proportion of the more polar solvent in the solvent systems probably results in stronger hydrogen bonding between the mobile phase and compound 8, which leads to a decreased retention and, therefore, to lower α values in all the solvent systems studied. It is likely that a similar interaction with compound 7 is precluded owing to the intramolecular hydrogen bond. The latter can also contribute to the less extensive localization in compound 7 compared with 8 (see below).

Further, an attempt was made to determine quantitatively the contribution of hydrogen bonding to the separation selectivity of the less polar compounds 7 and 8. In *n*-hexane–isopropanol and *n*-hexane–ethyl acetate systems (correspondingly mobile phases 5 and 57 in Table II), the monolayer on the silica surface is complete ($\theta_B > 0.88$) and solvent–solute localization has reached its steady level. Further increases in the proportions of isopropanol and ethyl acetate in the mobile phase, accompanied by certain changes in the solvent strength, $\Delta\varepsilon_{AB}$ (systems 3–4 and 55–56), may influence the separation selectivity only due to the hydrogen bonds and solvent strength. The influence of the latter on the separation of isomers is negligible[4,6,8]. As the absolute values of selectivity changes are determined by the arbitrarily chosen mobile phases,

TABLE IV

VALUES OF THE θ_B INTERVAL, SELECTIVITY CHANGE (ΔLOG α), MOBILE PHASE STRENGTH CHANGE ($\Delta\varepsilon_{AB}$) AND ΔLOG $\alpha/\Delta\varepsilon_{AB}$ RELATIONSHIP IN THE SOLVENT SYSTEMS USED FOR SEPARATION OF REGIOISOMERS 7 AND 8

*Solvent system**	θ_B *interval*	$\Delta log\ \alpha$	$\Delta\varepsilon_{AB}$	$\Delta log\ \alpha/\Delta\varepsilon_{AB}$
HX–IP	0.88–0.91	0.045	0.027	1.67
HX–EA	0.93–0.95	0.040	0.033	1.21
				Mean: 1.44
BE–IP	0.22–0.44	0.126	0.054	2.33
CH–IP	0.21–0.35	0.103	0.030	3.43
BE–AN	0.35–0.38	0.087	0.032	2.72
CH–AN	0.31–0.34	0.053	0.022	2.41
BE–AC	0.33–0.38	0.106	0.048	2.21
CH–AC	0.31–0.38	0.153	0.069	2.22
BE–EA	0.40–0.59	0.108	0.041	2.63
CH–EA	0.44–0.59	0.119	0.032	3.73
				Mean: 2.72

* Abbreviations as in Table I.

then in order to compare the selectivity changes in various mobile phases in this instance it is reasonable to relate the values of $\Delta\log\alpha$ to $\Delta\varepsilon_{AB}$. The $\Delta\log\alpha/\Delta\varepsilon_{AB}$ values form the absolute scale for selectivity changes.

As can be seen in Table IV, the mean $\Delta\log\alpha/\Delta\varepsilon_{AB}$ value for the systems with a complete monolayer afford about 50% of this value for eight systems with an incomplete monolayer. Therefore, the hydrogen bond and solvent–solute localization contribute to the separation selectivity of compounds 7 and 8 almost equally.

However, it should be borne in mind that a certain part of the hydrogen bonds in the mobile phase can be cancelled out by the corresponding bonds in the completed monolayer (see below).

It appears that in the resolution of compounds 7 and 8 the variation of the nonpolar or weakly polar solvent in the mobile phase in the sequence *n*-hexane–benzene–chloroform results in a greater increase in selectivity than with polar solvents (see Fig. 2). For example, the transition from *n*-hexane to benzene and from benzene to chloroform in the isopropanol-containing binary systems ($\Delta m = 0.6$) results in an approximately 0.5 unit increase in logα for the partially blocked ketonediols 7 and 8 (in

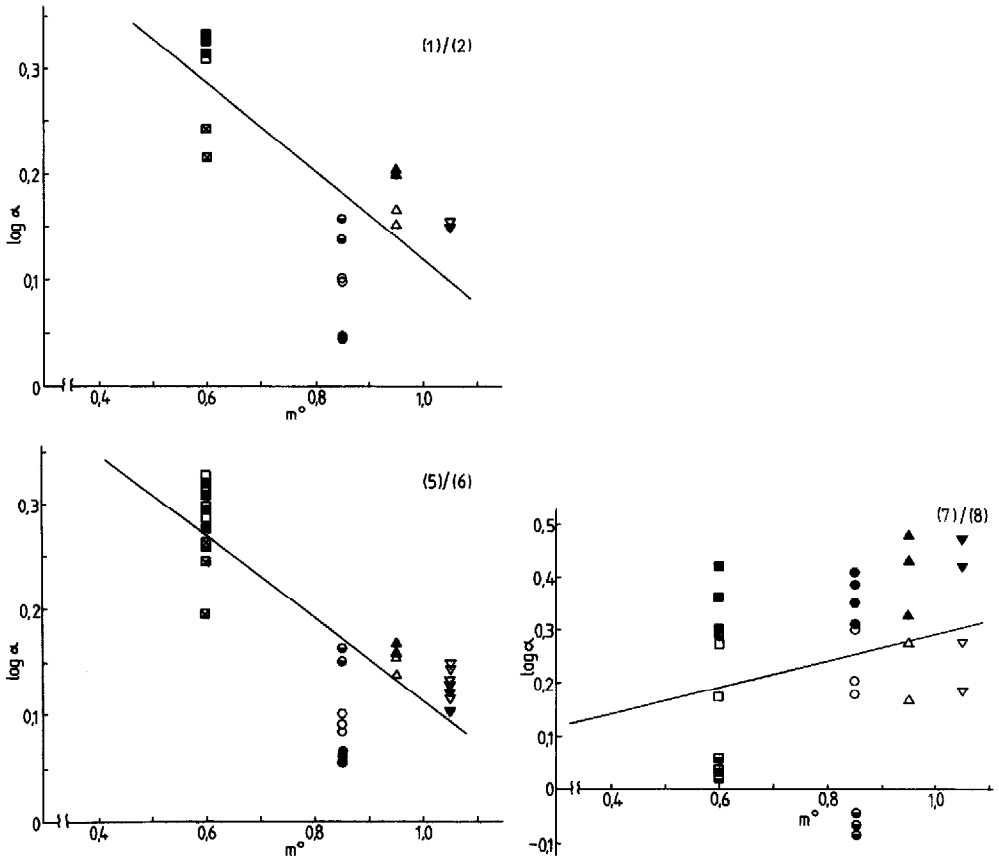
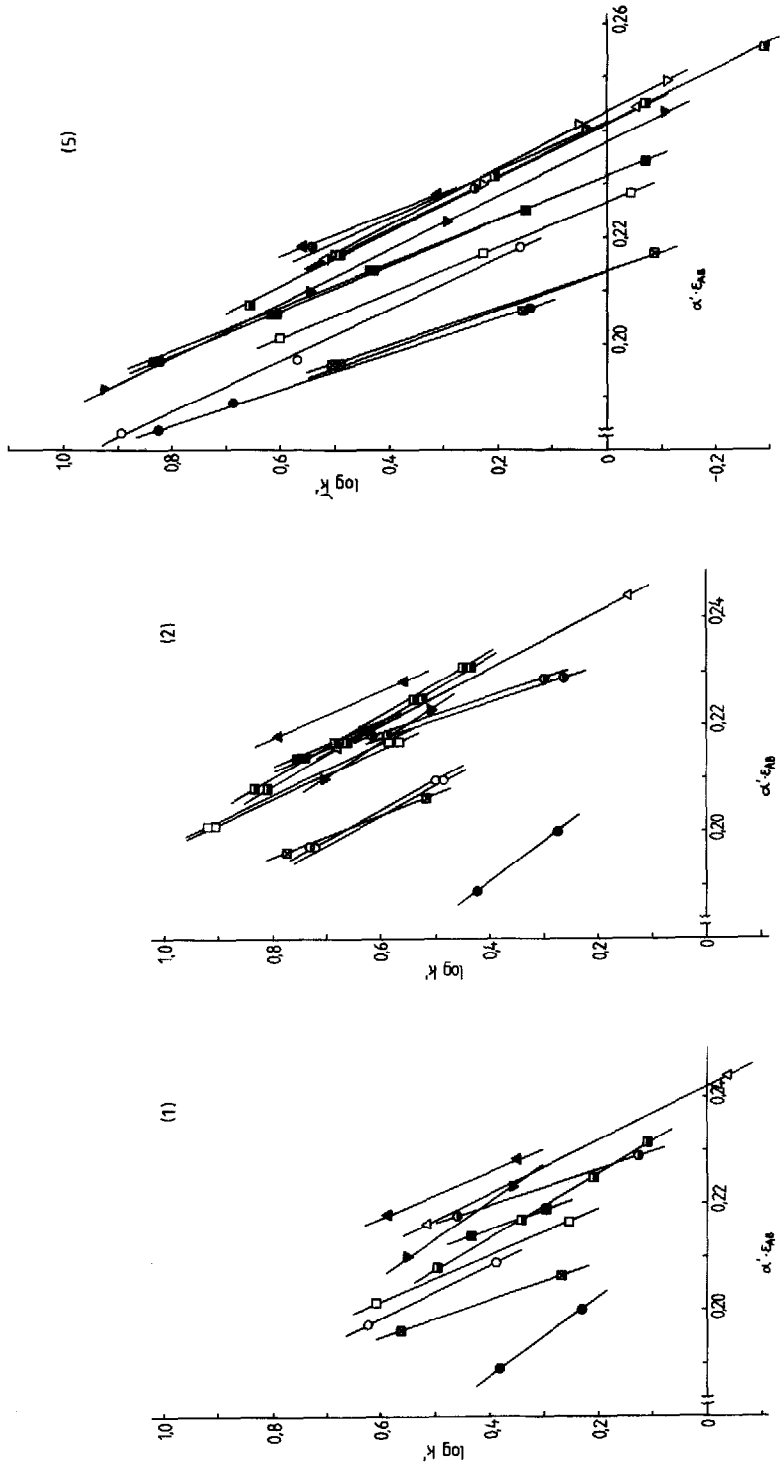


Fig. 3. Dependence of log α on the localization parameter of solvent B (m^0) for the resolution of compounds 1–2, 5–6 and 7–8 (r = 0.76, 0.83 and 0.25, respectively). Solvent systems as in Fig. 2.


(5)
log k'
α'·ε_AB
1,0
0,8
0,6
0,4
0,2
0
-0,2
0,20
0,22
0,26
(2)
log k'
α'·ε_AB
1,0
0,8
0,6
0,4
0,2
0
0,20
0,22
0,24
(1)
log k'
α'·ε_AB
1,0
0,8
0,6
0,4
0,2
0
0,20
0,22

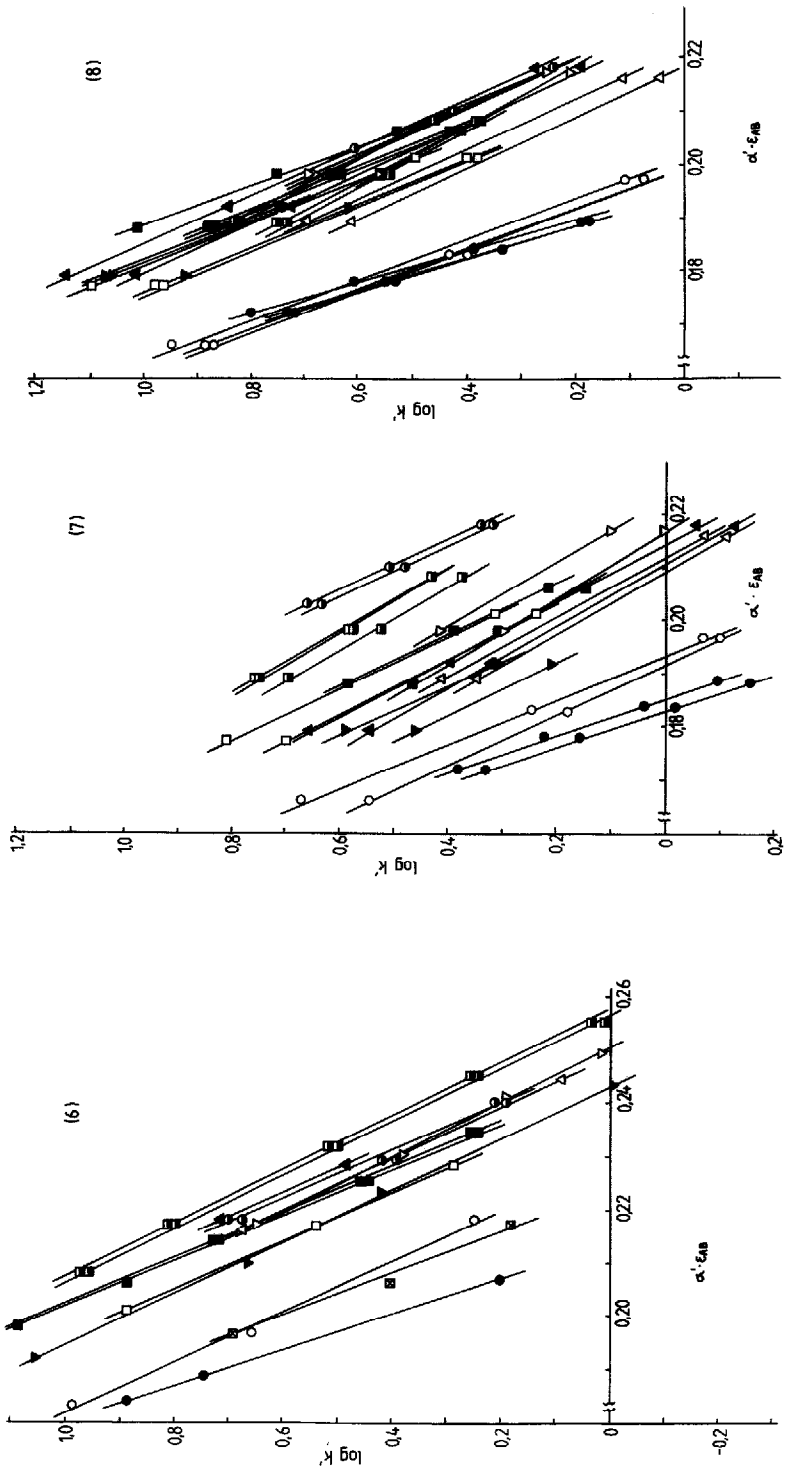


Fig. 4. Dependence of $\log k'$ on $\alpha' \varepsilon_{AB}$ for compounds 1, 2 and 5–8. Solvent systems as in Fig. 2.

the case of the first transition the elution order is reversed). With a change in the benzene-containing mobile phases isopropanol–ethyl acetate–acetone–acetonitrile ($\Delta m = 0.5$), logα increases only by about 0.1 unit. A similar change in the chloroform-containing systems ($\Delta m = 0.4$) gives about a 0.2-unit increase in log α. Therefore, for compounds 7 and 8, the best way to vary m and control the localization effects is to vary the less polar component in the mobile phase. In this case solvent–solute interactions remain almost unchanged.

Naturally this is not so in the chloroform-containing mobile phase in which, owing to the strong proton-donor properties of chloroform, an additional source of selectivity appears. This is clearly seen on comparing the separation selectivity of compounds 7 and 8 in the systems benzene–acetone ($N_B = 0.118$) and chloroform–acetone ($N_B = 0.131$) (mobile phases 45 and 48 in Table II). The change from benzene to chloroform is accompanied by a selectivity increase from 1.48 to 2.13.

As mentioned above, with the ketonediol pairs 1–2 and 5–6 strong hydrogen bonding results in the disappearance of the dependence of log α on m. This is also confirmed by the fact (as seen in Fig. 2) that in some solvent systems the selectivity of resolution increases with increasing concentration of more polar components in the mobile phase (corresponding to an increase in m), whereas in other systems it decreases.

Snyder *et al.*[12] concluded that in mixtures of weakly polar and strongly polar solvents the selectivity of resolution is determined by the strongly polar solvent and that in resolving the diastereomers of the substituted 2,3-diphenylglutaric acids a linear dependence of log α on the localization parameter of pure solvent B, m°, results. Therefore we examined the data on the resolution of compounds 1–2, 5–6 and 7–8 in the coordinates log α–m° (Fig. 3). As can be seen, the selectivity of the resolution of the partially masked ketonediols 7 and 8 does not depend on m°. On resolution of 1–2 and 5–6, a linear dependence of log α on m° ($r = 0.76$ and 0.83, respectively) can clearly be seen.

However, it is also seen from Fig. 3 that for the experimental points obtained by resolution with the mobile phases benzene–isopropanol and chloroform–isopropanol, a deviation from a straight line takes place. This phenomenon can be explained by Fig. 4, in which the dependence of log k' of compounds 1–2 and 5–8 on the product of α' and the solvent strength $\varepsilon_{AB}(\alpha', \varepsilon_{AB})$ of all the mobile phases used is shown. For all the compounds studied, the positions of the lines for the solvent systems benzene–isopropanol, chloroform–isopropanol and also dichloromethane–ethyl acetate are clearly different to those of the eight other systems. In other words, if these solvent systems are used to achieve the given retention, mobile phases with a significantly lower solvent strength are required. This phenomenon in the systems benzene–isopropanol and chloroform–isopropanol consist in the formation of hydrogen bonding associates between the solute and solvent molecules in the mobile phase. It is likely that in *n*-hexane–isopropanol the presence of such associates in the monolayer ($\theta_B \approx 1.0$) will cancel out the mobile phase influence and the ε_{AB} value in this system does not seem anomalously low. It seems difficult to us to explain why the retention is anomalous in dichloromethane–ethyl acetate.

If we consider the resolution in the solvent systems benzene–isopropanol, chloroform–isopropanol and dichloromethane–ethyl acetate as exceptional and reject the experimental points corresponding to these solvent systems in Fig. 3 for

compounds 1–2 and 5–6, then an increase in r to 0.94 and 0.97, respectively, results.

We consider that the 3-alkynyl-substituted isomers 2, 6 and 8 localize to a greater extent than the 2-alkynyl-substituted isomers. This is evident from Figs. 2 and 3 and the definition of selectivity (see Experimental). It means that 3-alkynyl-substituted isomers are structurally more suitable for interactive with the silanol OH groups on the silica surface.

CONCLUSIONS

The possibility of predicting the selectivity of the resolution of some regioisomeric bicyclic ketonediols (intermediates of prostaglandins) by means of the mobile phase localization parameters m and m^0 has been demonstrated. The resolution of partially blocked regioisomers can be described by solvent–solute localization; for their resolution it is necessary to proceed from the required retention ($k' = 2$–5). By using known techniques mobile phase compositions can be found, and these permit the calculation of m. The mobile phases for which the m values are lower afford the highest selectivity of resolution of compounds such as 7 and 8.

The resolution of regioisomers having free hydroxyl and carbonyl groups can be described by the localization parameter of pure strong solvents, m^0. To achieve maximum resolution of regioisomers, the use of mobile phases containing polar solvents with lower m^0 values is required.

It has also been shown that the resolution of the given compounds depends strongly on the hydrogen bonding between solutes and solvents whose prediction of α values is complicated using mathematical relationships. Therefore, the use of the localization parameters m and m^0 is suitable only for a preliminary and approximate choice of the mobile phase. To achieve maximum resolution and to elucidate the role of solute-solvent interactions, further study is required.

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