PAPER CHROMATOGRAPHY AND CHEMICAL STRUCTURE

II. THE CHROMATOGRAPHY OF PHENOLS, ALKOXYPHENOLS, COUMARANOLS AND CHROMANOLS. THE USE OF GROUP AND ATOMIC ΔR_M VALUES. STERIC AND ELECTRONIC EFFECTS IN CHROMATOGRAPHY

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INTRODUCTION

The relation between chemical structure and chromatographic behaviour has, in recent years, received the attention of several workers. Attempts to correlate structure with chromatography has so far been restricted to the study of relatively simple chemical or homologous series and they have met with varying degrees of success. In the preceding paper[1], we have discussed some of this work, and advanced reasons for believing that many of the difficulties experienced in demonstrating the validity of MARTIN's equation are largely caused by the practical difficulty of determining R_M values accurately enough over a wide enough range of compounds. It was shown that, by using reversed phase chromatography and "tankless" conditions, the experimental obstacles could probably be frequently overcome.

The conclusions of previous workers fall into two groups: some authors in general confirm MARTIN's postulates or, at any rate, use a theoretical approach based on them, whilst others differ in some respect and have criticisms of the validity of MARTIN's predictions. The first category includes OPIEŃSKA-BLAUTH, SAKŁAWSKA-SZYMONOWA AND KAŃSKI[2], who studied organic acids and concluded (incorrectly) that R_F values were additive; REICHL[3,4] and SCHAUER AND BULIRSH[5] who calculated average ΔR_M values for several substituent groups occurring in organic acids and amino acids and found them to be constant; and LEDERER[6] who has summarized a considerable body of work demonstrating the constancy of ΔR_M (CH_2) in several series of compounds. On the other hand, FRANC AND JOKL[7,8] have taken the opposite view: they consider MARTIN's equation to be invalid and have proposed a logarithmic relationship between ΔR_M and the homologous increment in homologous series. We have already criticized this point of view[1]. More recently HOWE[9], who studied 111 organic acids, including nine homologous series, was unable to find that ΔR_M was constant even for the well-studied CH_2 group. HOWE's conclusions, in view of his careful study, must be considered to illuminate the serious technical difficulties involved in the accurate determination of ΔR_M values by tank chromatography.

We were led to a study of the relation between structure and chromatographic behaviour through a series of investigations[10–16] on tocopherols, ubiquinones and ubichromenols. Some years ago GREEN AND MARCINKIEWICZ[17] posed the problem of

relating the chromatographic behaviour of a complex molecule like α-tocopherol, through a series of chromatograms, with that of a simple molecule such as phenol. In this study we have investigated the chromatography of several series of compounds necessary for the solution of this problem; these included phenols, hydroquinone mono-ethers (*p*-alkoxyphenols), fused-ring phenols, and fused-ring heterocycles such as 5-coumaranols and 6-chromanols.

CHROMATOGRAPHIC METHODS

Whatman No. 1 paper was used throughout. Sheets were impregnated with ethyl oleate by immersing them in a solution in diethyl ether and drying them by the "pile" technique as described in the preceding paper. The mobile phase was 25 % aqueous ethanol. This system is referred to in this and in succeeding papers as System 1. Ethyl oleate is sufficiently polar to be suitable for the chromatography of low molecular weight phenols and ethers containing a single hydroxy function. It can be used with strengths of ethanol up to about 40 % v/v, after which it becomes too soluble in the mobile phase.

Each substance was spotted as a line about 3 cm long, a technique that produces fairly narrow spots. Chromatography was, in the main, carried out under tankless conditions, but many additional and confirmatory chromatograms were run by conventional descending methods, particularly when fine *differences* in running (as opposed to accurate R_M determination) were being examined between a limited number of related compounds. The R_M value of each substance was determined from at least three separate chromatograms, often more. A run under tankless conditions might include 20–200 spots, always with internal controls. Key control substances of known R_F value were distributed on several papers at random throughout the pile, each paper normally containing a substance whose R_F had been determined in a previous run. "Edge" effects were carefully looked for, as, if for some reason a paper has been irregularly impregnated, distorted R_F values may be found near the edges of the paper. To obviate such discrepancies, no substance was run nearer than 2 cm to each lateral edge of the paper. By these means, great constancy was obtained, and any anomalous behaviour could be readily ascertained and discounted. R_F values determined on the same compound in different runs agreed to within 0.01.

Substances were visualised in two ways. Papers were pre-impregnated with zinc carbonate containing 10 p.p.m. of sodium fluorescein, according to our previously described techniques[10–17], and the substances were then observed under ultra-violet light (Hanovia "Chromatolite") as dark spots. For record purposes, papers were also sprayed with ferric chloride–dipyridyl solution or diazotised *o*-dianisidine solution, as previously described. Chromatography is virtually identical on papers with and without zinc carbonate, adsorption playing no part in this reversed phase system.

PREPARATION OF COMPOUNDS

Seventy-seven compounds were used in this study. They were chosen with specific structural features in view. Furthermore, their general chemical nature was such as to bear close relationships to the series of higher molecular weight compounds discussed in the succeeding paper of this series. A number of new compounds had to be prepared. Their preparation and properties are described below. Other compounds

listed in Table I were either obtained commercially or synthesised according to a previous literature description, which we have annotated below.

Phenols (compounds 1-24)

(i) Compounds 1–7, 9, 10, 11, 17, 19, 20 21, 22 and 24 were obtained commercially. The Aldrich Chemical Co. lists many relatively inaccessible phenols.

(ii) The following substances were prepared by methods described in the literature: *p*-*n*-propylphenol[18], b.p. 230–232°; *p*-cyclopentylphenol[19]; *p*-cyclohexylphenol[20], m.p. 130°; 3-methyl-4-*n*-propylphenol[21]; 3-methyl-4-isopropylphenol[22], m.p. 110–111°; *p*-isopropylphenol[23], m.p. 61°; *p-tert.*-amylphenol[24], m.p. 91–92°; *p*-*n*-propenylphenol[25], m.p. 93-94°.

Fused-ring phenols (compounds 25–33)

(i) Compounds 25, 26, 28 and 29 were obtained commercially.

(ii) 1-Tetralol was prepared by reduction of 1-naphthol, m.p. 74°; ref. [26] 71°. 2-Phenanthrol was prepared according to FIESER[27], and 9-phenanthrol was obtained in good yield according to the improved method of SOLOMON AND HENNESSY[28]. 1-Anthrol and 2-anthrol were prepared according to BATTEGAY AND BRANDT[29].

Ortho-substituted phenols (compounds 34–44)

(i) Compounds 34, 35, 36, 37, 38, 43, and 44 were obtained commercially.

(ii) *o*-Propylphenol[30] was prepared by hydrogenation of *o*-allylphenol. *o*-Propenylphenol[31] had m.p. 34°. *o*-Allylphenol[32] had b.p. 219–221°. *o*-α-Methylallylphenol[33] was prepared by thermal rearrangement of phenyl crotyl ether; it had b.p. 229–235°.

Mono-ethers of hydroquinones (compounds 45–69)

(i) *General method of preparation.* Compounds 45–57 and 59–61 were prepared by Williamson synthesis. Equimolecular quantities of the alkyl bromide, the quinol and sodium ethoxide were heated under reflux in ethanol for 1–3 h. Unchanged quinol and any di-ether formed during the reaction were separated from the required mono-ether by chromatography on alumina (Peter Spence, Type O). The di-ether could always be easily eluted with benzene, and then the pure mono-ether was eluted with 5 % v/v ethanol–benzene leaving unchanged quinol on the column. Final purification was by distillation or crystallization. Any departures from the general method are described below, under the appropriate compound.

(ii) *p*-Phenoxyphenol (No. 58) cannot be prepared by Williamson synthesis and was prepared by the method of KLARMAN, GATYAS AND SHTERNOV[34]. Compounds 45, 46, 47, 48, 49, 50, 51, 53, 58, 60, 61, 62, 63, 64 and 65 have all been described previously.

(iii) The following ethers are new compounds. They all analysed correctly (results not shown) and had infra-red spectra in accordance with their structures.

p-sec.-Butoxyphenol, b.p. 158°/20 mm; n_D^{27} 1.5149; *p-tert.-butoxyphenol*, m.p. 152–154°; *p-isoamyloxyphenol*, m.p. 97–98°; *p-pent-4-enyloxyphenol*, m.p. 51–52°; *p-cyclohexyloxyphenol*, m.p. 62–63°; and *p-cyclopentyloxyphenol*, m.p. 52° were all prepared by the general method. In the case of the *tert.*-butyl ether, the reaction was carried out for 48 h at room temperature because of the tendency of the product to cleave at elevated temperatures.

2-Crotyl-4-methoxyphenol was prepared by heating the sodium salt of *p*-methoxy-

phenol and crotyl bromide in benzene for several hours. The product was distilled in a short-path still [80° (bath)/0.2 mm] as a pale yellow oil, n_D^{21} 1.5421.

4-Methoxy-2-(α-methylallyl)-phenol was prepared by heating *p*-methoxyphenol (6.2 g), crotyl bromide (8.9 g), potassium carbonate (6.9 g) and acetone (40 ml) under reflux for 3 h. The product, *p*-methoxyphenyl crotyl ether, was obtained as a colourless oil [40° (bath)/$5 \cdot 10^{-3}$ mm], m.p. 17–18°. When this ether was heated at 220° under nitrogen for 1 h, it gave, by thermal rearrangement, the required mono-ether as a colourless oil, b.p. 80°/0.2 mm.

4-Methoxy-2-propenylphenol. 2 Allyl-4-methoxyphenol (1.7 g) was heated in methanol (12 ml) with KOH (3.0 g) until the distillate temperature reached 110°. After 5 h reflux, the product was worked up and distilled in a short-path still as a colourless oil [110–120° (bath)/0.5 mm], n_D^{23} 1.5788, λ_{max} 294 mμ, $E_{1cm}^{1\%}$ 211 (in ethanol).

4-Methoxy-2-propylphenol. 2-Allyl-4-methoxyphenol was hydrogenated over palladised charcoal. The product was a colourless oil, b.p. 142°/15 mm, n_D^{20} 1.5313.

Coumaranols and chromanols (compounds 70–77)

All these, except compound 70, have been previously described[35,36].

2,2-Dimethyl-6-chromanol. p-Methoxyphenol (8.2 g), zinc chloride (1.0 g) and acetic acid (100 ml) were heated on a steam bath while isoprene (10 g) was slowly added. After 2 h, one drop of sulphuric acid was added and heating continued for 1 h. The cooled mixture was poured into water and the oil extracted with ether. Distillation gave crude 2,2-dimethyl-6-methoxychroman as a pale yellow oil (2.4 g), b.p. 140–160°/16 mm, n_D^{19} 1.5248. The oil was refluxed with hydrogen bromide in acetic acid (40 ml, 20%) for 5 h, then evaporated. The residual oil was dissolved in ether and extracted with aqueous *N* sodium hydroxide. Acidification gave an oil, which was distilled, b.p. 85–90°/0.1 mm (1.0 g). The oil solidified and the chromanol crystallised from light petroleum as needles, m.p. 73–74°, and analysed correctly.

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The chromatographic results are given in Table I. Each R_M value is the mean from at least three runs. In each case, it was calculated *directly* from the measured migration of spot and solvent front, without the intervening calculation of the R_F value, and the third figure is usually significant. The next column indicates the maximum experimental deviation in any run from the mean (in most cases it was negligibly small). R_F values are of no interest from the structural point of view, but are given in the next column because of their more practical applications. They were, however, calculated *from* the R_M values and are—as is usual—quoted to two significant figures only. The last column in Table I gives the calculated R_M values for most of the compounds. They were obtained by the methods described below.

GROUP ΔR_M PARAMETERS

The $\Delta R_M(CH_2)$ parameter

The mean value of $\Delta R_M(CH_2)$ for the homologous increment CH_2 was calculated from two series of compounds, (1) *p*-ethylphenol to *p-n*-amylphenol, and (2) *p*-ethoxyphenol to *p-n*-heptyloxyphenol. The values were respectively, + 0.462 and + 0.448, giving a mean value of + 0.455. The maximum deviation in either series was only

TABLE I

CHROMATOGRAPHY OF PHENOLS, HYDROQUINONE MONO-ETHERS, CHROMANOLS AND COUMARANOLS IN SYSTEM I

Stationary phase: ethyl oleate; mobile phase: 25 % aqueous ethanol.

No.	Compound	R_F	Mean R_M	Max. deviation of R_M from mean R_M	Calculated R_M
	Phenols without ortho-substituents				
1	Phenol	0.92	—1.063	0.007	
2	*m*-Cresol	0.85	—0.767	0.003	
3	*p*-Cresol	0.85	—0.767	0.003	
4	3,4-Xylenol	0.735	—0.444	0	—0.473
5	3,5-Xylenol	0.735	—0.444	0	—0.473
6	3,4,5-Trimethylphenol	0.585	—0.149	0.006	—0.178
7	*p*-Ethylphenol	0.70	—0.376	0.010	
8	*p*-*n*-Propylphenol	0.45	+0.087	0.001	
9	*p*-*n*-Butylphenol	0.22	+0.556	0	
10	*p*-*n*-Amylphenol	0.09	+1.010	0.010	
11	*p*-(3-Methylbutyl)-phenol	0.09	+1.000	0.016	+1.024
12	*p*-Cyclopentylphenol	0.16	+0.724	0	+0.776
13	*p*-Cyclohexylphenol	0.055	+1.230	0.009	+1.231
14	3-Methyl-4-*n*-propylphenol	0.285	+0.396	0.017	+0.381
15	4-Isopropyl-5-methylphenol	0.34	+0.289	0.006	+0.313
16	*p*-Isopropylphenol	0.49	+0.013	0.013	+0.018
17	*p*-*tert.*-Butylphenol	0.285	+0.395	0.008	+0.411
18	*p*-*tert.*-Amylphenol	0.12	+0.857	0.008	+0.872
19	*p*-Crotylphenol	0.32	+0.325	0.006	+0.425
20	*p*-(3-Methylbut-2-enyl)-phenol	0.16	+0.724	0.012	+0.894
21	*p*-Benzylphenol	0.23	+0.530	0.004	+0.846
22	*p*-Cyclopent-2-enylphenol	0.30	+0.369	0	+0.646
23	*p*-*n*-Propenylphenol	0.47	+0.054	0.005	+0.024
24	*p*-Phenylphenol	0.22	+0.556	0.008	
	Phenols containing a fused-ring structure				
25	2-Indanol	0.595	—0.168	0.001	—0.142
26	2-Tetralol	0.44	+0.111	0.009	+0.217
27	1-Tetralol	0.39	+0.197	0.009	+0.343
28	1-Naphthol	0.41	+0.160	0.013	+0.136
29	2-Naphthol	0.495	+0.010	0	
30	2-Phenanthrol	0.09	+1.000	0	+1.081
31	9-Phenanthrol	0.07	+1.130	0.020	+1.207
32	1-Anthrol	0.07	+1.130	0.020	+1.207
33	2-Anthrol	0.09	+1.000	0	+1.081
	Phenols with ortho-substituents				
34	*o*-Cresol	0.78	—0.547	0.002	—0.641
35	2,3-Xylenol	0.64	—0.250	0.002	—0.347
36	2,4-Xylenol	0.64	—0.250	0.002	—0.347
37	2,5-Xylenol	0.64	—0.250	0.002	—0.347
38	2,6-Xylenol	0.63	—0.240	0.003	—0.221
39	*o*-Propylphenol	0.36	+0.245	0.003	+0.213
40	*o*-Propenylphenol	0.43	+0.136	0.006	+0.151
41	*o*-Allylphenol	0.53	—0.023	0	+0.082
42	*o*-α-Methylallylphenol	0.26	+0.458	0.004	+0.551
43	2,3,5-Trimethylphenol	0.44	+0.111	0.004	—0.052
44	2-Isopropyl-5-methylphenol	0.24	+0.495	0	+0.439

(continued on p. 47)

TABLE I (*continued*)

No.	Compound	R_F	Mean R_M	Max. deviation of R_M from mean R_M	Calculated R_M
	Mono-ethers of hydroquinones without ortho-substituents				
45	*p*-Methoxyphenol	0.92	—1.070	0	
46	*p*-Ethoxyphenol	0.88	—0.842	0.020	—0.911
47	*p*-*n*-Propoxyphenol	0.73	—0.420	0	—0.456
48	*p*-*n*-Butoxyphenol	0.50	—0.001	0.003	
49	*p*-*n*-Hexyloxyphenol	0.105	+0.933	0.011	+0.909
50	*p*-*n*-Heptyloxyphenol	0.04	+1.400	0	+1.364
51	*p*-Isopropoxyphenol	0.83	—0.688	0.020	
52	*p*-Isoamyloxyphenol	0.24	+0.501	0	+0.454
53	*p*-Allyloxyphenol	0.80	—0.602	0	—0.648
54	*p*-Pent-4-enyloxyphenol	0.35	+0.269	0.019	+0.262
55	*p*-Cyclohexyloxyphenol	0.35	+0.266	0.011	+0.485
56	*p*-*tert.*-Butoxyphenol	0.80	—0.602	0	
57	*p*-*sec.*-Butoxyphenol	0.64	—0.241	0.008	—0.233
58	*p*-Phenoxyphenol	0.33	+0.311	0.016	
59	*p*-Cyclopentyloxyphenol	0.55	—0.080	0.004	+0.031
60	*p*-Benzyloxyphenol	0.40	+0.185	0.007	+0.002
61	4-Methoxy-5-methylphenol	0.85	—0.772	0.003	
	Mono-ethers of hydroquinones with ortho-substituents				
62	2,3-Dimethyl-4-methoxyphenol	0.71	—0.381	0.001	—0.354
63	2,5-Dimethyl-4-methoxyphenol	0.71	—0.381	0.001	—0.354
64	4-Methoxy-2-methylphenol	0.835	—0.710	0	—0.649
65	2-Allyl-4-methoxyphenol	0.635	—0.236	0.014	—0.075
66	2-Crotyl-4-methoxyphenol	0.405	+0.167	0.026	+0.544
67	4-Methoxy-2-(α-methylallyl)-phenol	0.42	+0.137	0.006	+0.468
68	4-Methoxy-2-propenylphenol	0.48	+0.031	0.001	+0.143
69	4-Methoxy-2-propylphenol	0.50	+0.003	0.007	0.205
	Chromanols and coumaranols				
70	2,2-Dimethyl-6-chromanol	0.78	—0.547	0.002	—0.513
71	2,5,8-Trimethyl-6-chromanol	0.36	+0.245	0.004	+0.103
72	2,5,7,8-Tetramethyl-6-chromanol	0.225	+0.534	0.004	+0.524
73	2,2,5,7,8-Pentamethyl-6-chromanol	0.175	+0.676	0.002	+0.624
74	4-Methyl-5-coumaranol	0.84	—0.730	0.012	—0.856
75	6-Methyl-5-coumaranol	0.84	—0.730	0.012	—0.856
76	2,4,7-Trimethyl-5-coumaranol	0.67	—0.296	0.009	—0.332
77	2,4,6,7-Tetramethyl-5-coumaranol	0.51	—0.015	0.015	+0.089

0.032. Thus $\Delta R_M(CH_2)$ is constant, in agreement with the findings of LEDERER[6].

It must be stressed that $\Delta R_M(CH_2)$ is constant only if each successive CH_2 group is added sufficiently far removed from any functional group as to be regarded as free of any constitutive interaction with it (such an interaction could be steric or electronic in character or could involve an increased measure of internal hydrogen bonding). If this requirement is neglected, certain compounds may then appear to have "anomalous" R_F values—especially the first (and sometimes second) member of homologous series[6-9]. These "anomalous" R_F values are *real* deviations from MARTIN's equation. They are not to be confused with the experimental deviations that are also especially likely when first and second members of a series are run in the same system

as higher members. Under such conditions their R_F values are often either too high or too low to be determined accurately, and can be distorted by non-equilibrium. Even under ideal conditions, however, the R_M value of the first (and sometimes second) member of a series may be "anomalous" because in these compounds constitutive interaction of the first CH_2 group with the functional group exists. The chromatographic deviations are consistent with the fact that in a homologous series the first member is structurally unique and homology does not strictly begin until the second member of the series is reached. Whether the R_F "anomaly" of the first member is large enough to be observable would appear to depend on the nature of the series and of the system. Thus, although it is clear from the summary of FRANC AND JOKL[7] that some workers found a first member "anomaly" in the series of alkyl dinitrobenzoates, we did not do so, using a reversed phase system[1]. LEDERER[6] also shows that the first member "anomaly" can exist in some series but not in others. It is most frequently observed in series of organic acids[6,7]. HOWE[9], for example, found benzoic acid to be "anomalous" in a series of ω-phenyl-substituted monocarboxylic acids. HOWE[9], LONG, QUAYLE AND STEDMAN[37] and SEHER[38] all observed oxalic acid to be anomalous in series of dicarboxylic acids.

The ΔR_M(ring-attached CH_2) parameter

It will have been noticed that, for the calculation of $\Delta R_M(CH_2)$, the lowest member of the phenol series used was the third member, *p*-ethylphenol. It is clear that in the second member, *p*-cresol, the CH_2 group, being directly attached to an aromatic ring and under its electronic influence, is constitutively different from a homologous CH_2 group. In accordance with the views already expressed, *p*-cresol can be regarded as a special case of a lower member "anomaly". It is not unexpected therefore to find that ΔR_M(ring-attached CH_2) is different from $\Delta R_M(CH_2)$ itself. FRANC AND JOKL[8] studied several substituted phenols and observed such a difference. However, they were unable to draw the correct conclusions from this as they did not take into account the *steric* effects of substitution in their compounds.

ΔR_M(ring-attached CH_2) has been calculated from the data in Table I by comparing phenol with its mono-, di- and tri-methylated derivatives, but restricting the calculations to those phenols that do not contain substituents *ortho* to the hydroxy group (see discussion on the *ortho*-effect below). These were *m*- and *p*-cresol, 3,4-xylenol, 3,5-xylenol and 3,4,5-trimethylphenol. ΔR_M(ring-attached CH_2) was found to be $+ 0.305 \pm 0.018$, significantly different from the value of $\Delta R_M(CH_2)$.

The $\Delta R_M(OCH_3)$ parameter

The increment in R_M produced by the addition of an OCH_3 group to an aromatic ring can be derived from the R_M values of phenol and *p*-methoxyphenol. Its value in System 1 is -0.007. This parameter is compounded of two opposing effects, one due to the oxygen atom, the other due to the alkyl group. It is analysed further by the method of atomic parameters (see below).

The ortho-effect

If two substituent groups in a molecule are close to each other there may be an interaction between them. Such effects are familiar in several fields. They not only influence chemical reactivity by affecting the stability of the transition state, but they

can affect a number of the physical constants of substances. Since group interaction can affect both the molar volume and the cohesion energy of a molecule, it is therefore to be expected that it will affect R_M (this follows from DIKSTEIN's[39] thermodynamic derivation of R_F). We have only studied one such effect, the *ortho*-effect in phenols. If an alkyl group is substituted *ortho* to the OH group, some screening of the functional group occurs. This might be purely spatial (so-called steric hindrance), but, as in other aspects of organic chemistry, it is not always possible to distinguish the strictly steric nature of the screening from the electronic effects (if any) of the substituent on the functional group. Thus, when both groups are *ortho* to each other on an aromatic ring, interactions might include polar effects ranging from small inductive effects to permanent polarizations and major intramolecular disturbances could arise through the possibilities of internal hydrogen bonding or even tautomerism. Although in the series of compounds studied here (where the *ortho*-effect is limited to that produced by simple alkyl groups) polar effects can probably be regarded as minimal, the complex nature of the origin of the effect makes it hardly likely that ΔR_M(*ortho*-effect) would be constant. Its magnitude will depend not only on the size and electronic character of the alkyl group, but, as ROUBALOVA's work on aurones has shown[40], will be determined by the total structure of the molecule in which it occurs. It follows that R_M(*ortho*-effect)—even for the same *ortho*-group—will not be constant, and, at present, we have only found it possible to treat the *ortho*-effect empirically.

ΔR_M(*ortho*-effect)—that is, the *additional* R_M increment produced by an *o*-alkyl group over and above the normal ΔR_M value of the same alkyl group when substituted elsewhere in the molecule—was calculated from three pairs of phenols whose R_M values are given in Table I. From *o*- and *m*-cresol the value is + 0.220; from 2,3-xylenol and 3,4-xylenol, + 0.194; from *o*- and *p*-propylphenol, + 0.158. The mean value is thus + 0.161, about a third of $\Delta R_M(CH_2)$. When two *ortho*-groups are present in the same compound, as in 2,6-xylenol (Table I), it appears that the effect of the second group may be slightly less than that of the first. (Because of the large variation in the magnitude of ΔR_M (*ortho*-effect), however, data from one compound may be misleading. In all subsequent calculations of R_M values (see below) we have arbitrarily taken the effect of two *ortho*-groups as twice that of one. Any error involved is, in any case, small.)

In the hydroquinone mono-ether series, ΔR_M(*ortho*-effect) is different again. From a comparison of *p*-methoxy-2-methylphenol and *p*-methoxy-5-methylphenol, it is found to be only + 0.062. This may be due to some electronic interaction between the *p*-methoxy and the hydroxy group altering the steric effect of the methyl group, and is in accord with ROUBALOVA's work[40]. The mean value of ΔR_M(*ortho*-effect) in all compounds listed in Table I is + 0.126 and this has been used (see below) in all the calculations in which it occurs.

The ΔR_M parameter for ether oxygen

The two main series of compounds in Table I, phenols and hydroquinone mono-ethers, are related to each other by the introduction of a *p*-alkoxy group into the phenolic nucleus. The value of ΔR_M(O) due to the introduction of the new oxygen atom can be calculated in the usual way by comparing the R_M values of a series of *p*-*n*-alkylphenols with those of the corresponding *p*-*n*-alkoxyphenols. If this is done, the value is in fact found to be fairly constant between the ethyl and butyl compounds, being

— 0.510 ± 0.047. However, closer inspection reveals that there is a steady variation in the value of ΔR_M(O) over this range of compounds, the actual values being — 0.557, — 0.507 and — 0.466 for the pairs of butyl, propyl and ethyl compounds respectively. Whereas, if the R_M values of the pairs of amyl, hexyl and heptyl compounds (which can be easily found by extrapolation) are compared, it is found that over the range butyl to heptyl, ΔR_M(O) is much more constant at + 0.541 ± 0.023. If, on the other hand, *p*-methoxyphenol is compared with *p*-cresol, ΔR_M(O) is found to be only — 0.303, significantly different from any of the above values. The variation in ΔR_M(O) is not restricted to primary ethers. If the value of ΔR_M(O) is calculated for a typical secondary ether by comparing the R_M values of *p*-isopropoxyphenol and *p*-isopropylphenol, it is found to be — 0.801. The value of ΔR_M(O) is thus profoundly affected by the nature of the alkyl substituent attached to the oxygen atom. This phenomenon is dealt with in more detail below, in the discussion on atomic ΔR_M parameters.

The ΔR_M(double bond) parameter

The presence of a double bond in a molecule always (with the one exception to be noted later) increases its R_F value in reversed phase systems such as System 1. This agrees with the observation that in direct phase systems, unsaturation usually leads to a decrease in R_F. Thus SUNDT AND WINTER[41] observed that hexen-1-al migrated more slowly than hexan-1-al in dimethylformamide–decalin. We have shown else-

TABLE II

ΔR_M(DOUBLE BOND) VALUES CALCULATED FROM EIGHT PAIRS OF COMPOUNDS CHROMATOGRAPHED IN SYSTEM 1

For R_M data, see Table I.

No.	Compound	ΔR_M(double bond)
9	*p*-*n*-Butylphenol	—0.231
19	*p*-*n*-Crotylphenol	
11	*p*-(3-Methylbutyl)-phenol	—0.276
20	*p*-(3-Methylbut-2-enyl)-phenol	
12	*p*-Cyclopentylphenol	—0.355
22	*p*-Cyclopent-2-enylphenol	
8	*p*-*n*-Propylphenol	—0.033
23	*p*-*n*-Propenylphenol	
39	*o*-Propylphenol	—0.109
40	*o*-Propenylphenol	
39	*o*-Propylphenol	—0.268
41	*o*-Allylphenol	
47	*p*-*n*-Propoxyphenol	—0.182
53	*p*-Allyloxyphenol	
*	*p*-*n*-Pentyloxyphenol	—0.198
54	*p*-Pent-4-enyloxyphenol	

* This compound was not run in System 1, but its R_M value can be calculated with a high degree of accuracy from the mean of the R_M values for *p*-*n*-butoxyphenol and *p*-*n*-hexyloxyphenol.

where[42] that reversed phase systems are especially suitable for measuring olefinic unsaturation.

If ΔR_M(double bond) were a constant chromatographic parameter in System 1, it could be calculated in the usual way by comparing pairs of compounds differing in their structures only by one double bond. This has been done for eight such pairs of compounds and the results are shown in Table II. It will be observed that, for the six pairs of substituted phenols, the value is not constant. This is perhaps to be expected. The "constitutive" surroundings of the double bond in these compounds with respect to the aromatic ring vary widely and there is thus no reason to suppose that the double bond will behave as a regular "additive group". In the hydroquinone half-ether series, however, which is represented by two pairs of compounds (*p*-allyloxyphenol and *p*-propoxyphenol; *p*-*n*-pentyloxyphenol and *p*-pent-4-enyloxyphenol) where the double bond is separated from the neighbourhood of the aromatic ring by an oxygen atom, the agreement is good, and it will be shown later that the calculated R_M values for these compounds agree well with the experimental values. Table II suggests that the variation in ΔR_M(double bond) may be due to interaction of the double bond with the aromatic ring. Thus if ΔR_M(double bond) calculated from the two pairs of *p*-alkoxyphenols is taken as — 0.190, then the value is clearly less for the two propenyl compounds and more for the four allyl-type compounds, being particularly high in the case of *p*-cyclopent-2-enylphenol, which is a cyclic allyl compound. The nature of these variations and an explanation of their origin is discussed below.

ATOMIC ΔR_M PARAMETERS

MARTIN's equation can only be applied to every group and atom in a molecule if all their constitutive relationships are considered. The correlation of R_M values of compounds varying in a more complex way than do members of a homologous series must therefore involve an analysis of these relationships. It is the complexity of this task, even in relatively simple compounds, that prevents the universal application of MARTIN's equation to problems of structure. For example, the R_M value of *p*-cyclopentylphenol cannot be calculated with any degree of accuracy from that of the straight-chain *p*-*n*-amylphenol, or the R_M values of the fused-ring structures, 2-indanol and 2-tetralol, from the analogous *p*-*n*-propylphenol and *p*-*n*-butylphenol, by simply using the value for $\Delta R_M(CH_2)$. In addition, it is essential to know the ΔR_M increments for CH groups and quaternary C atoms and something about the additive properties of such groups when they occur in rings. From the data in Table I it would be possible, as a first approximation, to devise a correction parameter for these ring compounds, as follows: ΔR_M(saturated ring) = — 0.305, but the maximum deviation of such a correction is large, about ± 0.140. In any case, the use of a correction does not solve the problem, which arises anew with every series of compounds. Thus, the R_M values of compounds containing fused aromatic rings—naphthols, phenanthrols and anthrols —cannot be calculated from phenol by the addition of increments for CH_2 even if a ring correction factor is used: for the R_M value of 2-naphthol (+ 0.010) is much less in System 1 than that of the analogous C_{10} compound, *p*-*n*-butylphenol (+ 0.556); and the R_M value of 9-phenanthrol (+ 1.130) departs even more from the calculated R_M value (+ 2.372) for *p*-*n*-octylphenol.

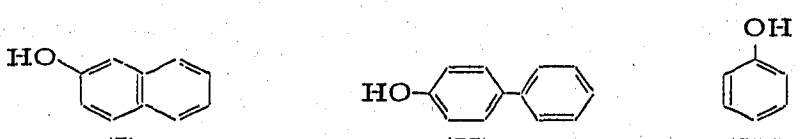
The difference between $\Delta R_M(CH_2)$ and ΔR_M(ring-attached CH_2), which has al-

ready been discussed, provides another simple but important example. In System 1, this difference is appreciable, amounting to about one-third of $\Delta R_M(CH_2)$ itself. When more than one ring-attached CH_2 group is present the effect is multiplied accordingly and may in fact lead to a clear-cut chromatographic separation between isomers. Thus, 3,4,5-trimethylphenol and *p*-*n*-propylphenol are readily separated in System 1, where their R_M values differ by 0.236. Indeed, the difference between the ΔR_M increments produced by constitutively different CH_2 groups is not confined to the ring-attached CH_2 group alone. As is shown below the difference extends, on a diminishing scale, to CH_2 groups α and β to the aromatic system as well. This is why FRANC AND JOKL[8] were able to observe a significant difference in the R_F values of 3,4-dimethylphenol and *p*-ethylphenol. (They were prevented from observing the larger difference between a trimethylphenol and *p*-propylphenol by the fact that their compounds were *ortho*-substituted. Since ΔR_M(*ortho*-effect) may be approximately equal in magnitude and opposite in direction to the difference between $\Delta R_M(CH_2)$ and ΔR_M(ring-attached CH_2) in this series of compounds, this is to be expected.)

All these differences derive from the differing constitutive relationships of the carbon and hydrogen atoms in these compounds, compared to those existing in the homologous series. The method of atomic ΔR_M parameters now to be discussed provides a way of dealing with such constitutive effects in molecules, and its use resolves many of the problems inherent in the use of group ΔR_M values. It consists, in principle, of extending MARTIN's equation by considering carbon and hydrogen atoms separately and assigning to each a ΔR_M value that is determined by both the normal "additive" quantity and also by a "constitutive" quantity depending on the structural or constitutive relation of the atom to the rest of the molecule. Although the experimental determination of such ΔR_M values for carbon and hydrogen is theoretically possible, in practice it would involve the greatest difficulties, both with regard to the amount of chromatographic data required and also the tedious mathematical treatment that would be necessary. Thus, in all but the simplest molecules, there would be many types of carbon and hydrogen atom all with different "constitutive" relationships and hence all necessitating the assignment of different ΔR_M increments. This otherwise complex treatment can be simplified by the use of the following mathematical device. In this treatment, all carbon atoms are assigned the *same* ΔR_M value, whatever their position or structural relationship in a molecule, *and all other variations in the* ΔR_M *values of groups containing only carbon and hydrogen are considered to be due solely to variations in the* ΔR_M *contributions of structurally different hydrogen atoms.* This reduces the experimental requirements at once. Consider, for example, an alkylated phenol, such as one given in Table I. All the carbon atoms are assumed to have one ΔR_M value, while all the hydrogen atoms—regardless of whether they are in side chains, the aromatic nucleus, fused ring or in ether groupings—can be considered as being α, β, γ, etc. to the aromatic nucleus. The experimental problem is reduced to determining the ΔR_M values for these different types of hydrogen atoms. If this is done, the atomic ΔR_M values can be used in MARTIN's equation. (This is theoretically desirable in any case. The R_F value of a substance is partly related to its molecular volume and the latter is in principle determined by the sum of independent carbon and hydrogen contributions. The fact that, for the reasons outlined we have included the unknown ΔR_M(carbon) variation into the experimental values for ΔR_M(H) in no way invalidates this.)

The calculation of ΔR_M values for carbon and hydrogen

It is first necessary to calculate the "constant" ΔR_M parameter for the carbon atom. This is done by the following process, in which the structures of 2-naphthol (I), *p*-phenylphenol (II) and phenol (III) are compared and their R_M values correlated.



(I) (II) (III)

2-Naphthol contains seven CH groups and three quaternary C atoms. *p*-Phenylphenol, on the other hand, contains nine CH groups and three quaternary C atoms. The R_M difference between the two compounds, 0.546, can thus be considered to be formally due to a difference in two CH groups. Therefore, ΔR_M(CH) is + 0.273. (This treatment ignores any differences of bond order, resonance energy or other manifestations of "aromaticity" between the two compounds (see later).) Phenol and 2-naphthol differ formally by two CH groups plus two quaternary carbon atoms, and they differ in R_M by 1.073.

$$2 \times \Delta R_M(\mathrm{C}) = R_M(\text{naphthol}) - R_M(\text{phenol}) - 2 \times \Delta R_M(\mathrm{CH})$$

Then,

$$\Delta R_M(\mathrm{C}) = + 0.263$$

The next stage is to calculate the various ΔR_M values for hydrogen, as follows:

(*i*) ΔR_M(*aromatic H*).

$$\Delta R_M(\text{aromatic H}) = \Delta R_M(\mathrm{CH}) - \Delta R_M(\mathrm{C}) = + 0.010$$

(*ii*) ΔR_M(*α-hydrogen*). The R_M values of phenol and cresol are compared.

$$R_M(\text{cresol}) - R_M(\text{phenol}) = \Delta R_M(\mathrm{C}) + 3 \times \Delta R_M(\alpha\text{-hydrogen}) - \Delta R_M(\text{aromatic H})$$

Then,

$$\Delta R_M(\alpha\text{-hydrogen}) = + 0.014$$

(*iii*) ΔR_M(*β-hydrogen*). Similarly,

$$R_M(p\text{-ethylphenol}) = R_M(\text{phenol}) - \Delta R_M(\text{aromatic H}) + 2 \times \Delta R_M(\mathrm{C}) + 2 \times \Delta R_M(\alpha\text{-hydrogen}) + 3 \times \Delta R_M(\beta\text{-hydrogen})$$

Then,

$$\Delta R_M(\beta\text{-hydrogen}) = + 0.048$$

By analogous methods, the ΔR_M parameters for γ-, δ-, and ε-hydrogen atoms can be calculated by comparing the higher alkylated phenols with phenol itself. Their values are + 0.082, + 0.096 and + 0.096 respectively.

The ΔR_M(H) values thus increase with the distance of the atom from the ring up to the δ-hydrogen, after which they remain constant.

Atomic ΔR_M parameters for oxygen

It has already been shown that, if the "group" ΔR_M parameter for oxygen is calculated from a comparison of alkylphenols with corresponding alkoxyphenols, the

value varies markedly depending on the pair of substances chosen. As a result, if an attempt is made to calculate, say, the R_M values of alkoxyphenols from the chromatographic data obtained from the alkylphenols, MARTIN's equation cannot be used because the "group" ΔR_M parameter is not constant. This situation can now be considered afresh.

(*i*) ΔR_M(*O in* OCH_2R). Consider first the comparison of straight-chain primary alkylphenols with straight-chain primary alkoxyphenols. In *p*-*n*-propylphenol, there are two α-hydrogens, two β-hydrogens and three γ-hydrogens, and these have different ΔR_M values. It is not known, however, whether the same values should apply to the corresponding hydrogen atoms of the alkoxy group in *p*-*n*-propoxyphenol. Since these hydrogen atoms are no longer influenced electronically by the aromatic ring, it is probable that the variation in ΔR_M no longer applies. In any case, since the value for ΔR_M(O) is affected so much by substitution at the oxygen atom, variations in the value for ΔR_M(H) are relatively insignificant. We therefore assume that in the case of hydrogen atoms in the alkoxy radical, ΔR_M(H) is constant and equal to + 0.096, the same value as for hydrogen atoms remote from the aromatic ring in alkylphenols. The value of ΔR_M(O in OCH_2R) can now be calculated as follows, choosing *p*-butoxyphenol as a suitable compound.

$$R_M(p\text{-butoxyphenol}) = R_M(\text{phenol}) - \Delta R_M(\text{aromatic H}) + 4 \times \Delta R_M(\text{C}) + 9 \times \Delta R_M(\text{H}) + \Delta R_M(\text{O in } OCH_2R)$$

Then

$$\Delta R_M(\text{O in } OCH_2R) = -0.844$$

If similar calculations are made for the whole series of alkoxyphenols from the *p*-propoxy to the *p*-heptyloxy compound, the value of this parameter is found to be virtually constant. If, however, in an exactly similar manner, ΔR_M(O in OCH_2R) is calculated from a comparison of *p*-ethoxyphenol and phenol, it is already somewhat different and has a value of only — 0.775. As will be seen from study of the branched ethers, ΔR_M(O) is profoundly influenced by vicinal branching. The ethyl group itself can be considered as a limiting case of "branching" at the carbon atom attached to oxygen, for this carbon is uniquely substituted by two hydrogen atoms and one CH_3 group. It thus provides another example of a "lower member" anomaly and one that is extraordinarily sensitive to constitutive effects. Subsequent CH_2 group addition in the alkoxy radical no longer affects the α-carbon atom and ΔR_M(O) is constant for all higher alkoxy groups.

It will be observed that the value of ΔR_M(O in OCH_2R) found by the method of atomic parameters differs considerably from the previously-calculated "group" parameter for OCH_2R, —0.557. This is, of course, simply due to the fact that the "group" parameter is calculated from a direct comparison of an alkylphenol and an alkoxyphenol and therefore integrates all the variations of ΔR_M(H) in the R_M value of the former. The atomic ΔR_M(O) parameter is calculated *ab initio* from phenol and does not include variable ΔR_M parameters for hydrogen atoms in the alkoxy group: if these exist they are included in the atomic ΔR_M(O) parameter. It follows that, in calculating the R_M values of compounds containing ether groupings from R_M(phenol), the atomic ΔR_M parameter must be used, as shown below.

(*ii*) ΔR_M(*O in* OCH_3). It has already been shown that the "group" ΔR_M value for OCH_3 is considerably less negative than that of other alkoxy groups. This difference

can be considered as arising from the unique nature of the substitution at the carbon atom attached to oxygen in a methyl ether. This carbon atom bears three hydrogen atoms, whereas in other primary ethers it is attached to only two. The atomic ΔR_M parameter for oxygen in OCH_3 is calculated as follows:

$$R_M(p\text{-methoxyphenol}) = R_M(\text{phenol}) - \Delta R_M(\text{aromatic H}) + \Delta R_M(\text{C}) + 3 \times \Delta R_M(\text{H}) + R_M(\text{O in } OCH_3)$$

Then,

$$\Delta R_M(\text{O in } OCH_3) = -0.558$$

(*iii*) ΔR_M(*O in* $OCHR_2$). Since the value of ΔR_M(O) in primary ethers is so markedly affected by changes in the substitution at the carbon atom attached to oxygen, it is not surprising that its value should prove to be different for secondary ethers. Table I shows this is so. *p*-Isopropoxyphenol runs faster than *p*-*n*-propoxyphenol and *p*-*sec*.-butoxyphenol faster than *p*-*n*-butoxyphenol. Therefore, a new atomic ΔR_M(O) parameter must be calculated for secondary ethers. By similar methods to those already shown, comparing R_M(*p*-isopropoxyphenol) with R_M(phenol), ΔR_M(O in $OCHR_2$) is found to be — 1.076.

(*iv*) ΔR_M(*O in* OCR_3). Table I shows that *p*-*tert*.-butoxyphenol runs much faster than *p*-*n*-butoxyphenol. Indeed, the former compound runs almost as fast as *p*-ethoxyphenol. This indicates that the atomic ΔR_M parameter for oxygen in tertiary ethers must be even more negative than in any other type of ether. Comparison of R_M (*p*-*tert*.-butoxyphenol) with R_M(phenol) and calculating as above gives ΔR_M(O in OCR_3) as — 1.445.

(*v*) ΔR_M(*O in OPh*). Replacement of the alkyl group in alkoxyphenols by an aromatic radical can also be expected to introduce a pronounced new constitutive effect on the value of ΔR_M(O). This is so. As Table I shows, *p*-phenoxyphenol runs much slower than *p*-hexyloxyphenol, even though it contains fewer (and only aromatic) hydrogen atoms. This implies that ΔR_M(O in OPh) must be much more positive than ΔR_M(O in OCH_2R). (In the calculation of the former parameter, the five hydrogen atoms in the phenoxy group are given their aromatic ΔR_M values of + 0.010, since they are themselves part of an aromatic system.) Thus,

$$R_M(\text{O in OPh}) = R_M(p\text{-phenoxyphenol}) - R_M(\text{phenol}) - 6 \times R_M(\text{C}) - 4 \times \Delta R_M(\text{aromatic H}) = -0.244$$

CALCULATION OF R_M VALUES

Table III summarizes the values of the atomic ΔR_M parameters for carbon, hydrogen and oxygen, which have been obtained by the methods described above. By using these values, it is now possible to calculate the R_M values of the compounds in Table I from the R_M value of phenol. The calculated values are shown in Table I. The same atomic ΔR_M parameters were used, irrespective of whether the atoms concerned were in a ring or a chain. (Calculated values are not given for those compounds that were used for the derivation of the various ΔR_M parameters.)

Phenols without ortho-substituents

In this group (compounds 1–24) the agreement between calculated and experimental

TABLE III

ΔR_M PARAMETERS FOR CARBON, HYDROGEN AND OXYGEN IN SYSTEM I

Substituent	ΔR_M
C	+0.263
Aromatic hydrogen	+0.010
α-Hydrogen	+0.014
β-Hydrogen	+0.048
γ-Hydrogen	+0.084
δ-Hydrogen	+0.096
ε-Hydrogen	+0.096
O in OCH_2R	−0.844
O in $OCHR_2$	−1.076
O in OCR_3	−1.445
O in OCH_3	−0.558
O in OPh	−0.242

R_M values is good. A typical calculation is for *p*-(3-methylbutyl)-phenol (Table IV).

Only four compounds in this group have an R_M value that differs from the calculated value by more than ± 0.052. The discrepancies are thus less than can be attributed to one-fifth of a carbon atom. The four compounds (19–22) that show larger discrepancies are *p*-crotyl, *p*-(3-methylbut-2-enyl)-, *p*-benzyl- and *p*-cyclopent-2-enylphenol. These discrepancies can be attributed to the special structures of these substances, which are all "allyl"-type compounds. The nature and origin of the "allyl" effect is discussed below. It may be noted here, however, that the R_M value of *p*-propenylphenol, in which the side-chain double bond is conjugated with the ring, is in excellent agreement with the calculated value, and *p*-cyclopentylphenol, which has a saturated cyclic side-chain, also shows no R_M anomaly. Attention is drawn to the calculation for the ring-containing phenol, *p*-cyclohexylphenol. In this molecule, there is only *one* α-hydrogen, four β-hydrogens, four γ-hydrogens and two δ-hydrogens. The calculated R_M value is in excellent agreement with the experimental value.

TABLE IV

CALCULATION OF R_M FOR *p*-(3-METHYLBUTYL)-PHENOL

Constituent	*Increment*	
	+	−
R_M(phenol)		1.063
$-\Delta R_M$(aromatic H)		0.010
$+ 5 \times \Delta R_M$(C)	1.315	
$+ 2 \times \Delta R_M$(α-hydrogen)	0.028	
$+ 2 \times \Delta R_M$(β-hydrogen)	0.096	
$+ \Delta R_M$(γ-hydrogen)	0.082	
$+ 6 \times \Delta R_M$(δ-hydrogen)	0.576	
Sum of R_M increments	2.097	1.073

Calculated R_M = + 1.024
Experimental R_M = + 1.000

Phenols containing fused rings

The calculated R_M values for these compounds (25–33) are in good agreement with the experimental values. The two tetralols run a little faster than required by theory (by about one-third to one-half of a carbon atom), although 2-indanol runs correctly.

TABLE V

CALCULATION OF R_M FOR *p*-PENT-4-ENYLOXYPHENOL

Constituent	*Increment*	
	+	—
R_M(phenol)		1.063
+ 9 × ΔR_M(hydrogen)	0.864	
+ 5 × ΔR_M(C)	1.315	
+ ΔR_M(O in OCH_2R)		0.844
— ΔR_M(aromatic H)		0.010
Sum of R_M increments	2.179	1.917

Calculated R_M = + 0.262
Experimental R_M = + 0.185

In the calculation of 1-tetralol, 1-naphthol, 1-anthrol and 9-phenanthrol, an increment for ΔR_M(*ortho*-effect) was included. (There is clear chromatographic evidence that an *ortho*-effect does exist in fused-ring compounds, since 1- and 2-naphthol, 1- and 2-tetralol, and 1- and 2-anthrol can all be separated in System 1. The *ortho*-effect is due to some undefined interaction of the hydroxy group with the *peri* CH_2 or CH group of the second ring. There is considerable evidence, both chemical and physical, that confirms this. Thus ARNOLD and his co-workers[43–45] have demonstrated steric hindrance due to the *peri* methylene group in a variety of chemical reactions and also by a study of Raman spectra, while HUNSBERGER *et al.*[46] have demonstrated a similar effect by a study of infra-red spectra.) A typical calculation in this group is for 1-anthrol: R_M(1-anthrol), calculated from R_M(phenol) by adding 8 × ΔR_M(C), 4 × ΔR_M (aromatic H) and ΔR_M(*ortho*-effect), is found to be + 1.207, in excellent agreement with the experimental R_M value of + 1.130.

Mono-ethers of hydroquinones, without ortho-substituents

Calculated R_M values for eleven compounds are given in Table I. The appropriate ΔR_M(O) values, which are given in Table III, were used in each case, depending on whether the ether was primary, secondary, etc. The experimental R_M values of all the ethers that do not contain a ring-containing alkoxyl group agree excellently with the calculated values. The calculation for *p*-pent-4-enyloxyphenol is shown in Table V.

p-Cyclopentyloxyphenol and *p*-cyclohexyloxyphenol, however, run rather faster than required, by an amount equivalent to about one quarter to one half of ΔR_M(C). This may be due to the fact that the use of ΔR_M(O in $OCHR_2$), which is derived from R_M(isopropoxyphenol), is probably not entirely justified when calculating the R_M values of secondary ethers containing cyclic alkoxy groups. It should be noted that the R_M values of *p*-allyloxyphenol and *p*-pent-4-enyloxyphenol are in good agreement

with their calculated values (*cf.* the corresponding alkylated phenols, which show anomalies, and DISCUSSION).

The calculation for *p*-benzyloxyphenol is of some interest as it involves a special feature. The five ring hydrogens of the benzyloxy group must be evaluated as aromatic hydrogens (ΔR_M = 0.010); and the two hydrogen atoms of the methylene moiety must be evaluated as α to an aromatic ring. Thus,

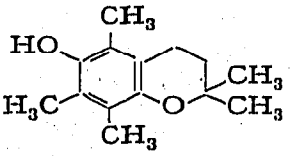
$$R_M(p\text{-benzyloxyphenol}) = R_M(\text{phenol}) + 7 \times \Delta R_M(\text{C}) + 2 \times \Delta R_M(\alpha\text{-hydrogen}) + 4 \times \Delta R_M(\text{aromatic H}) + \Delta R_M(\text{O in } OCH_2R)$$

The calculated value (Table I) is in fair agreement with the experimental value. The chromatography of *p*-phenoxyphenol is of especial interest. The value for ΔR_M(O) in this compound is much more positive than in any other ether (— 0.244). In *p*-cyclohexyloxyphenol, on the other hand, ΔR_M(O) is at least — 1.076, and probably even somewhat more negative. As a result, formal reduction of *p*-phenoxyphenol to *p*-cyclohexyloxyphenol leads to chromatographic *acceleration*. As already noted, reduction of all other types of carbon unsaturated compound leads to a decrease in R_F values.

The unique case of *p*-phenoxyphenol is, of course, due to the destruction of the aromatic character of the aryloxy group on formal reduction.

Chromanols and coumaranols

The eight compounds in this series are structurally the most complex used in this study. For R_M calculations the appropriate oxygen parameters were used, depending on whether the compound contained a cyclic secondary or tertiary ether grouping, and where necessary (as in all compounds except No. 70) the increment for the *ortho*-substituent (0.126) was added. The agreement is in general good, the maximum de-



(IV)

parture from theory being found in 2,5,8-trimethyl-6-chromanol, which ran slower than required by an amount due to about one-third of a CH_2 group.

The calculation for compound 73 (IV), which illustrates several points, is given in Table VI.

Phenols and hydroquinone mono-ethers, with ortho substituents

The calculations of the two groups of compounds with *ortho*-substituents include the increment due to ΔR_M(*ortho*-effect) and we have used throughout the mean value of + 0.126, although, as already shown, the value of this parameter is not very constant. The calculated R_M values are, in spite of this, in moderate agreement with experimental values. In the phenol series, the maximum deviation is only about one-quarter of $\Delta R_M(CH_2)$. In the hydroquinone mono-ether series, it is clear that ΔR_M(*ortho*-substituent) is much more markedly influenced by the size of the *ortho*-group. Thus, compounds 65, 66 and 67, where the groups are large, show deviations from theory by amounts almost equivalent to one CH_2 group.

TABLE VI

CALCULATION OF R_M FOR 2,2,5,7,8-PENTAMETHYL-6-CHROMANOL (IV)

Constituent	Increment +	Increment −
R_M(phenol)		1.063
$-5 \times \Delta R_M$(aromatic H)		0.050
$+8 \times \Delta R_M$(C)	2.104	
$+11 \times \Delta R_M$(α-hydrogen)	0.154	
$+2 \times \Delta R_M$(β-hydrogen)	0.096	
$+6 \times \Delta R_M$(δ-hydrogen)	0.576	
$+\Delta R_M$(O in OCR_3)		1.445
$+2 \times \Delta R_M$(*ortho*-effect)	0.252	
Sum of R_M increments	3.182	2.558

Calculated $R_M = +0.624$
Experimental $R_M = +0.676$

o-Allylphenol and *o*-propenylphenol are just separable chromatographically: this is another example of the "allyl" effect.

DISCUSSION

The results of this study, in which the R_M values of seventy-seven derivatives of phenol have been correlated with their structure, demonstrate that MARTIN's equation is rigorously obeyed for several group and atomic ΔR_M parameters. They support the assumption that MARTIN's equation is probably obeyed for all groups and that, where deviations are observed, they are likely to be caused either by experimental difficulties in obtaining ideal conditions or, if these can be satisfactorily discounted, by constitutive effects in molecules.

With regard to the former, the technical difficulties in measuring R_M values accurately must certainly not be underestimated. Failure to distinguish between experimental and constitutive deviations from MARTIN's equation would still appear to be one of the most serious obstacles preventing further advances in structural analysis by chromatography. (Thus, although BUSH[47], in his extensive treatise, clearly illuminates the nature and origin of experimental deviations, he sometimes fails to distinguish them from constitutive effects: the pronounced anomalies he has noted in the value of $\Delta R_M(CH_2)$ in the first five members of a series (C_1–C_{25}) of fatty acid dinitrophenylhydrazides[48] are probably not due to aberrant solute–solvent interactions as suggested by BUSH, but appear—from the R_F data— to be attributable to non-ideal conditions, perhaps coupled, in the case of the first and second members, with a true constitutive interaction of the CH_2 group with the hydrazide function.) Providing experimental effects are satisfactorily eliminated, structural correlation must depend on the accurate calculation of ΔR_M parameters for constitutive effects. The method of atomic parameters described here illustrates a convenient way of doing this and, as we have shown, such parameters are additive as are other group ΔR_M values. Our approach is similar to and extends the work of REICHL[3,4] and SCHAUER AND BULIRSH[5], who calculated several ΔR_M parameters for amino acids. However, as BARK AND GRAHAM[49]

have said, these workers did not deal adequately with the constitutive effects in their compounds.

Constitutive interactions in molecules can be of various kinds. They can be polar (inductive, hyperconjugative or due to ionic bond formation) or steric. In addition, they can affect internal hydrogen bonding (chelation) and they can introduce tautomeric possibilities into the molecule. Any of these effects can affect R_M, but with the exception of steric factors, none of them has been adequately studied. As a result, the influence of steric effects on R_M has sometimes been over-emphasized. MARTIN[50] first suggested that deviations from group additivity would be mainly due to steric effects, and BUSH[47], in his comprehensive study of steroids, considers most ΔR_M variations in these molecules as being stereochemical in origin. BARK AND GRAHAM[49] also considered only steric factors as affecting the chromatography of their series of nuclear-substituted phenoxyacetic acids and did not include the possibility of polar interactions between the substituent groups. As we have already suggested, the term "steric" is itself misleading, since many so-called steric effects are only partly spatial in character and, in fact, may include polar contributions. TAFT[51], for example, considers the *ortho*-effect in benzenoid compounds as a clear example of the dual nature of a "steric" effect, and our findings on the chromatography of *o*-substituted phenols confirm this view. Certain observations by other workers are also revealing in this connection. BATE-SMITH AND WESTALL[52], for example, found no difference between the R_F values of either catechol and resorcinol or pyrogallol and phloroglucinol in an acetic acid–butanol system, but observed a strong *ortho*-effect in catechol and pyrogallol in an acetic acid–cresol system. This marked dependence on solvent is difficult to correlate with a purely spatial effect. Furthermore, these authors found, in the same acid–butanol system that gave no *ortho*-effect with the hydroxy compounds, a pronounced *ortho*-effect when *o*-hydroxybenzoic acid was compared with the *m*- and *p*-compound. These results show that the nature of any internal hydrogen bonding between two vicinal groups (and this is partly polar in character) must affect ΔR_M-(*ortho*-effect).

Polar effects on ΔR_M values are caused by electronic interactions between the atoms and groups in a molecule, which may arise by a variety of mechanisms. We regard the variation in ΔR_M(H) that we have found in alkylated phenols as being primarily due to the electronic effects in these molecules. (It will be apparent that, although we discuss a variation in ΔR_M(H), in physical reality the variation must lie in the nature of the CH groups themselves. The fact that we have arbitrarily made ΔR_M(C) constant merely transforms a real variation in ΔR_M(CH) into a variation in ΔR_M(H).)

Consider first what may be the origin of the exceptionally small value of ΔR_M-(aromatic H) compared to ΔR_M(δ-hydrogen), which is the normal increment for hydrogen in a long alkyl chain or in a cyclohexane ring. The ΔR_M(aromatic H) parameter is derived from a study of five compounds: phenol, 2-naphthol, *p*-phenylphenol, 2-phenanthrol and 2-anthrol. If the R_M values of these compounds are plotted against the number of carbon atoms in each (Fig. 1) the relationship is found to be linear. Since the four polynuclear compounds are formally derived from phenol by removal of two hydrogens and adding n CH groups, and since by definition ΔR_M(C) is constant, this demonstrates that ΔR_M(aromatic H) is also constant for all five compounds. It follows, therefore, that since the conjugative displacements in the five molecules are

different, *polarization* effects cannot account for the low value of ΔR_M(aromatic H). It further follows that any differences in the incipient ionization of the phenolic OH group in these five phenols can certainly be neglected. We regard the low value of ΔR_M(aromatic H) as being primarily due to the large molar volume difference between benzene and cyclohexane, resulting in a relative compression of aromatic CH groups

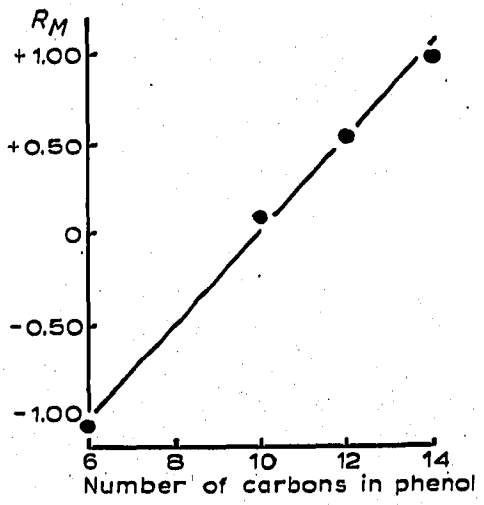


Fig. 1. Relationship between R_M and number of carbon atoms in polynuclear phenols.

compared to aliphatic CH_2 groups. As DIKSTEIN has shown[39], this can be expected to affect the free energy of transfer, and in System I this produces a decrease in R_M. This may not be the only effect, however. It is known that aromatic rings can directly partake in hydrogen bonding by means of their π-bonds. Thus, aromatic bonds may well affect solute–solvent interactions differently from normal C–C bonds, in a manner not dealt with by DIKSTEIN's equation (see later).

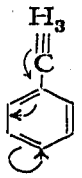
The sequential order of variation in ΔR_M(H) from α- to δ-hydrogen is considered to be due to other factors. Any difference between the molar volume effects of CH_2 groups α and β to the ring must be minute compared to the effect of "aromatization", and there is, in fact, no evidence that substitution of an aromatic hydrogen atom by any alkyl group, however branched, leads to a shortening of the C–C bond between the ring and the alkyl group[53]. We regard this variation, therefore, as a consequence of the electronic interactions of alkyl groups with the aromatic ring. In order to understand how these might affect chromatography, it is necessary to discuss such interactions in some detail.

Although any alkyl group is, of necessity, neutral when attached to hydrogen or aliphatic carbon, it is subject to a polarization when attached to a conjugated or aromatic system. This usually manifests itself in the direction of the ring (vinyl groups are an exception), and thus alkyl groups, compared to hydrogen, are considered to repel electrons into the ring. Such a polarization affects certain physical properties of the molecule, such as its dipole moment, and also its chemical reactivity. Study of the various alkylated derivatives of benzene, however, by chemical and physical means, leads to the observation that there are in fact *two* orders of electron release by alkyl groups and hence to the concept that two mechanisms are involved. One of

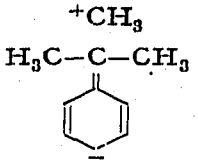
these is the general inductive effect (+ I)[53], the magnitude of which varies in the order,

$$C(CH_3)_3 > CH(CH_3)_2 > C_2H_5 > CH_3$$

The other is hyperconjugation[54], which is usually regarded as being due to the conjugation of single C–H bonds with an aromatic ring (V).



(V)



(VI)

This hyperconjugative mechanism, depending as it does on the availability of α-hydrogen atoms, means that the electron-releasing effect of the CH_3 group must be greater than that of a *tert.*-butyl group: thus the magnitude of the hyperconjugative effect is observed to vary inversely to that of the inductive effect—the so-called BAKER-NATHAN order. Hyperconjugation is essentially a resonance phenomenon; or, in INGOLD's terms[53], since it involves an electronic displacement, includes a mesomeric effect (+ M). Hyperconjugation therefore results in a permanent polarization in alkylbenzenes, and, as shown by the evidence of dipole moments and spectra, is undoubtedly operative in the ground state. The inductive effect of alkyl groups attached to a benzene ring also exists in the ground state, but is not stabilized by a mesomeric interaction[53]. WHELAND[55] regards the inductive effect as a permanent resonance effect, initiated by carbon–hydrogen hyperconjugation (this, however, fails to explain the existence of two different orders of electron release).

There are thus two mechanisms of electronic displacement that may be concerned with the variation in ΔR_M(H). The approach of BERLINER AND BONDHUS[56] has been found rewarding. They unify the two mechanisms by considering them both as resonance effects. Unlike WHELAND, however, they propose that while the BAKER-NATHAN order is due to carbon–hydrogen hyperconjugation (V), the inductive effect is due to carbon–carbon hyperconjugation. Thus, the *tert.*-butyl group is considered to release electrons and partake in resonance through the contribution of "no-bonded" structures such as (VI). Since this type of resonance does not depend on α-hydrogens, the order is the inductive order. It also implies stabilization in the ground state.

It does not appear possible to associate the sequential variation in ΔR_M(H) exclusively with either mechanism of electron release. If the chromatographic effect of adding an alkyl group to the ring is compared with the effect of adding the same group remote from the ring, then there is clearly a larger deviation in the case of the *tert.*-butyl group than with the *n*-butyl group. This supports an inductive order of polarization and hence an effect due to carbon–carbon hyperconjugation. However, this comparison involves a change in the relative numbers of α- and β-hydrogen atoms, and consideration of the replacement of α-hydrogens in *p*-cresol by successive CH_3 groups leads to the conclusion that carbon–hydrogen hyperconjugation may also be involved. To take the matter further it is necessary to consider now how these effects of resonance (by whatever mechanism they are produced) affect R_M. It would seem

that every polarization involving alkyl groups and the ring, being the result of hyperconjugation, results in a relative loosening of the hydrogen atoms attached to the carbon atoms involved in the delocalization. This appears to be true whether carbon–hydrogen or carbon–carbon hyperconjugation is involved (a study of "no-bonded" structure VI shows that the hydrogen attached to the charged carbon atom will be held more loosely than in the unperturbed molecule). As a result, all alkyl group polarizations lead to an increased measure of hydrogen bonding with solvent molecules (usually water or an alcohol). The chromatographic effect, therefore, will be one of increased solubility in the more polar phase: in reversed phase systems, such as System 1, this means that R_M will be decreased. The diminishing values of ΔR_M(H) therefore, are a measure of this loosening of hydrogen atoms, which increases nearer the ring. The large chromatographic deviation of the *tert.*-butyl group can thus be regarded as due to the loosening of the bonds attached to the nine β-hydrogen atoms of this alkyl group. It must be noted that we do not regard the polarization itself—that is, the existence of a finite separation of charges due to either the inductive effect or the BAKER-NATHAN effect— as *directly* affecting the partition coefficient. Indeed there is some evidence from Table I that—as expected, if the above hypothesis approximates to the truth —even the *direction* of the polarization with respect to the ring is unimportant. Thus, the R_M value of *p*-propenylphenol is in good agreement with the value calculated by the use of atomic parameters, although the propenyl group, unlike the other alkyl groups, is electron-attractive[53]. In a subsequent paper we shall present further evidence that the charges on carbon due to the inductive effect play little part in affecting R_M. Our concept of the way in which the polar effects of alkyl groups affect R_M, therefore, places the constitutive change *in the substituent alkyl group itself*. We do not regard the effects on R_M as being, in any way, due to a change in the phenolic OH function (*cf.* SUNDT[57]).

To examine these views further, we have compared the effects of alkyl group resonance on R_M with two other physical and chemical phenomena in alkylated benzenes,

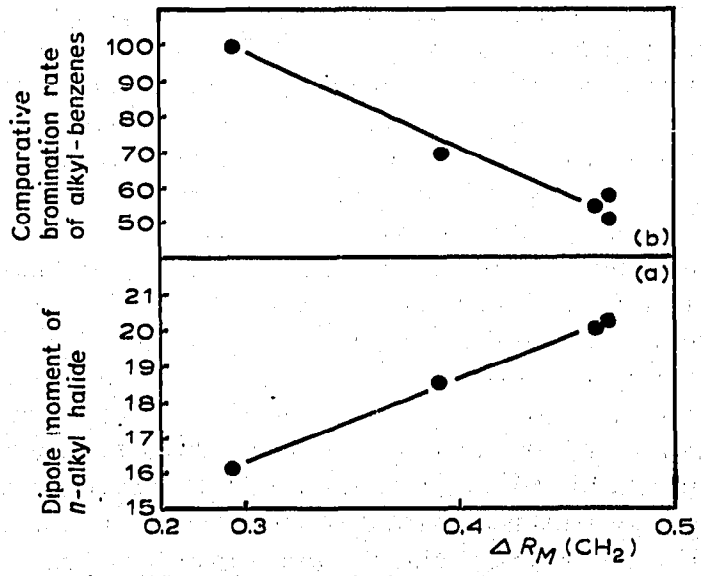


Fig. 2. Relationship between $\Delta R_M(CH_2)$ in *p*-methyl-, *p*-ethyl-, *p*-propyl-, and *p*-butylphenol and (a) dipole moments of the *n*-alkyl halides and (b) comparative rates of bromination of methyl-, ethyl-, propyl-, butyl-, and amylbenzene.

which are also generally ascribed to resonance. We have plotted in Fig. 2 the four successive values of $\Delta R_M(CH_2)$ for the series, phenol to *p*-butylphenol, against (a) the dipole moments of *n*-alkyl halides (methyl to butyl)[58], and (b) the rates of bromination of *n*-alkylbenzenes (toluene to *n*-amylbenzene)[59]. Both curves are approximately linear. (Although in (b) the point for *n*-butylbenzene is slightly anomalous, BERLINER AND BERLINER[59] state that the rate of bromination of this compound is in fact abnormal, because of an exceptional hyperconjugation effect involving the δ-hydrogen and the ring.) The dipole moment order is usually attributed to the inductive effect, whilst the affect on bromination rates is due to carbon–hydrogen hyperconjugation.

It is now possible to consider in more detail the origin of the "allyl" effect on R_M. As described in the experimental section, alkylated phenols that contain a double bond in the allylic position run significantly faster in System 1 than calculated. This can now be attributed to the enhanced effects of resonance in allyl compounds, of which there is also clear chemical evidence. Thus, allyl halides are more reactive than alkyl halides, allyl ethers can be readily cleaved by hydrogenolysis and the allyl radical is considerably more stable than the propyl radical. These properties are considered to be due to the "triad" nature of resonance in the allyl radical (VII).

$$\overline{CH_2} - CH = \overset{+}{CH_2} \leftrightharpoons \overset{+}{CH_2} = CH - \overline{CH_2}$$

(VII)

The observed direction of the constitutive effect of the allyl group on R_M is seen to be the same as that of the *tert.*-butyl group. In accordance with the views already expressed, the "allyl" effect on R_M is considered as being due to the increase in hyperconjugation of the α-CH_2 group of the allyl group, because of the extension of conjugation by the allyl double bond. The effect of this is to loosen the hydrogen atoms of the allyl group even more than can be accounted for by the normal decrease in $\Delta R_M(H)$ for hydrogen atoms in the vicinity of the ring. This results in increased hydrogen bonding with the polar phase, and thus a decrease in R_M in System 1.

It is not surprising that the largest "allyl" effect is observed in *p*-benzylphenol, whose R_M value is 0.316 less than calculated—equivalent to more than one carbon atom. This is attributed to resonance in the benzyl group. (*Cf.* the marked reactivity of benzyl halides and the stability of the benzyl radical arising from the exceptional stabilization of structures involving the hyperconjugated CH_2 moiety.) The loosening of the two α-hydrogen atoms in *p*-benzylphenol is thus reinforced by the proximity of two benzene rings, which account for the unusual magnitude of the "allyl" effect in this compound. Confirmation of this concept of the "allyl" effect in the allylphenols is provided by comparing the R_M values of the allyl ethers. These, in contrast, show no anomalies and agree well with the calculated values. This is because, in ethers, the oxygen atom prevents interaction of the allyl group with the ring. (Indeed, *p*-benzyloxyphenol runs rather more *slowly* than required by theory—probably because it is not quite justifiable to use ΔR_M(O in CH_2R), which is derived from aliphatic primary alkoxy groups, for the calculation of benzyloxy compounds.)

Turning now to the ether series, the chromatography of the alkoxyphenols reveals a remarkable variation in the value of $\Delta R_M(O)$, depending on the nature of the group attached to oxygen. We regard this effect also as electronic in origin and as

primarily due to a variation in the degree of polarization of the C–O bond. Although the steric effects of alkyl groups could operate by screening the oxygen atom, our results show that any such effects are overshadowed by the polar effects. A bulky group attached to oxygen would tend to make ΔR_M(O) more positive in System 1. But ΔR_M(O) in *p-tert.*-butoxyphenol is much more negative than in *p-n*-butoxyphenol, in spite of the considerable screening effect of the *tert.*-butyl group.

Hyperconjugation is no longer possible when alkyl groups are separated from the ring by an oxygen atom—as is demonstrated by several chemical studies. Thus, JONES[60] found pure inductive order in the rates of chlorination of alkyl phenyl ethers, compared to the BAKER-NATHAN order found in alkylbenzenes. The effect of different alkyl groups on ΔR_M(O) is, indeed, clearly related to their inductive effects. BERLINER AND BONDHUS[56] regard the inductive order in alkyl aromatic *ethers* as due to partial ionic bond formation, which in turn depends on the stability of the incipient alkyl carbonium ion (a resonance effect), and there is no doubt that the variation in ΔR_M(O), as shown in Table III, closely parallels the order of stability of the alkyl or aryl ion (or radical) involved. Thus, tertiary ethers are more readily cleaved by acids than primary ethers, while phenyl ethers are the most stable of all. The magnitude of the variation in ΔR_M(O) clearly rules out the possibility that molar volume effects are involved (in any case, the bond stretching in tertiary ethers would require a chromatographic effect in the opposite direction to that found, if molar volume were the determining factor). The chromatographic effect on ΔR_M(O) is almost certainly, then, due to the variation of electron density on oxygen due to resonance effects in the substituent group. Unlike the inductive effect on C–C polarization, this must profoundly affect the availability of the oxygen atom for interaction with solvent molecules; for example, by hydrogen bonding or formation of ether hydrates. (The anomalous $\Delta R_M(CH_2)$ values obtained by SMITH[61] and quoted by BUSH[47] for a homologous series of alkyl sulphides are, we believe, due to a similar variation in the value of ΔR_M(S). We would regard this as a further example of the way in which an undisclosed con-

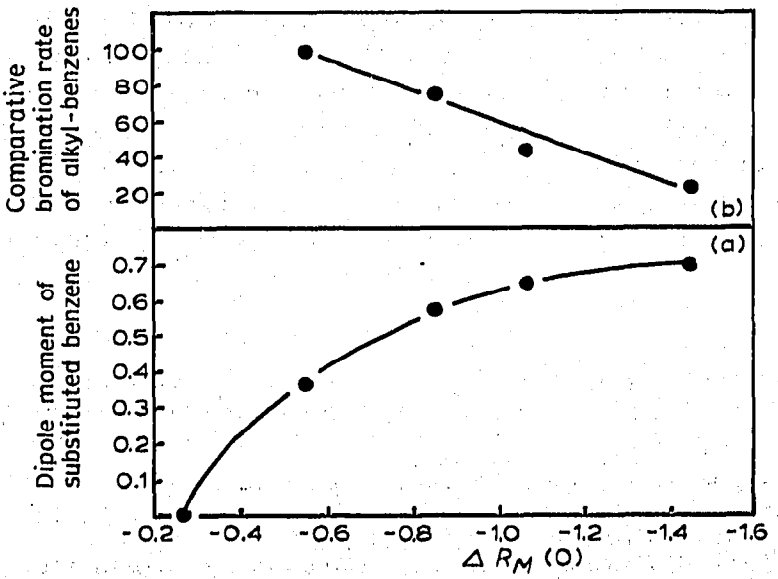


Fig. 3. Relationship between ΔR_M(O) in phenyl, primary, secondary, and tertiary phenyl ethers and (a) dipole moments of substituted benzenes and (b) comparative rates of bromination of alkylbenzenes.

stitutive effect can lead to results in apparent disagreement with MARTIN's equation.)

In order to illustrate the close relationship of the chromatographic parameters for oxygen with the permanent electronic polarizations of molecules, we have (as for the hydrogen parameters above) plotted the values of ΔR_M(O) against sets of physical and chemical data known to be attributable to such polarization effects. Curve (a) in Fig. 3 shows a plot of the atomic parameter ΔR_M(O) in phenyl, methyl, ethyl, isopropyl and *tert.*-butyl ethers against the dipole moments of a series of alkylated benzenes (*p*-diphenyl to *tert.*-butylbenzene)[62]. The smooth curve that is obtained provides evidence of the relationship between inductive order and chromatographic parameters. Curve (b) is a plot of ΔR_M(O) against the rates of bromination of alkylbenzenes (toluene to *tert.*-butylbenzene)[63]. Although (as might be expected since reaction rates are greatly susceptible to transition state effects) the points show rather more scatter, the relationship is similar to that demonstrated in Fig. 2 (b), the plot tending to be linear. If plots are made of ΔR_M(O) against the rates of chlorination of a series of branched ethers[62] and *p*-alkoxybenzoic acids[64] similar, almost linear, relationships are observed.

As already indicated in the experimental section, small differences in the resonance energy of similar molecules do not appear to affect R_M if they do not introduce a permanent polarization into the molecule. Thus, anthrols and phenanthrols have identical R_F values, although anthracene and phenanthrene differ in resonance energy by about 8 kcal.

SUMMARY

The chromatographic behaviour of seventy-seven phenols and closely related substances has been studied in a reversed phase system (ethyl oleate against 25 % aqueous ethanol) and the relationships between their R_M values and their structures elucidated and discussed. Constitutive effects in chromatography were studied by means of a new method, the use of atomic ΔR_M parameters. The methods of calculating these parameters for carbon, hydrogen and oxygen are described and illustrated. By this method it is possible to calculate the R_M value of any of these compounds from the R_M value of phenol itself. It is shown that the ΔR_M parameters for CH groups (arbitrarily expressed for convenience as atomic ΔR_M(H) parameters) vary depending on their proximity to the aromatic ring. Similarly, the atomic ΔR_M(O) parameters in ethers are profoundly influenced by the nature of the substituent vicinal to the oxygen atom. These effects are considered to be produced by permanent polarizations due to the resonance effects of alkyl groups in the molecules under consideration.

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