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Comparison of Partition Chromatographic Parameters of Lipophilic Organic Electrolytes for Solvents of Various Donor–Acceptor Properties. VII. Discussion of the Correlation Method from the Viewpoint of the Additivity Principle

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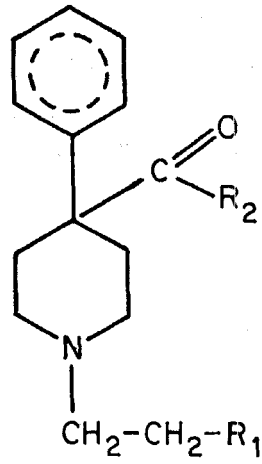
Abstract

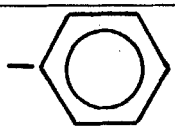
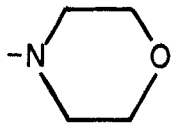
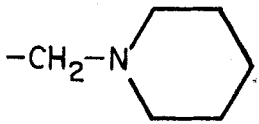
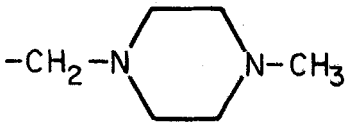
A graphical correlation method proposed by Rchrschneider and Littlewood for gas chromatography is applied to liquid–liquid partition of five homologous series of organic bases. The experimental data are interpreted in terms of the additivity of R_M values. Graphical estimation of partition coefficients of more complex molecules from group ΔR_{Ms} values and the correlation line of a simpler solute is described.

Eluotropic series of solvents, arranged for adsorption chromatography (*1*), liquid–liquid partition chromatography (*2*), and extraction (*3*) provide only a qualitative basis of choice of solvent systems for the separation of mixtures. A significant step forward in the characterization of solvents was the application of graphical correlation of the polarity of stationary phases by Rohrschneider (*4*) and Littlewood (*5*), which permitted a quantitative estimation of the solvent strength of various liquids. The method was applied to gas chromatographic analysis of various groups of solutes (*6*), the mathemathical discussion being provided by Karapetyants (*7*).

TABLE 1

Structures of the Compounds



	R_2				
R_1	$-CH_3$	$-C_2H_5$	$-C_3H_7$	$-C_4H_9$	$-C_6H_5$
	PhMe	PhEt	PhPr	PhBu	PhPh
	MMe	MEt	MPr	MBu	MPh
$-CH_2-N(CH_3)_2$	AMe	AEt	APr	ABu	APh
	PMe	PEt	PPr	PBu	PPh
	ZMe	ZEt	ZPr	ZBu	ZPh

In the earlier papers in this series (*8*, *9*) we applied the correlation method to estimate quantitatively the extraction strength of various solvents in liquid–liquid partition systems and in solubility studies (*10*) and the solvent effects in optical activity (*11*). Since solvation effects play an important role in liquid–liquid partition, it was found impossible to arrange a universal solvent series valid for all types of compounds (*8*, *9*).

The task of arranging a solvent series for a group of related solutes possessing a single polar (H-bonding) group is relatively simple; however, a more complex situation arises for two- and multifunctional solutes (*9*). To accumulate further experimental data in the present study, five homologous series of nitrogen bases were chromatographed in solvent systems of the polar solvent/aqueous buffer solution type. The compounds were synthesised by L. Rylski and co-workers (to whom the authors are indebted for sending the samples) at the Department of Chemical Technology of Drugs, Medical Academy, Gdańsk, Poland (*12*). The structures of the compounds and their notation are given in Table 1, the first symbol denoting the R_1 radical (Ph = phenyl, M = *N*-morpholylo, A = trimethylamino, P = methylpiperidino, Z = *N*,*N*-dimethylpiperazino) and the second denoting the R_2 radical (Me = methyl, etc.).

EXPERIMENTAL

In view of the lipophilic character of the bases in their un-ionized form, the extraction strength of the solvents was estimated from the R_M vs pH relationships which were determined using the "moist buffered paper method" with a controlled amount of aqueous buffer solution in the paper (0.5 ml/1 g of dry paper). (For details of the experimental technique, see Ref. *8a*.) The extraction strength of the solvents are characterized by the pH_i values at which the R_M vs pH line crosses the pH axis ($R_M = 0.0$, $R_F = 0.50$, which corresponds to equal amounts of the solute in the two liquid phases). The R_M vs pH relationships for the solvents investigated [Class B (*13*)] were found to be mostly linear, the slope being ~ 1.0 when $R_1 = C_6H_5$ (monoprotic bases), and then pH_i is simply related to the pK_a value of the base and the partition coefficient at suppressed ionization (*14*). For the remaining series of biprotic bases the R_M vs pH lines are often more steep, approaching the limiting slope of 2.0 in some cases, and then differences in pH_i values (horizontal distances) correspond to higher differences in extraction strengths (vertical distances). Some typical R_M vs pH relationships are illustrated in Figs. 1a–1c.

The pH_i values thus determined for various solvents of Class B (ethers,

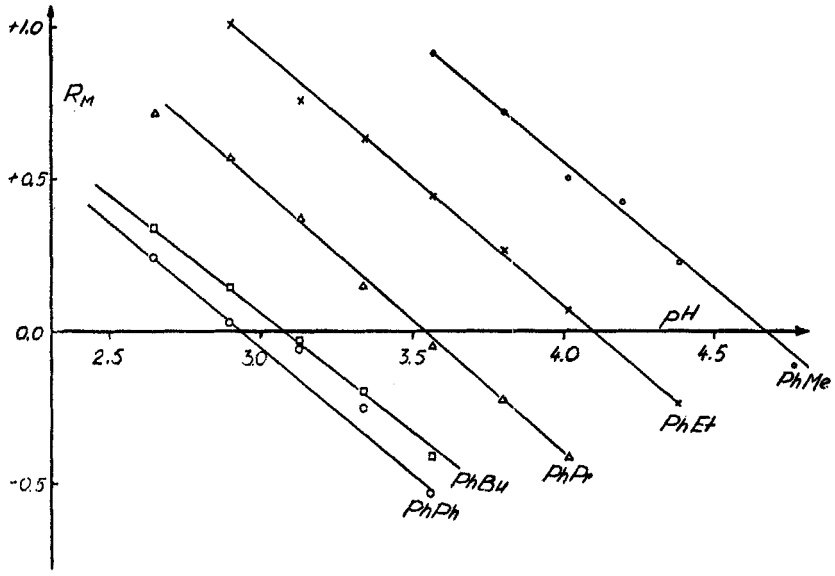


FIG. 1a. R_M vs pH relationships. Mobile phase: di-*n*-butyl ether.

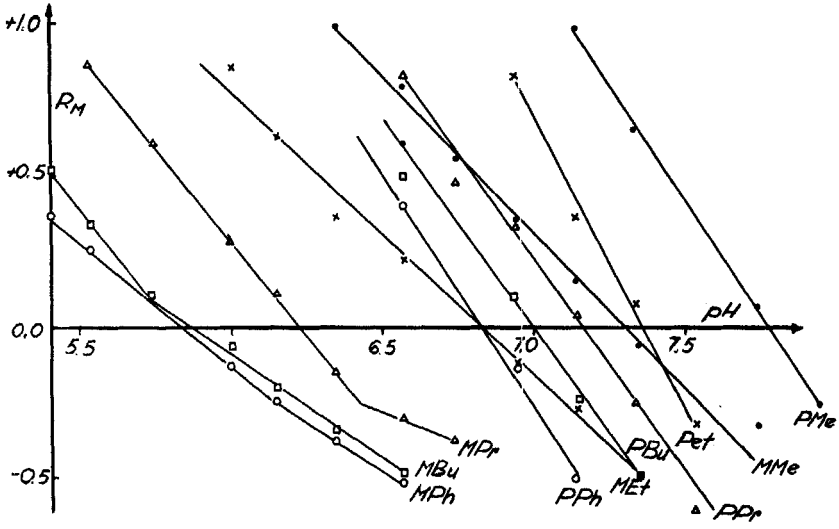


FIG. 1b. R_M vs pH relationships. Mobile phase: di-*n*-butyl ether.

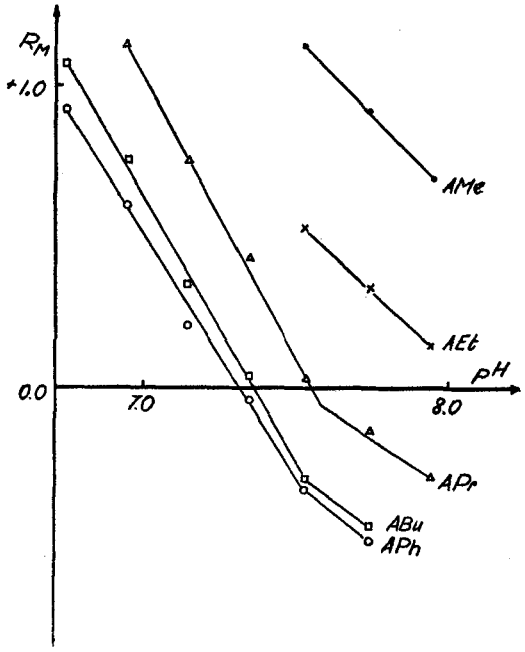


FIG. 1c. R_M vs pH relationships. Mobile phase: di-*n*-butyl ether.

ketones) are presented in Fig. 2 as pH_i–solvent spectra (solvents of Class A and especially N used as the mobile phase resulted in badly trailing spots). The solvents on the abscissa are arranged after Littlewood's method (*5*) in the following way. One of the bases in each homologous series is chosen as the reference solute, and the positions of the solvents are chosen so that the pH_i values of the reference solute are on a straight line of unit slope. The simple system requires only one reference solvent instead of the two solvents employed in previous papers (heptane and chloroform) (*8*), and the scale on the abscissa corresponds directly to ΔpH_i values, i.e., it is a quantitative measure of differences in the extraction strengths of individual solvents. Unfortunately, it was impossible to estimate the pH_i values for hydrocarbon solvents for which zero solvent strength could be assumed and therefore only relative values of extraction strengths can be estimated from the plots. The ΔpH_i values in the scale with one reference solvent are proportional to the values for the two-solvent reference system used in the previous papers (*8*), the recalculation factor being 0.01 [pH_i(heptane) − pH_i(chloroform)], or for R_M–solvent spectra, $0.01\Delta R_M$ (heptane − chloroform).

RESULTS AND DISCUSSION

The pH_i–solvent spectra are presented in Figs. 2–6. In most cases the points of the remaining four compounds follow correlation lines parallel to the line representative of the series chosen as the reference solute. Only minor scatter of the points is observed, due presumably to experimental errors and the contributions of other effects, such as adsorption on the liquid–liquid interface. However, the relative positions of the solvents is differentiated for the five homologous series, although the general sequence is similar for all cases, the extraction strength increasing in parallel with the polarity of the solvent (decreasing molecular weight of ethers and then ketones).

Comparison of the solvent characteristics for compounds from different series is presented in Fig. 7, where the solvents are arranged on the abscissa as in Fig. 3, taking PEt as the reference. The phenyl series of mononitrogen bases behaved in an individual manner owing to much lower pH_i values, and the pH_i values of PhEt reflect this individual behavior. It should be pointed out that the slopes of the correlation lines also depend on the slopes

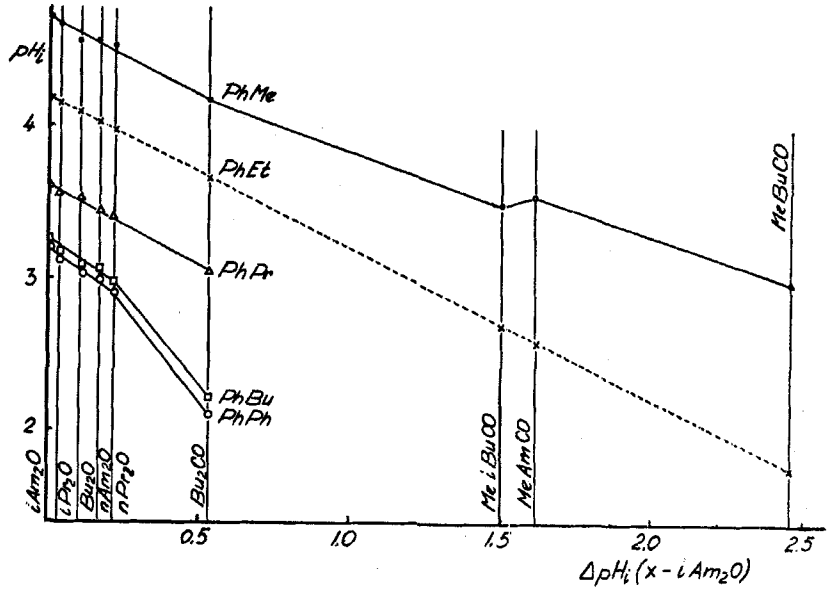


FIG. 2. pH_i–solvent correlations for the phenyl series.

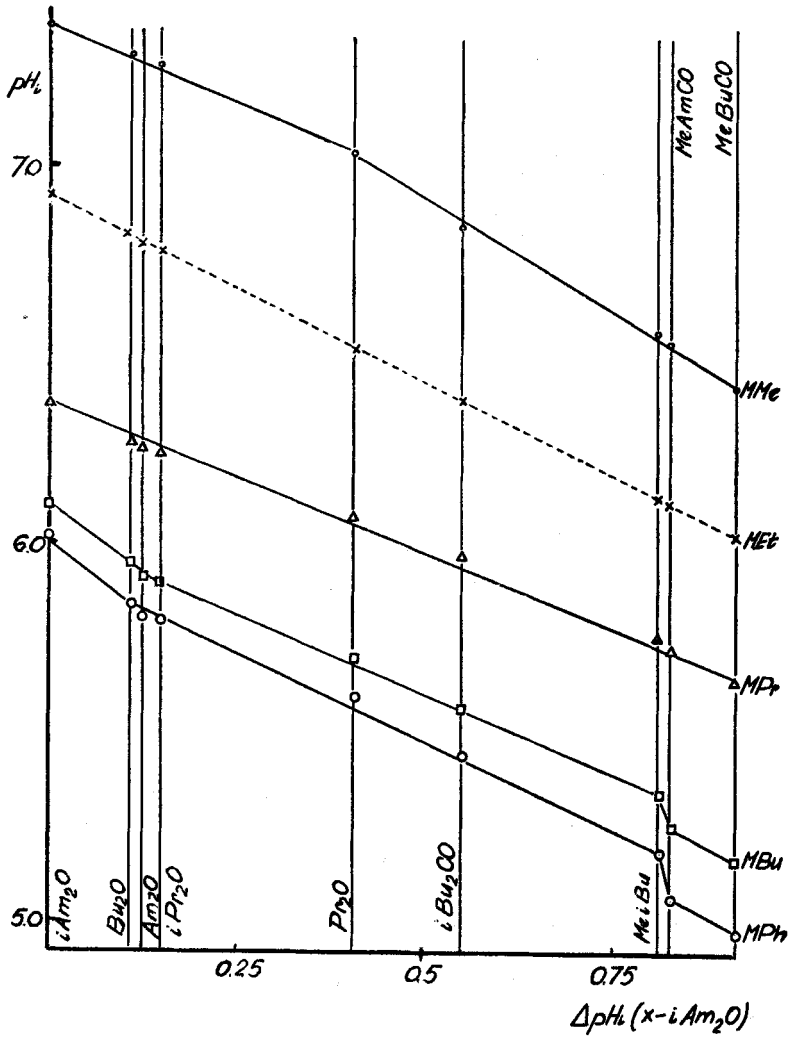


FIG. 3. pH_i–solvent correlations for the morpholine series.

of R_M vs pH lines, which in turn depend on the pK_a values of the bases; for instance, $\Delta pH_i = 1.0$ corresponds to $\Delta R_M = 2.0$ for double ionization and 1.0 for a monoprotonized base (corresponding to extraction coefficients increased by a factor of 100 and 10, respectively).

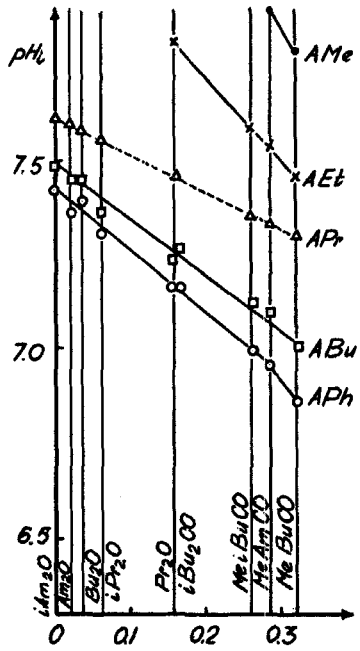


FIG. 4. pH_i–solvent correlations for the trimethylamine series.

It can be seen from Fig. 7 that in spite of differences in molecular structures of the five homologous series, the points of the representative compounds generally follow straight lines, which shows that the graphical classification of the solvents reflects semiquantitatively their increasing extraction strength for all the compounds investigated. Still better is the agreement within groups of related compounds, e.g., homologs.

The theoretical basis of the correlation method can be formulated in terms of the additivity concept, taking into account that the difference of ordinate values of a given compound for two solvents, e.g., heptane and chloroform, is the familiar ΔR_{Ms}value (*15*):

$$\Delta R_M(\text{heptane} - \text{chloroform}) = R_M(\text{chloroform}) - R_M(\text{heptane})$$

1. For alkyl groups the ΔR_{Ms} is usually low, approximating zero for a single methylene group (unless steric effects are brought into play) and therefore the points of homologs of a given series follow parallel correlation lines [strictly speaking, for solvents of widely differing polarities the

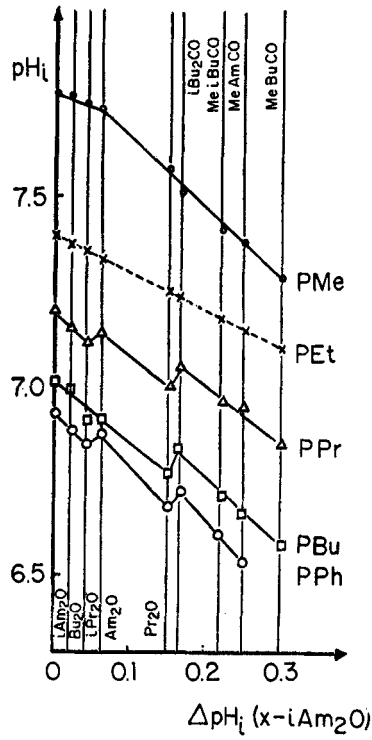


FIG. 5. pH_i–solvent correlations for the piperidine series.

$\Delta R_{Ms}(CH_2) \neq 0$ so that the lines tend to converge for more polar solvents (*8a*), for which $\Delta R_M(CH)_2$ values are lower] (Figs. 8a, 8b, and 8c). The ΔR_M(alkyl) value is mainly determined by the nature of the more polar associated liquid phase (e.g., water, formamide).

2. It can be expected that addition of an identical polar group to the molecule of a monofunctional solute should result in a linear R_M vs solvent correlation of a double slope; for instance (see Figs. 8c and 8d):

$$\Delta R_{Ms}(p\text{-dihydroxybenzene}) = 2\Delta R_{Ms}(\text{phenol})$$

or

$$\Delta R_{Ms}(2OH) = 2\Delta R_{Ms}(OH)$$

(assuming that the groups are in the same steric situation and that there is

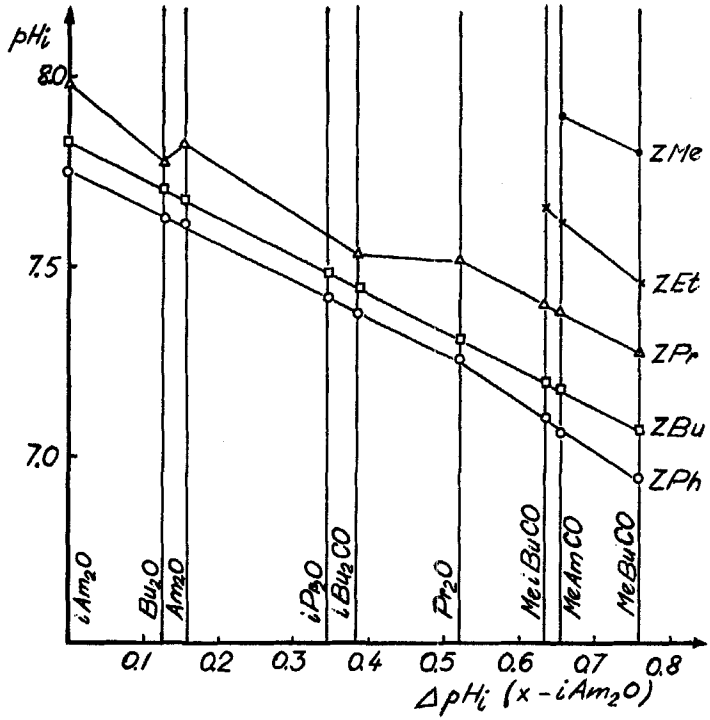


FIG. 6. pH_i–solvent correlations for the piperazine series.

no mutual interaction as, for instance, in *o*-dihydroxybenzene, where internal H-bonds can be formed).

3. If the second functional group is different from the first one but its interactions with the solvents (e.g., H-bonding properties) are similar

(e.g., —COOH and —OH, or —CO—CH_3, —CO—CH_3, and —O—CH_3), then for some solvents the ΔR_{Ms} values of the groups can be proportional, and then the R_M vs solvent correlations are approximately linear with points occasionally deviating from the straight lines for more selectively interacting solvents. The present data illustrate this point for functional groups containing a tertiary nitrogen atom.

4. As illustrated in previous papers (*8c*, *9*), the greatest discrepancies are obtained when compounds of different H-bonding properties are com-

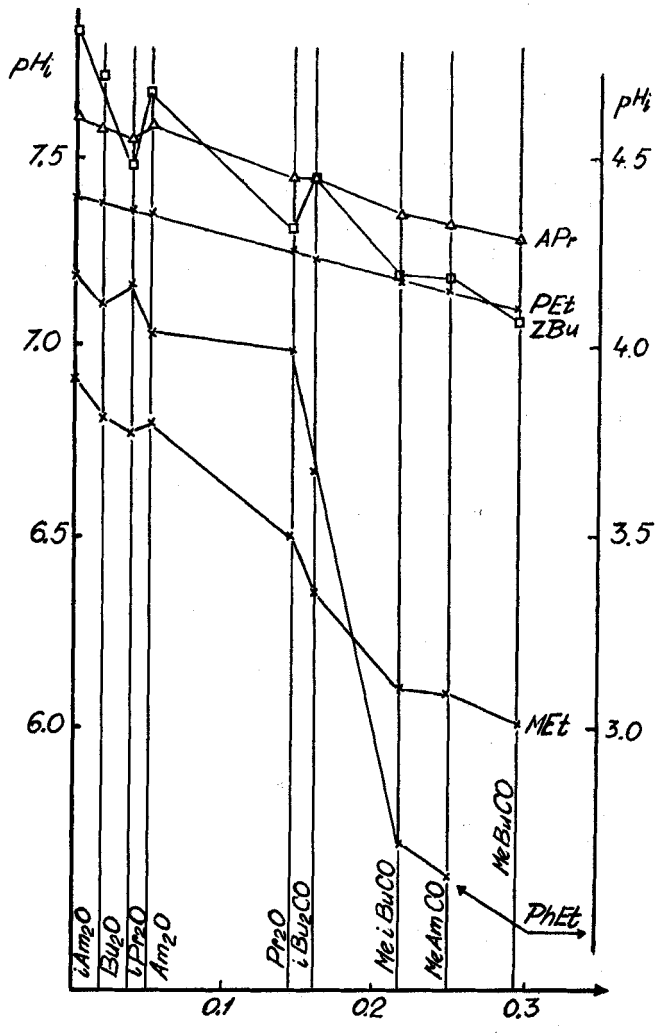


FIG. 7. pH_I–solvent correlations for the reference solutes from different homologous series.

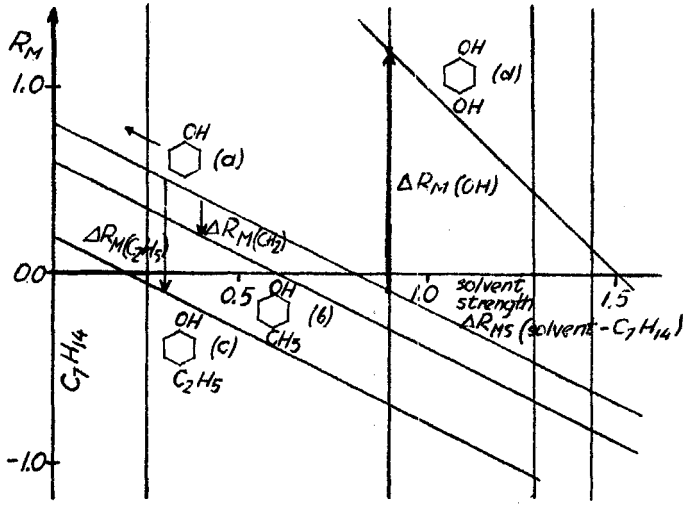


FIG. 8. R_M–solvent correlations for three homologues solutes (*a*, *b*, *c*) with a single polar group and an analogous bifunctional solute (*d*).

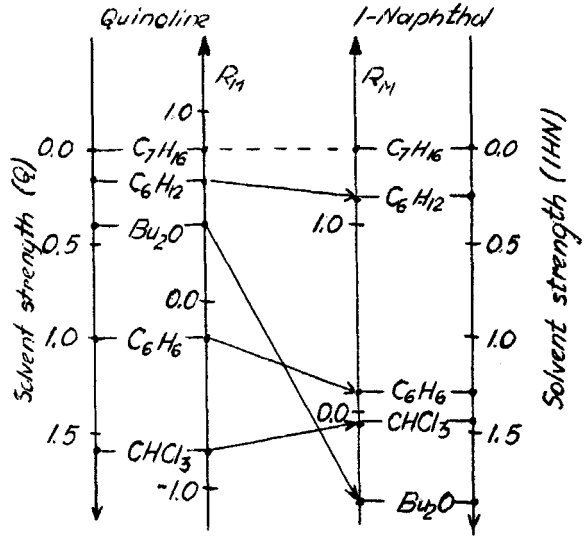


FIG. 9. Comparison of R_M values and solvent strength scales for quinoline (Q) and 1-naphthol (1HN).

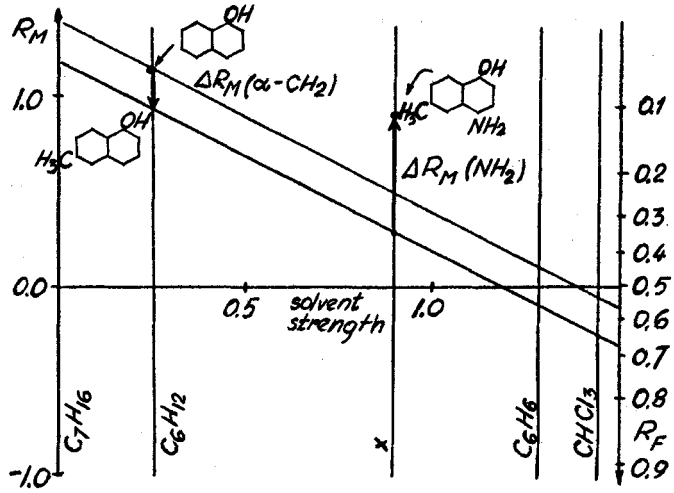


FIG. 10. Graphical estimation of the R_M value of a complex compound from its simpler analog.

pared. The changes are interpreted in terms of the additivity concept in Fig. 9, where the extraction strength scales are compared for quinoline and naphthol. The main changes in solvation interactions for the two compounds are due to replacement of an aromatic nitrogen atom by the $\rangle$COH grouping. The shifts of R_M values relative to *n*-heptane (ΔR_{Ms} values) are different for the individual solvents due to the specific H-bonding interactions, and thus the solvent strength scales are quite individual for the two reference solutes. Bifunctional solutes with functional groups of different types would require still different, intermediate characteristics of solvent strength.

As stated in previous papers in this series, it is thus impossible to devise a universal solvent strength scale which would enable the prediction of R_M values of solutes of a given molecular structure for any solvent. It seems, however, that at least a partial solution of the problem is possible. One of the ways, at least for two- or three-functional solutes, is to simplify the task by referring to a simple parent compound for which the R_M–solvent correlation line is known, and then add the ΔR_M values of alkyl and aryl groups or fused aromatic rings (characteristic for the polar phase) and the ΔR_{Ms} values of the remaining polar groups. For instance, in the case of 1-hydroxy-4-amino-6-methylnaphthalene chromatographed in aqueous systems, the graphical estimation of R_M value can be made by starting

from the correlation line of 1-naphthol (Fig. 10), drawing a parallel lower line at a distance of $0.2R_M$ units [$\Delta R_M(\alpha\text{-}CH_3)$ (*8a*, *15*)], and then adding the $\Delta R_M(NH_2)$ vertical vector for a given solvent [$\Delta R_M(NH_2)$ is pH-dependent in the acidic range, and $\Delta R_M(OH)$ in the alkaline range (*14*)].

An alternate method is also possible by starting from 1-aminonaphthalene as the parent reference compound. The method would require tabulating ΔR_{Ms} values for individual solvents and polar functional groups; it is more promising in static liquid–liquid partition equilibria where the complicating chromatographic effects are absent. To obtain more accurate values, it is necessary to take constitutional effects into account (*15–17*).

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