STUDIES IN THE RELATIONSHIP BETWEEN MOLECULAR STRUCTURE AND CHROMATOGRAPHIC BEHAVIOUR

V. THE BEHAVIOUR OF SOME ALKYL ETC. PHENOLS CHROMATOGRAPHED ON ALUMINA-IMPREGNATED PAPERS AND ON THIN LAYERS OF ALUMINA

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INTRODUCTION

In the thin-layer chromatographic separation of alkylphenols the following substrates have been used: silica gel[1–4], polyamide[5,6], unbound alumina[7,8] and ion-exchange resins[9].

For isomeric cresols[1], it was found that the R_F values of the *m*- and *p*-compounds showed little difference from those of the parent phenol, but that the R_F value of *o*-cresol was higher.

PETROWITZ[2] showed that the R_F values of the isomeric xylenols were similarly dependent upon the presence, and the number of *o*-methyl groups. These findings for the behaviour of these compounds on silica gel have been confirmed by other workers[3,4].

Attempts to substantiate the MARTIN additivity[10] principle for an homologous series, have been made by HALMEKOSKI AND HANNIKAINEN[5]. These workers chromatographed phenol and the first three members of the alkylphenols (methyl, ethyl, *n*-propyl) both on silica gel and polyamide layers, using a series of solvent systems.

On polyamide layers, there is evidence that the MARTIN[10] additivity principle is valid for these phenols in each solvent system. The separations using silica gel are such that no convincing evidence is available to substantiate the validity of the principle.

The results obtained by WANG[6], using polyamide layers, confirm the effect of *ortho* substituents and using his results, it is possible to show for phenols substituted in the *meta* or *para* positions that the MARTIN relation is approximately correct.

Using loose layers of alumina, HERMANEK and co-workers[7] showed that the R_F values of phenol, and 3-methyl- and 4-methylphenol, were approximately the same, but the values obtained for 2-methylphenol were all significantly higher, showing an increased mobility of the phenol, over the polar substrate.

KHEIFITS *et al.*[8] also confirmed this *ortho* effect of substituents, when some other alkylphenols were chromatographed on alumina. They also found that alkyl

groups in the 3- or 4-position had little effect on the R_F values relative to those of phenol, even when the alkyl group was a bulky one, *e.g.* a *tert.*-butyl group.

In an earlier work dealing with the separation of nitrophenols on alumina-impregnated papers[12], we stated that the mechanism of the chromatographic process was a result of hydrogen bonding between:

(1) the oxygen atom of the phenolic group, and

(2) any other proton acceptor group within the molecule, and the hydrogen atoms of the hydroxyl groups on the alumina surface.

In this present work, we have chromatographed a large number of alkylphenols, a small number of arylphenols, and some alkoxyphenols on the same grades of alumina-impregnated papers previously used[12], and also on thin layers of unbound alumina. The results obtained, under carefully standardised conditions, are considered in terms of the chromatographic process outlined above. The validity of the MARTIN[10] relation, and reasons for deviations from it are also considered.

The choice of a suitable solvent system in all forms of chromatography cannot be isolated from a consideration of the nature of the molecule to be separated and the nature of the stationary phase to be used. Suitable guides to the suitability of any eluent systems are the so-called elutiotropic series, which arrange organic liquids in order of their increasing polarities either qualitatively[11,13,14] or semi-quantitatively[15]. SNYDER[15] reported that the calculated eluent strengths agreed with the experimental strengths for the same solvent mixtures. It is considered that these series are only of value when it is not possible for solute–eluent interactions[16] to occur. When studying the behaviour of nitrophenols on alumina-impregnated papers, with special reference to hydrogen bonding between the alumina and the solute, we[12] chose anhydrous cyclohexane as the solvent, in order to minimise interactions (*viz.* hydrogen bonding) between the phenols and the development solvent. In this work, where hydrogen bonding between the alkylphenols and the solvent is probably reduced because of the generally lower polarity of the alkylphenols, compared with the nitrophenols, other solvent systems were used. These were chosen to give a variation in the relative polarities of the solute–solvent system.

EXPERIMENTAL

Chromatography on impregnated paper

The four grades of alumina-impregnated papers were:

(a) cellulose paper (Whatman No. 1) impregnated with 2 % of alumina;

(b) cellulose paper (Whatman No. 1) impregnated with 7.5 % of alumina;

(c) glass fibre "paper" (Whatman) impregnated with 7.5 % of alumina;

(d) cellulose paper (Schleicher and Schüll No. 288) impregnated with 25 % of alumina.

The pretreatment of the papers, the application of the phenols and the development conditions were as previously described[12].

Thin-layer chromatography

Alumina (Hopkin and Williams M.F.C. (Camag) grade, neutral, Brockmann activity I–II, 100–200 mesh) was used as the substrate.

Preliminary experiments showed that this grade was too coarse to given satis-

factory layers when slurried with water. The alumina was therefore crushed and sieved, and the various sieve fractions tested, that passing a 200-mesh sieve but retained by a 230-mesh sieve gave a material suitable for the preparation of the thin layers.

Alumina (40 g) was slurried with water (40 ml) and applied to clean, grease-free glass plates using a Shandon thin-layer applicator*. The quantities given were sufficient to coat 5 glass plates (20 × 20 cm), layer thickness 0.25 mm.

When the surplus water had evaporated, the coated plates were stored in racks and air dried for 24 h at a constant temperature of 25° ± 0.5°.

In order to equate the results obtained from the thin layers with those obtained from the impregnated papers, the activation of the layers was the same as for the papers[12], namely, heating in an air oven for 15 min at 110°, followed by cooling in an evacuated desiccator over molecular sieve type 4 A (British Drug Houses).

The application of the phenols and development conditions

The phenols (1 μl of 0.25 % v/v solutions in suitable solvents) were applied to the activated plates with the multiple-spotting device previously described[17].

The prepared plates were placed in a double saturation chamber[17] and eluted by an ascending technique at a constant temperature of 25° ± 0.5°. The length of run was standardised as being $14^1/_2 \pm {}^1/_2$ cm. The time taken for the solvent front to travel this distance was 90 min.

Eluent systems

The following eluents were used:

(I) Cyclohexane (see below)
(II) Dioxane (see below)
(III) Cyclohexane–dioxane (75:25, v/v)
(IV) Cyclohexane–dioxane (1:1, v/v)
(V) Benzene–methanol (95:5, v/v)
(VI) Benzene–ethanol (95:5, v/v)
(VII) Benzene–ethyl acetate (3:7, v/v).

Purification of the solvents

Cyclohexane. This was purified as previously described[12].

Dioxane. DASLER AND BAUER[18] recommended the removal of explosive peroxides and water from dioxane by standing the solvent (Analar grade) over alumina. This was done here. The solvent was then distilled from sodium wire and the fraction boiling at 101° under 759 mm pressure was collected.

Benzene. Benzene (Hopkin and Williams, M.F.C. grade) was dried over sodium wire. The dried solvent was distilled, and the fraction boiling at 80° under 760 mm pressure was collected.

Methyl alcohol. Methyl alcohol (Hopkin and Williams, Analar grade) was dried over alumina. The solvent was redistilled and the fraction boiling at 65° under 760 mm pressure was collected.

Ethyl alcohol. Super dry alcohol was prepared as previously described[19].

* Available from Shandon Scientific Co., Pound Lane, London.

Ethyl acetate. This was purified by heating ethyl acetate (Hopkin and Williams, M.F.C. grade), acetic anhydride and a little concentrated sulphuric acid under reflux for 4 h. The mixture was distilled, and the distillate was neutralised by shaking it with anhydrous potassium carbonate. After removal of the excess solid the solvent was redistilled; the fraction boiling at 77° under 760 mm pressure was used.

Preparation of the mixed eluents

Eluent mixtures were prepared by mixing together the appropriate volumes of the components.

All eluents were allowed to come to the temperature at which the chromatograms were to be eluted.

Detection of the phenols

After elution, the chromatograms were dried and then sprayed with an alkaline potassium permanganate solution (0.515 g anhydrous sodium carbonate and 0.5 g potassium permanganate in 100 ml of aqueous solution). The phenols appeared as yellow spots on a pale purple background. The spots were stable long enough to permit the marking of the spots.

RESULTS

The results are shown in Table I. Each result is the average of at least four runs on plates or papers carrying an internal standard. For the results obtained to be considered, the results for the standard on each plate/paper had to agree within $\pm$ 0.01 R_F units with the pre-determined mean for that standard when run under the same conditions as the subsequent chromatograms. No chromatograms had to be discarded. Further, the R_F values for each individual phenol did not vary more than $\pm$ 0.01 R_F unit from the mean values quoted.

DISCUSSION OF RESULTS

Solvent effect

SNYDER[15,20] when discussing the role of the solvent in linear elution column chromatography attempted to quantitise the strength of the solvents discussed, and quoted the values for cyclohexane as 0.04 units, dioxane as 0.63 units and benzene as 0.32 units. The strengths of the mixed eluents used were calculated, assuming the additivity of strengths, thus the relative strengths of the eluents used are:

Eluent	*Strength*
Cyclohexane	0.04
Cyclohexane–dioxane (75:25, v/v)	0.19
Cyclohexane–dioxane (50:50, v/v)	0.34
Dioxane	0.63
Benzene–methanol (95:5, v/v)	0.35
Benzene–ethylacetate (30:70, v/v)	0.19
Benzene–ethanol (95:5, v/v)	0.35 (approx.)

Key	Phenol	R_F values for solvent/support system No.													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Phenol	0.10	0.05	0.06	0.00	1.00	1.00	1.00	0.25	0.00	0.48	0.95	0.26	0.29	0.50
2	2-Methyl	0.24	0.12	0.13	0.00	1.00	1.00	1.00	0.49	0.00	0.65	1.00	0.40	0.38	0.67
3	3-Methyl	0.14	0.07	0.12	0.00	1.00	1.00	1.00	0.29	0.00	0.53	1.00	0.34	0.32	0.56
4	4-Methyl	0.12	0.06	0.10	0.00	1.00	1.00	1.00	0.27	0.00	0.52	1.00	0.33	0.32	0.55
5	2,3-Dimethyl	0.26	0.12	0.18	0.00	1.00	1.00	1.00	0.55	0.00	0.75	1.00	0.43	0.41	0.70
6	2,4-Dimethyl	0.25	0.11	0.19	0.00	1.00	1.00	1.00	0.53	0.00	0.74	1.00	0.41	0.40	0.69
7	2,5-Dimethyl	0.28	0.12	0.19	0.00	1.00	1.00	1.00	0.55	0.00	0.75	1.00	0.43	0.41	0.70
8	2,6-Dimethyl	0.56	0.36	0.43	0.00	1.00	1.00	1.00	0.76	0.00	0.87	1.00	0.52	0.54	0.80
9	3,4-Dimethyl	0.16	0.08	0.14	0.00	1.00	1.00	1.00	0.32	0.00	0.53	1.00	0.32	0.33	0.58
10	3,5-Dimethyl	0.19	0.18	0.14	0.00	1.00	1.00	1.00	0.35	0.00	0.53	1.00	0.32	0.32	0.60
11	2,3,4-Trimethyl	0.26	0.14	0.20	0.00	1.00	1.00	1.00	0.59	0.00	0.73	1.00	0.39	0.42	0.70
12	2,3,5-Trimethyl	0.27	0.16	0.21	0.00	1.00	1.00	1.00	0.62	0.00	0.76	1.00	0.39	0.44	0.72
13	2,3,6-Trimethyl	0.54	0.34	0.37	0.05	1.00	1.00	1.00	0.84	0.03	0.85	1.00	0.52	0.56	0.83
14	2,4,5-Trimethyl	0.26	0.16	0.19	0.00	1.00	1.00	1.00	0.61	0.00	0.75	1.00	0.39	0.44	0.72
15	2,4,6-Trimethyl	0.54	0.34	0.36	0.05	1.00	1.00	1.00	0.84	0.03	0.85	1.00	0.50	0.55	0.83
16	3,4,5-Trimethyl	0.12	0.08	0.05	0.00	1.00	1.00	1.00	0.32	0.00	0.53	1.00	0.30	0.33	0.62
17	2,3,4,5-Tetramethyl	0.30	0.16	0.20	0.00	1.00	1.00	1.00	0.62	0.00	0.73	1.00	0.39	0.44	0.70
18	2,3,4,6-Tetramethyl	0.55	0.34	0.38	0.04	1.00	1.00	1.00	0.85	0.03	0.89	1.00	0.52	0.54	0.86
19	2,3,5,6-Tetramethyl	0.55	0.36	0.39	0.04	1.00	1.00	1.00	0.86	0.03	0.90	1.00	0.54	0.55	0.86
20	2-Ethyl	0.28	0.15	0.16	0.00	1.00	1.00	1.00	0.67	0.00	0.73	1.00	0.45	0.46	0.75
21	3-Ethyl	0.14	0.07	0.08	0.00	1.00	1.00	1.00	0.37	0.00	0.53	1.00	0.36	0.36	0.59
22	4-Ethyl	0.12	0.06	0.07	0.00	1.00	1.00	1.00	0.35	0.00	0.54	1.00	0.35	0.36	0.58
23	2-*n*-Propyl	0.32	0.18	0.19	0.02	1.00	1.00	1.00	0.76	0.00	0.81	1.00	0.49	0.49	0.84
24	4-*n*-Propyl	0.18	0.07	0.07	0.00	1.00	1.00	1.00	0.37	0.00	0.53	1.00	0.35	0.35	0.62
25	2-Isopropyl	0.18	0.07	0.08	0.00	1.00	1.00	1.00	0.40	0.00	0.55	1.00	0.41	0.38	0.62
26	4-Isopropyl	0.19	0.07	0.07	0.00	1.00	1.00	1.00	0.37	0.00	0.53	1.00	0.35	0.35	0.62
27	4-*n*-Butyl	0.19	0.07	0.07	0.00	1.00	1.00	1.00	0.37	0.00	0.53	1.00	0.35	0.35	0.63
28	2-*sec.*-Butyl	0.41	0.26	0.26	0.02	1.00	1.00	1.00	0.79	0.00	0.91	1.00	0.56	0.51	0.85
29	4-*sec.*-Butyl	0.25	0.08	0.19	0.00	1.00	1.00	1.00	0.40	0.00	0.63	1.00	0.38	0.40	0.65
30	2-*tert.*-Butyl	0.59	0.29	0.27	0.02	1.00	1.00	1.00	0.84	0.02	1.00	1.00	0.61	0.59	0.92
31	3-*tert.*-Butyl	0.27	0.10	0.10	0.00	1.00	1.00	1.00	0.51	0.00	0.63	1.00	0.45	0.40	0.65
32	4-*tert.*-Butyl	0.28	0.10	0.13	0.00	1.00	1.00	1.00	0.51	0.00	0.64	1.00	0.45	0.43	0.65
33	4-*n*-Amyl	0.24	0.10	0.11	0.00	1.00	1.00	1.00	0.46	0.00	0.58	1.00	0.35	0.35	0.65
34	4-*sec.*-Amyl	0.31	0.10	0.10	0.00	1.00	1.00	1.00	0.53	0.00	0.68	1.00	0.38	0.39	0.67
35	4-*tert.*-Amyl	0.28	0.11	0.09	0.00	1.00	1.00	1.00	0.49	0.00	0.67	1.00	0.44	0.43	0.67
36	4-(3-Methylbutyl)	0.13	0.07	0.06	0.00	1.00	1.00	1.00	0.40	0.00	0.56	1.00	0.35	0.35	0.64
37	4-*tert.*-Octyl	0.14	0.08	0.08	0.00	1.00	1.00	1.00	0.53	0.00	0.76	1.00	0.44	0.45	0.78
38	2-*n*-Octyl	0.60	0.40	0.39	0.03	1.00	1.00	1.00	0.90	0.03	0.98	1.00	0.63	0.62	0.92
39	4-*n*-Nonyl	0.14	0.06	0.09	0.00	1.00	1.00	1.00	0.53	0.00	0.68	1.00	0.42	0.42	0.74
40	2-Allyl	0.24	0.09	0.10	0.00	1.00	1.00	1.00	0.63	0.00	0.68	1.00	0.47	0.48	0.70
41	4-Allyl	0.10	0.04	0.06	0.00	1.00	1.00	1.00	0.34	0.00	0.46	1.00	0.35	0.35	0.53
42	4-Crotyl	0.11	0.06	0.06	0.00	1.00	1.00	1.00	0.35	0.00	0.50	1.00	0.36	0.36	0.56

44	4-Phenyl	0.07	0.03	0.03	0.00	1.00	1.00	1.00	0.13	0.00	0.33			
45	4-Benzyl	0.08	0.03	0.03	0.00	1.00	1.00	1.00	0.16	0.00	0.44	1.00	0.40	0.42	0.69
46	4-Cumyl	0.08	0.03	0.03	0.00	1.00	1.00	1.00	0.34	0.00	0.50	1.00	0.42	0.44	0.71
47	4-Cyclopentyl	0.14	0.07	0.06	0.00	1.00	1.00	1.00	0.39	0.00	0.55	1.00	0.36	0.37	0.66
48	4-Cyclopent-2-enyl	0.12	0.06	0.05	0.00	1.00	1.00	1.00	0.32	0.00	0.53	1.00	0.37	0.37	0.64
49	2-Cyclohexyl	0.33	0.11	0.11	0.03	1.00	1.00	1.00	0.84	0.00	0.81	1.00	0.54	0.54	0.81
50	4-Cyclohexyl	0.17	0.08	0.08	0.00	1.00	1.00	1.00	0.38	0.00	0.60	1.00	0.38	0.39	0.69
51	2-Methyl-4-*tert.*-butyl	0.28	0.17	0.16	0.02	1.00	1.00	1.00	0.55	0.00	0.76	1.00	0.42	0.44	0.81
52	3-Methyl-5-ethyl	0.16	0.06	0.07	0.01	1.00	1.00	1.00	0.42	0.00	0.58	1.00	0.35	0.35	0.62
53	3-Methyl-4-isopropyl	0.16	0.06	0.09	0.00	1.00	1.00	1.00	0.46	0.00	0.61	1.00	0.35	0.35	0.68
54	3-Methyl-5-isopropyl	0.19	0.06	0.09	0.02	1.00	1.00	1.00	0.47	0.00	0.60	1.00	0.35	0.35	0.66
55	3-Methyl-5-*sec.*-butyl	0.24	0.07	0.13	0.01	1.00	1.00	1.00	0.54	0.00	0.66	1.00	0.40	0.42	0.69
56	3,5-Di-*tert.*-butyl	0.33	0.12	0.20	0.00	1.00	1.00	1.00	0.86	0.00	0.70	1.00	0.48	0.49	0.86
57	2-Methyl-4-octyl	0.30	0.11	0.11	0.02	1.00	1.00	1.00	0.58	0.00	0.80	1.00	0.46	0.46	0.84
58	2-*tert.*-Butyl-3-methyl	0.59	0.28	0.28	0.05	1.00	1.00	1.00	0.93	0.03	1.00	1.00	0.63	0.64	1.00
59	2-*tert.*-Butyl-4-methyl	0.59	0.28	0.26	0.04	1.00	1.00	1.00	0.96	0.03	1.00	1.00	0.63	0.64	1.00
60	2-Octyl-4-methyl	0.70	0.40	0.40	0.11	1.00	1.00	1.00	0.97	0.04	1.00	1.00	0.63	0.63	1.00
61	2,6-Dimethyl-4-*n*-propyl	0.60	0.45	0.51	0.09	1.00	1.00	1.00	0.91	0.04	0.97	1.00	0.60	0.56	0.89
62	2,6-Dimethyl-4-allyl	0.59	0.42	0.47	0.08	1.00	1.00	1.00	0.90	0.06	0.93	1.00	0.60	0.58	0.89
63	2,6-Di-*tert.*-butyl	0.97	0.93	0.91	0.83	1.00	1.00	1.00	1.00	0.57	1.00	1.00	1.00	0.97	1.00
64	2-Methyl-4,6-di-*tert.*-butyl	0.90	0.84	0.83	0.75	1.00	1.00	1.00	0.96	0.10	0.96	1.00	0.77	0.77	1.00
65	2,6-Di-*tert.*-butyl-4-methyl	0.98	0.91	0.89	0.81	1.00	1.00	1.00	1.00	0.54	1.00	1.00	1.00	0.97	1.00
66	2-Methoxyl	0.25	0.13	0.13	0.00	1.00	1.00	1.00	0.33	0.00	0.55	1.00	0.30	0.41	0.68
67	3-Methoxyl	0.03	0.00	0.04	0.00	1.00	1.00	1.00	0.23	0.00	0.38	0.76	0.20	0.39	0.65
68	4-Methoxyl	0.04	0.00	0.04	0.00	1.00	1.00	1.00	0.24	0.00	0.40	0.78	0.20	0.38	0.66
69	3,5-Dimethoxyl	0.00	0.00	0.00	0.00	1.00	0.92	0.93	0.07	0.00	0.25	0.70	0.15	0.28	0.39
70	4-Ethoxyl	0.05	0.00	0.00	0.00	1.00	1.00	1.00	0.26	0.00	0.50	0.82	0.22	0.37	0.65
71	4-Cyclopentyloxyl	0.11	0.00	0.00	0.00	1.00	1.00	1.00	0.26	0.00	0.60	0.90	0.22	0.37	0.67
72	4-Heptoxyl	0.07	0.00	0.00	0.00	1.00	1.00	1.00	0.31	0.00	0.72	0.90	0.25	0.44	0.70
73	4-Dodecyloxyl	0.07	0.00	0.00	0.00	1.00	1.00	1.00	0.35	0.00	0.80	0.90	0.26	0.43	0.70
74	4-Tetradecyloxyl	0.06	0.00	0.00	0.00	1.00	1.00	1.00	0.39	0.00	0.80	0.90	0.32	0.43	0.70
75	4-Hexadecyloxyl	0.07	0.00	0.00	0.00	1.00	1.00	1.00	0.40	0.00	0.82	0.90	0.32	0.43	0.71
76	4-Phenoxyl	0.05	0.00	0.00	0.00	1.00	1.00	1.00	0.14	0.00	0.45	0.65	0.21	0.39	0.58
77	2,5-Dicarbamethoxyl	0.00	0.00	0.00	0.00	1.00	1.00	1.00	0.02	0.00	0.08	0.31	0.12	0.11	0.22

* Key to solvent/support system Nos.:

1 = Cyclohexane/cellulose paper and 2% of alumina
2 = Cyclohexane/cellulose paper and 7.5% of alumina
3 = Cyclohexane/glass fibre paper and 7.5% of alumina
4 = Cyclohexane/cellulose paper and 25% of alumina
5 = Cyclohexane–dioxane (75:25, v/v)/cellulose paper and 2% of alumina
6 = Cyclohexane–dioxane (75:25, v/v)/cellulose paper and 7.5% of alumina
8 = Cyclohexane–dioxane (75:25, v/v)/cellulose paper and 25% of alumina
9 = Cyclohexane/alumina thin layers
10 = Cyclohexane–dioxane (1:1, v/v)/alumina thin layers
11 = Dioxane/alumina thin layers
12 = Benzene–methanol (95:5, v/v)/alumina thin layers
13 = Benzene–ethanol (95:5, v/v)/alumina thin layers
14 = Benzene–ethyl acetate (3:7, v/v)/alumina thin layers.

The strength of the benzene–ethanol system could not be calculated accurately because SNYDER has not determined a value for ethanol. However, for the purposes of the discussion, it was assumed that the value for ethanol will lie between that for isopropanol (0.82) and methanol (0.95) and is probably nearer to the latter value. Hence the strength of the benzene–ethanol system will be close to that of benzene–methanol.

From a comparison of the eluent strengths it would be expected that the R_F values obtained from thin-layer chromatograms would be in the order:

Cyclohexane < cyclohexane–dioxane (50 : 50, v/v) < benzene–ethyl acetate (30 : 70, v/v) < benzene–ethanol (95 : 5, v/v) < benzene–methanol (95 : 5, v/v) < dioxane.

The results show that this is not so and would in our opinion indicate some solute/eluent interaction in the systems containing esters or alcohols.

To simplify the overall picture, the phenols are subdivided by an arbitrary classification, and eluent systems in which no separation is achieved are omitted. In these systems the phenols either stayed at the point of application or moved with the solvent front.

(*a*) *Methylated phenols*

Here, the effect of the addition of successive methyl groups to the phenyl nucleus has to be considered. Electronically, it would be expected that because of the inductive effect of the methyl group, electrons would be displaced into the ring and hence towards the phenolic oxygen atom. This, in turn, would increase the strength of the hydrogen bond between this atom and the hydroxylated alumina surface. In addition, the effect of the eluent on this hydrogen bonding, and also steric effects have to be considered.

The results in Table II show that the effects of the addition of one or more methyl groups to the phenyl nucleus are dependent on the position of the substituent group or groups relative to the phenolic group. This means that these phenols can be classified into three groups.

Group 1: no ortho substituent. In all eluents, the addition of a single methyl group to either the 3- or 4-position causes a slight increase in R_F values relative to that of the unsubstituted phenol, the 4-compound having lower R_F values than the 3-compound. Further additions of methyl groups to these positions to give the 3,4-, 3,5-, and 3,4,5-compound result in little or no change in the R_F values, except in the system benzene–ethyl acetate, where a progressive increase in R_F values with increased methylation results. These results suggest that the fine electronic effects of the methyl group on the strong bond formed between the phenolic oxygen atom and the hydroxylated alumina are offset by the increase in the solubility of the non-polar part of the molecule in the organic mobile phases.

Group 2: one ortho substituent. The addition of a methyl group *ortho* to the parent phenolic group results in a substantial increase in the R_F value of the 2-methylphenol relative to that of the parent compound. Addition of further methyl groups to the 3-, and 4-positions of the molecule has little effect on the R_F values relative to that of the 2-methylphenol. Evidence of the effects of the position of substituents relative to each other is seen in so far as the R_F values of the 2,4-dimethylphenol are slightly lower than the 2,3-, and 2,5-dimethylphenols in all systems. The 2,3,4-trimethylphenol is generally lower than the 2,3,5-, or the 2,4,5-isomers.

TABLE II

R_F VALUES (× 100) OF METHYLATED PHENOLS

Phenol	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
Phenol	10	5	6	25	48	26	29	50
2-Methyl	24	12	13	49	65	40	38	67
3-Methyl	14	7	12	29	53	34	32	56
4-Methyl	12	6	10	27	52	33	32	55
2,3-Dimethyl	26	12	18	55	75	43	41	70
2,4-Dimethyl	25	11	19	53	74	41	40	69
2,5-Dimethyl	28	12	19	55	75	43	41	70
2,6-Dimethyl	56	36	43	76	87	52	54	80
3,4-Dimethyl	16	8	14	32	53	32	33	58
3,5-Dimethyl	19	18	14	35	53	32	32	60
2,3,4-Trimethyl	26	14	20	59	73	39	42	70
2,3,5-Trimethyl	27	16	21	62	76	39	44	72
2,3,6-Trimethyl	54	34	37	84	85	52	56	83
2,4,5-Trimethyl	26	16	19	61	75	39	44	72
2,4,6-Trimethyl	54	34	36	84	85	50	55	83
3,4,5-Trimethyl	12	8	5	32	53	30	33	62
2,3,4,5-Tetramethyl	30	16	20	62	73	39	44	70
2,3,4,6-Tetramethyl	55	34	38	85	89	52	54	86
2,3,5,6-Tetramethyl	55	36	39	86	90	54	55	86

Group 3: two ortho substituents. Table III shows the R_F values of 2,6-dimethyl-substituted phenols relative to those of 2-methylphenol and phenol. It can be seen that the presence of a second methyl group in an *ortho* position greatly increases the R_F-values. Once again, however, addition of methyl groups to the 3- or 4-position of the molecule has little effect on the R_F values, though results indicate that the 2,3,4,6-tetramethylphenol is slightly more strongly adsorbed than its 2,3,5,6-isomer.

From the results, it would appear that the major constitutive effect modifying the strength of the hydrogen bond between the phenolic group and the substrate is one of complete or partial steric hindrance, and that electronic interactions, if they occur, are small.

TABLE III

R_F VALUES (× 100) OF PHENOLS WITH TWO *ortho* SUBSTITUENTS

Phenols	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
Phenol	10	5	6	25	48	26	29	50
2-Methyl	24	12	13	49	65	40	38	67
2,6-Dimethyl	56	36	43	76	87	52	54	80
2,3,6-Trimethyl	54	34	37	84	85	52	56	83
2,4,6-Trimethyl	54	34	36	84	85	50	55	83
2,3,4,6-Tetramethyl	55	36	39	86	90	54	55	86
2,3,5,6-Tetramethyl	55	36	39	86	90	54	55	86

(*b*) *Other alkyl, etc., phenols*

Once again these may be classified into 3 groups according to the number of positions *ortho* to the phenolic group which are substituted.

Group 1: no ortho substituents. Talbe IV shows that the addition of hydrocarbon groups of increasing chain length to either the 3- or, more particularly, the 4-position has little or no effect on the strength of the hydrogen bond between the phenolic group and the substrate when a straight-chain hydrocarbon is considered. This is in accord with the findings of KHEIFITS *et al.*[8].

TABLE IV

R_F VALUES (× 100) OF ALKYLATED PHENOLS

Phenol	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
Phenol	10	5	6	25	48	26	29	50
3-Methyl	14	7	12	29	53	34	32	56
4-Methyl	12	6	10	27	52	33	32	55
3-Ethyl	12	6	8	37	53	36	36	59
4-Ethyl	12	6	7	35	54	35	36	58
4-*n*-Propyl	18	7	7	37	53	35	35	62
4-*n*-Butyl	19	7	7	37	53	35	35	63
4-*n*-Amyl	24	10	11	46	58	35	35	65
4-*n*-Nonyl	14	6	9	53	68	42	42	74

This is particularly so for the alcoholic eluents (KHEIFITS *et al.*[8] used benzene–methanol (9:1, v/v) in their investigation). There are, however, some non-regular deviations from this generalisation. These are probably caused by differences in the solubilities of individual phenols in a given eluent system. The R_F values in the benzene–ethyl acetate system show a slight but fairly regular increase with increasing chain length. This behaviour parallels that of the methylated phenols in this system.

TABLE V

EFFECT OF A DOUBLE BOND IN THE SIDE CHAIN ON R_F VALUES (× 100)

Phenol	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
Phenol	10	5	6	25	48	26	29	50
4-*n*-Propyl	18	7	7	37	53	35	35	62
4-Allyl	10	4	6	34	46	35	35	53
4-*n*-Butyl	19	7	7	37	53	35	35	63
4-Crotyl	11	6	6	35	50	36	36	56
4-Cyclopentyl	14	7	6	39	55	36	37	66
4-Cyclopent-2-enyl	12	6	5	32	53	37	37	64
4-Cyclohexyl	17	8	8	38	60	38	39	69

The effect of the presence of a double bond in the side chain is shown in Table V. With the exceptions of the two systems which contain an alcohol, the presence of a double bond slightly lowers the R_F values, probably as a result of the interaction between the π-electrons of the double bond and the hydroxyl groups of the substrate.

In the case of the alcoholic systems, it is probable that such interaction is nullified by a competitive mechanism involving the double bond and the hydroxyl group of the alcohol.

TABLE VI

R_F VALUES (× 100) OF ARYLPHENOLS

Phenol	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
Phenol	10	5	6	25	48	26	29	50
4-Phenyl	7	3	3	15	33	30	30	42
4-Benzyl	8	3	3	26	44	40	42	69
4-Cumyl	8	3	3	34	50	42	44	71

The effect of the addition of an aromatic substituent to the 4-position is shown in Table VI. In the eluent systems other than the alcoholic ones, the addition of a phenyl group reduces the R_F value relative to that of phenol. That this cannot be caused simply by the presence of 3 additional double bonds to the molecule can be seen from the results for *p*-benzyl- and *p*-cumylphenol. These contain the same number of double bonds as the phenyl derivative but have higher R_F values. In these last two, however, the conjugated double bond system is destroyed by the presence of the essentially aliphatic group separating the phenyl rings. It would therefore appear that the presence of a conjugated double bond system has a greater effect on R_F values than a non-conjugated double bond system. This is in accord with the views of LISBOA[21], for the separation of steroids. The results for the alcoholic benzene systems may be caused in part by the increased solubilities of these aromatic systems in the aromatic fraction of the eluent, and in part to the interaction of the π-electrons with the alcoholic hydroxyl groups.

The effect of a bulky group in the 4-position is shown in Table VII. From the results it can be seen that such a group can have some effect on the R_F values. It is suggested that these groups prevent the adsorbed molecule from lying in the plane of the substrate, forcing the non-polar part of the molecule into the mobile phase, thus slightly increasing the solubility in the non-polar phase and hence the R_F values. The value for *tert.*-octylphenol in system 1 is considered to be anomalous.

The results for the poly-alkylated phenols (Table VIII) are, qualitatively, the expected ones. The additional alkyl group having little effect on the R_F values, except where bulky groups are involved.

Group 2: one ortho substituent. From the results in Table IX, it can be seen that the addition of a straight-chain hydrocarbon to the 2-position results in a fairly regular increase in R_F values. It has already been shown that the addition of a straight-chain hydrocarbon to the phenyl nucleus has little polar effect, hence it must be concluded that the increases in R_F values are a result of a steric effect, the *o*-alkyl

TABLE VII

EFFECT OF THE SIZE OF THE SUBSTITUENT ON R_F VALUES (× 100)

Phenol	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
4-*n*-Propyl	18	5	7	36	53	35	35	62
4-Isopropyl	19	7	7	37	53	35	35	62
4-*n*-Butyl	19	7	7	37	53	35	35	63
4-*sec.*-Butyl	25	8	19	40	63	38	40	65
3-*tert.*-Butyl	27	10	10	51	63	45	40	65
4-*tert.*-Butyl	28	10	13	51	64	45	43	65
4-*n*-Amyl	24	10	11	46	58	35	35	65
4-*sec.*-Amyl	31	10	10	53	68	38	39	67
4-*tert.*-Amyl	28	11	9	49	67	44	43	67
4-(3-Methyl butyl)	13	7	6	40	56	35	35	64
4-*tert.*-Octyl	14	8	8	53	76	44	45	78

TABLE VIII

R_F VALUES (× 100) OF POLY-ALKYLATED PHENOLS

Phenol	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
4-*n*-Propyl	18	7	7	36	53	35	35	62
3-Methyl-5-ethyl	16	6	7	42	58	35	35	62
3-Methyl-4-isopropyl	16	6	9	46	61	36	35	68
3-Methyl-5-isopropyl	19	6	9	47	60	35	35	66
3-Methyl-5-*sec.*-butyl	24	7	13	54	66	40	42	69
3,5-Di-*tert.*-butyl	33	12	20	86	70	48	49	86

TABLE IX

EFFECT OF AN *ortho* GROUP ON THE R_F VALUES (× 100) OF ALKYLATED PHENOLS

Phenol	*Solvent/support system No.*							
	1	*2*	*3*	*8*	*10*	*12*	*13*	*14*
Phenol	10	5	6	25	48	26	29	50
2-Methyl	24	12	13	49	65	40	38	67
2-Ethyl	28	15	16	67	73	45	46	75
2-*n*-Propyl	32	18	19	76	81	49	49	84
2-*iso*-Propyl	18	7	8	40	55	41	38	62
2-*sec.*-Butyl	41	26	26	79	91	56	51	85
2-*tert.*-Butyl	59	29	27	84	100	61	59	92
2-*n*-Octyl	60	40	39	90	98	63	62	92
2-Allyl	24	9	10	63	68	47	48	70
2-Phenyl	32	14	16	66	75	51	53	76
2-Cyclohexyl	33	11	11	84	81	54	54	81
2-Methyl-4-*tert.*-butyl	28	17	16	55	76	42	44	81
2-Methyl-4-octyl	30	11	11	58	80	46	46	89
2-*tert.*-Butyl-3-methyl	59	28	28	93	100	63	64	100
2-*tert.*-Butyl-4-methyl	59	28	26	96	100	63	64	100
2-Octyl-4-methyl	70	40	40	79	100	63	63	100

substituent reducing the availability of the phenolic group for hydrogen bonding with the alumina surface. This view is further substantiated by a consideration of the results for 2-*sec.*-butyl- and 4-*tert.*-butylphenols, where branching of the hydrocarbon chain results in an increase in the size of the *ortho* substituent, giving an increased contribution to the steric effect, and hence higher R_F values. The values for 2-isopropylphenol are anomalous. The results for 2-*tert.*-butyl-3-methyl-, 2-*tert.*-butyl-4-methyl- and 2-octyl-4-methylphenol are the expected ones, the addition of the methyl group to the 3-, or 4-positions having no effect on the R_F values. The addition of the 4-*tert.*-butyl group to 2-methylphenol has the expected effect of slightly increasing the R_F value relative to 2-methylphenol. Spectroscopic evidence has shown that hydrogen bonding between the phenolic hydrogen atom and the π-electrons of the double bond in the 2-allyl group is possible[22]. It would therefore be expected that the R_F value of 2-allylphenol should be higher than that of 2-*n*-propylphenol. This is not so, probably because of the formation of a competing, and stronger, hydrogen bond between the double bond electrons and the hydroxyl groups of the substrate. In contrast to the behaviour of the 4-phenyl substituent, which has a lower R_F value than phenol, the same substituent in the 2-position greatly increases the R_F value relative to phenol. This again suggests that for substituents in the 2-position, steric effects are of greater significance than polar ones. That the R_F value of 2-phenyl- is lower than that of 2-cyclohexylphenol, an alicyclic derivative containing the same number of carbon atoms, may be taken as evidence that polar effects are not entirely absent. It is therefore suggested that where the gross effect of hydrogen bonding between the phenolic group and the substrate is weakened, the MARTIN[10] relation is valid, modified, however, by constitutive effects of chain branching, double bonds, and ring systems. The relation cannot be extended to include substituents in the 3-, or 4-positions of *ortho*-substituted phenols.

TABLE X

EFFECT OF DI-*ortho* SUBSTITUTION ON R_F VALUES (× 100) OF ALKYLATED PHENOLS

Phenol	*Solvent/support system No.*								
	1	*2*	*3*	*8*	*9*	*10*	*12*	*13*	*14*
Phenol	10	5	6	25	0	48	26	29	50
2,6-Dimethyl	56	36	43	76	0	87	52	54	80
2,6-Dimethyl-4-*n*-propyl	60	45	51	91	4	97	60	56	89
2,6-Dimethyl-4-allyl	59	42	47	90	6	93	60	58	89
2,6-Di-*tert.*-butyl	97	93	91	100	57	100	100	97	100
2-Methyl-4,6-di-*tert.*-butyl	90	84	83	96	10	96	77	77	100
2,6-Di-*tert.*-butyl-4-methyl	98	91	89	100	54	100	100	97	100

Group 3: *two ortho substituents.* The results for these are as expected (Table X). Di-*ortho* substitution with 2 bulky *tert.*-butyl groups greatly increase the R_F value of this compound relative to that of 2,6-dimethylphenol. The additivity of steric effects, proposed for mono-*ortho*-substituted phenols, is supported by the results for 2-methyl-4,6-di-*tert.*-butyl- and 2,6-di-*tert.*-butylphenols. Increase in the R_F values of the 2,6-dimethyl-, 4-substituted phenols (4-*n*-propyl- and 4-allyl) are probably caused by solubility effects.

(c) *Alkoxyphenols*

The R_F values for these compounds are given in Table XI.

The presence of the methoxyl group *ortho* to the phenolic group increases the R_F value relative to phenol and relative to the 3- and 4-methoxyl isomers. This is probably a steric effect rather than a polar one. The lower R_F values of the 3- and 4-methoxyl and also the 4-phenoxyphenol compared with that of phenol are probably the result of hydrogen bonding between the ether oxygen atom and the hydroxyl

TABLE XI

R_F VALUES (× 100) OF ALKOXYPHENOLS

Phenol	*Solvent/support system No.*						
	1	*8*	*10*	*11*	*12*	*13*	*14*
Phenol	10	25	48	95	26	29	50
2-Methoxyl	25	33	55	100	30	41	68
3-Methoxyl	3	23	38	76	20	39	65
4-Methoxyl	4	24	40	78	20	38	66
3,5-Dimethoxyl	0	7	25	70	15	28	39
4-Ethoxyl	5	26	50	82	22	37	65
4-Cyclopentoxyl	11	26	60	90	22	37	67
4-Heptoxyl	7	31	72	90	25	44	70
4-Dodecyloxyl	7	35	80	90	26	43	70
4-Tetradecyloxyl	6	39	80	90	32	43	70
4-Hexadecyloxyl	7	40	82	90	32	43	71
4-Phenoxyl	5	14	45	65	21	39	58
3,5-Carbamethoxyl	0	2	8	31	12	11	22

groups of the substrate. That the phenoxyl derivative has a lower R_F value than the 3- or 4-methoxyl derivatives is probably caused by the greater inductive effect of the phenyl nucleus, compared with the methyl radical building up the electron density at the ether oxygen atom to form a stronger intramolecular hydrogen bond with the surface. This is in accord with the view expressed by GRAHAM AND STONE[23]. The presence of additional oxygen centres for the formation of more such intramolecular hydrogen bonds probably accounts for the R_F values of 3,5-dimethoxyl and 3,5-dicarbamethoxyphenols. These results are also in agreement with the above suggestions and with the mechanism postulated earlier[12]. With increasing chain length of the alkyl group, attached to the ether oxygen atom, the R_F values show corresponding increases.

CONCLUSION

In the systems studied, the gross effect of the intramolecular hydrogen bonding between the phenolic group and the hydroxylated alumina is so strong that in the simple alkylphenols, with no *ortho* substituents, the substituent effect on the chromatographic behaviour is negligible, and hence the MARTIN relation is not valid for these nuclear substituted compounds. Where these substituents are present in one or both *ortho* positions, the R_F values increases with an increase in chain length and the number of methylene groups added. This is attributed to steric effects rather than to

electronic effects. It is suggested that there is steric hindrance of the approach of the phenolic group to the surface. The long-chain substituents cause some hindrance, but the same number of methylene groups as a bulky unit causes a greater effect. The bulkier is the substituent group, then the greater is this effect.

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SUMMARY

Seventy-seven alkyl-, aryl- and alkoxyphenols were chromatographed using 14 different stationary phase/mobile phase systems, each containing alumina in the stationary phase. From a consideration of the R_F values, mechanisms for the separations obtained are suggested. The effect of substituents *ortho* to the phenolic group is pronounced and is discussed in detail. It is suggested that variations in the behaviour of such compounds is mainly attributable to steric hindrance of the approach of the phenolic group to the surface, and hence to the variations in the strength and amount of hydrogen bonding possible between the phenol and the alumina.

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