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INVESTIGATIONS OF THE RELATIONSHIPS BETWEEN MOLECULAR STRUCTURE AND CHROMATOGRAPHIC PARAMETERS

XI. EXTRACTION OF SOLUTES CONTAINING TWO OR THREE FUNCTIONAL GROUPS USING MIXTURES OF CHLOROFORM AND ELECTRON-DONOR SOLVENTS

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SUMMARY

The R_M *vs.* composition relationships of several solutes containing two or three functional groups (hydroxyl, amino and nitro groups), chromatographed in the system chloroform + electron-donor solvent–water, were compared with analogous plots obtained using simpler systems: cyclohexane + chloroform–water and cyclohexane + electron-donor solvent–water. For systems with tributyl phosphate as the donor solvent, the extraction strengths of the binary mixed solvent are significantly lower than estimated from the additivity principle. The discrepancies were different for different solutes.

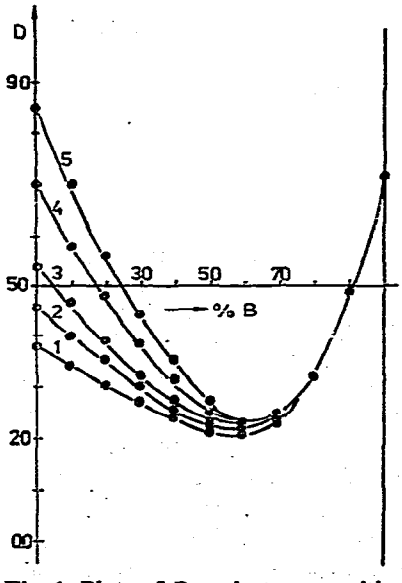
INTRODUCTION

The preceding paper in this series[1] discussed a mathematical model of extraction of monofunctional solutes with mixtures of proton-donor and electron-donor solvents. For the liquid–liquid partition of more complex solutes the model must be extended to include the formation of more complicated solvates. It should be pointed out that the theoretical description of liquid–liquid partition, based on analogies with gas–liquid systems[2,3], has so far been successful only for simple solutes, especially monofunctional ones. The theory of partition (and adsorption[4,5]) of solutes with two or more functional groups is still far from satisfactory, although the additivity principle frequently provides a good description of the molecular structure effects. The molecular interactions involved become still more complex in the case of mixed polar extractants. However, although non-polar and monofunctional solutes are frequently easily chromatographed in gas–liquid systems, most solutes analysed by high-performance liquid chromatography (HPLC) (such as drugs and their metabolites and other solutes of biomedical interest) are polyfunctional. It seems, therefore, that in spite of the complexity of the system, even a partial description of the structural effects would be of practical interest.

In the present study we investigated the extraction of several organic solutes with mixtures of chloroform and tributyl phosphate or diisobutyl ketone (A + B type), and compared it with extraction by simpler cyclohexane solutions of chloroform (N + A type) or electron-donor solvents (N + B type).

THEORETICAL

For the extraction of a monofunctional solute Z with mixtures of proton-donor (A) and electron-donor (B) solvents the formation of AZ and BZ solvates should be considered, as well as the mutual reduction of the extraction strength due to formation of AB solvates. For a bifunctional solute Z the formation of A_2Z, ABZ and B_2Z solvates should also be taken into account; in some cases the formation of the mixed ABZ solvate is enhanced, which gives rise to distinct synergic effects[6]. The mathematical description is somewhat simpler if some of the formation constants of the more complex solvates can be neglected. For instance, for a solute containing one group of AB type (*e.g.*, OH) and one of B type (*e.g.*, NO_2), the interaction of the latter group with the electron-donor solvents is relatively weak (no H-bonds formed). The effect of the appearance of the A_2Z term in eqn. 1 (see ref. 1) is shown in Fig. 1 for various values of K_{A_2Z}($K_{A_2Z} = 0$ corresponds to the case of monofunctional



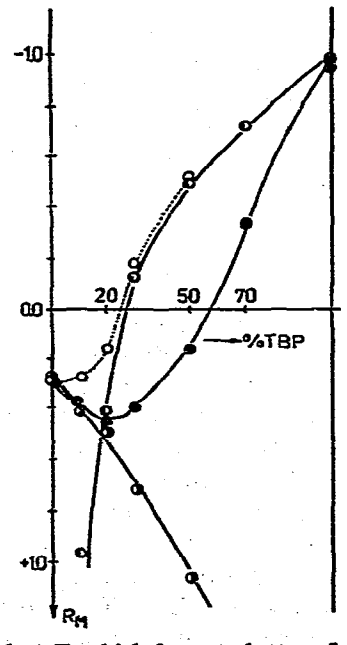


Fig. 1. Plots of D against composition, calculated from eqn. 1, for solute Z, which forms solvates of the types AZ, A_2Z and BZ with the solvents A and B. The values of K_{A_2Z} are: 0 (1), 0.05 (2), 0.1 (3), 0.2 (4) and 0.3 (5). $K_{AB} = 1$, $K_{BZ} = 20$, $K_{AZ} = 3$, $k_d = 1$.

Fig. 2. R_M values of 2,4-dinitrophenol plotted against the concentration (%, v/v) of chloroform and tributyl phosphate in the developing solvent: ◐, cyclohexane + TBP; ◑, cyclohexane + chloroform; ○, points calculated from the additivity principle from the two systems; ●, chloroform + TBP.

solute discussed in ref. 1). The formation of a higher solvate causes the appearance of a lower minimum on the log D *vs.* composition plot.

$$D = k_{d(Z)}(1 + K_{AZ}C_A + K_{A_2Z}C_A^2 + K_{BA}C_B) \quad (1)$$

Some information on the molecular interactions involved can be obtained by comparing the log D ($-R_M$) *vs.* composition plots of the A + B systems with those obtained for the two simpler systems (N + A, N + B) produced by dilution of either of the polar solvents with a non-polar diluent, N[7]. When the A–B interactions are weak, the donor and acceptor properties of the A + B mixture should be additive[8] so that, to a first approximation, for 1:1 complexes:

$$D_{AB} = D_A \cdot \%A \cdot 0.01 + D_B \cdot \%B \cdot 0.01 \quad (2)$$

where D_A, D_B and D_{AB} are, respectively, the distribution coefficients obtained with pure A and B and with the A + B mixtures*. For simpler mixtures N + A and N + B, taking into account that $D_N \ll D_A$, D_B:

$$D_{NA} \approx \text{const} + D_A \cdot \%A \cdot 0.01 \quad (2a)$$
$$D_{NB} \approx \text{const} + D_B \cdot \%B \cdot 0.01 \quad (2b)$$

when $D_N \approx 0$, the constant may be neglected and the terms of eqn. 2 can be determined from the log D *vs.* composition relationships (eqns. 2a, 2b) obtained for the N + A and N + B systems, provided that the A–B interactions (formation of AB solvates) are not sufficient to cause partial cancellation of the donor and acceptor properties of the mixed solvent A + B.

EXPERIMENTAL

Whatman No. 4 paper strips were impregnated with McIlvaine's buffer solution (pH 6.5) and blotted between two sheets of filter paper. The solutes, 2,4-dinitro-1-naphthol, 2,4-dinitrophenol and 2-aminopyridine were spotted as 0.1% solutions in chloroform. The paper strips were then dried to 50% humidity and transferred to all-glass tanks for descending development[10]. 2-Aminophenol was chromatographed in a similar manner, the paper being impregnated with distilled water. 2-Aminopyridine was detected under UV light and the phenols by spraying the strips with a saturated solution of $NaHCO_3$ and coupling with bis-diazotized benzidine. The theoretical curves (Fig. 1) for various values of the solvation constants were calculated using an Algol program for the complex functions by assuming that $C_A = C_A^0 - C_{AB}$ and $C_B = C_B^0 - C_{AB}$, and substitution into eqn. 1 of the formula for C_{AB} given in eqn. 3 of ref. 1.

Two solvents were used as the electron-donor components of the mixed mobile phases: tributyl phosphate (TBP, strong electron-donor properties) and diisobutyl ketone (weak electron-donor properties, K_{AB} value smaller by an order of magnitude than that of TBP[1]). R_F values are given in Table I.

* The equation has been verified for numerous cases of gas–liquid partition chromatography; additivity of log D values is equally frequent: *cf.* discussion in ref. 9.

TABLE I

$R_F \times 100$ VALUES OF SOLUTES FOR VARIOUS CONCENTRATIONS OF ELECTRON-DONOR AND PROTON-DONOR COMPONENTS IN THE DEVELOPING SOLVENT

Type	*% (v/v)*	*2,4-Dinitro-phenol*	*2,4-Dinitro-1-naphthol*	*2-Amino-pyridine*	*2-Amino-phenol*
Cyclohexane + chloroform	50	8	12	8	12
	70	16	22	17	20
	80	24	26	20	22
	90	30	35	27	24
	95	32	40	29	25
	100	34	44	32	26
Cyclohexane + tributyl phosphate	0	—	—	—	8
	5	6	8	—	45
	10	10	28	6	75
	20	28	66	10	86
	30	56	80	26	90
	50	75	90	38	—
	70	84	—	44	—
	100	90	—	—	—
Chloroform + tributyl phosphate	0	34	44	32	26
	5	32	38	28	45
	10	30	26	24	60
	20	26	22	20	72
	30	28	25	22	80
	50	40	62	26	90
	70	66	90	40	—
	100	90	—	—	—
Cyclohexane + diisobutyl ketone	20	—	—	—	18
	30	—	—	—	26
	50	8	8	8	46
	60	11	12	11	54
	70	13	16	14	62
	80	15	18	16	66
	90	17	20	17	72
	100	20	24	18	76
Chloroform + diisobutyl ketone	0	34	44	32	26
	5	32	38	28	34
	10	30	34	26	40
	20	28	28	22	46
	30	24	24	20	50
	50	20	18	15	54
	70	20	20	16	62
	100	20	24	18	76

RESULTS AND DISCUSSION

Figs. 2–5 represent the R_M *vs.* composition plots obtained for partition systems with TBP as the electron-donor component. The diagrams are analogous to plots illustrating the vapour pressure of binary mixtures in accordance with Nernst's law. The half-filled circles correspond to the two simpler systems, cyclohexane + chloroform (%$CHCl_3$ = 100 − %TBP) and cyclohexane + TBP. The open circles and the

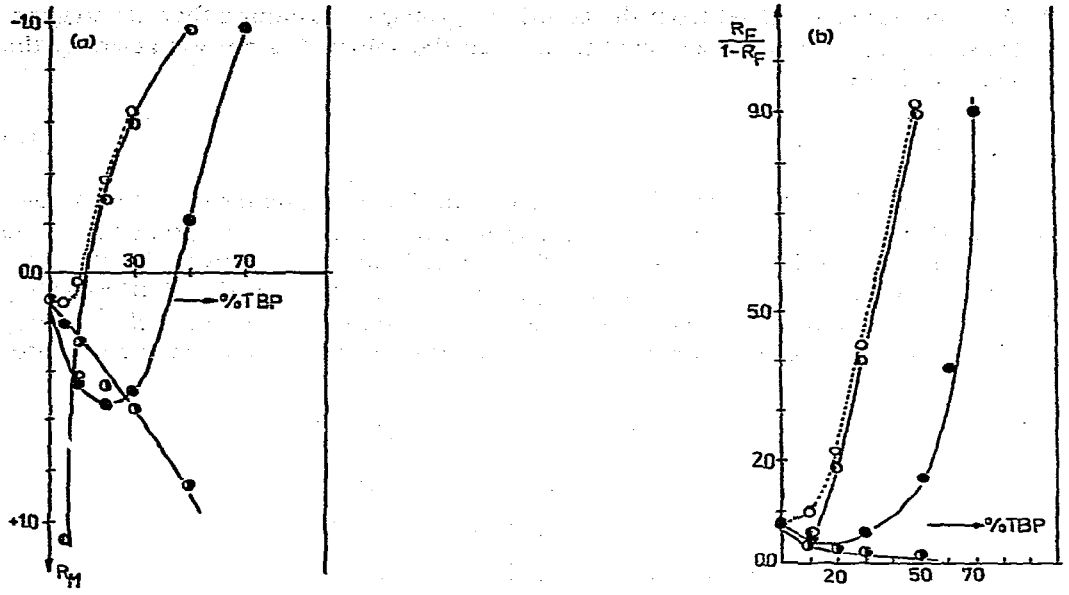


Fig. 3. (a) R_M values of 2,4-dinitro-1-naphthol plotted against the concentration (%, v/v) of chloroform and tributyl phosphate; solvents as in Fig. 2. (b) As in (a) but plotted in the co-ordinate system $R_F/(1 - R_F) = Dr = 1/k'$, where $r = v_{org}/v_w$; *cf.*eqns. 2, 2a and 2b.

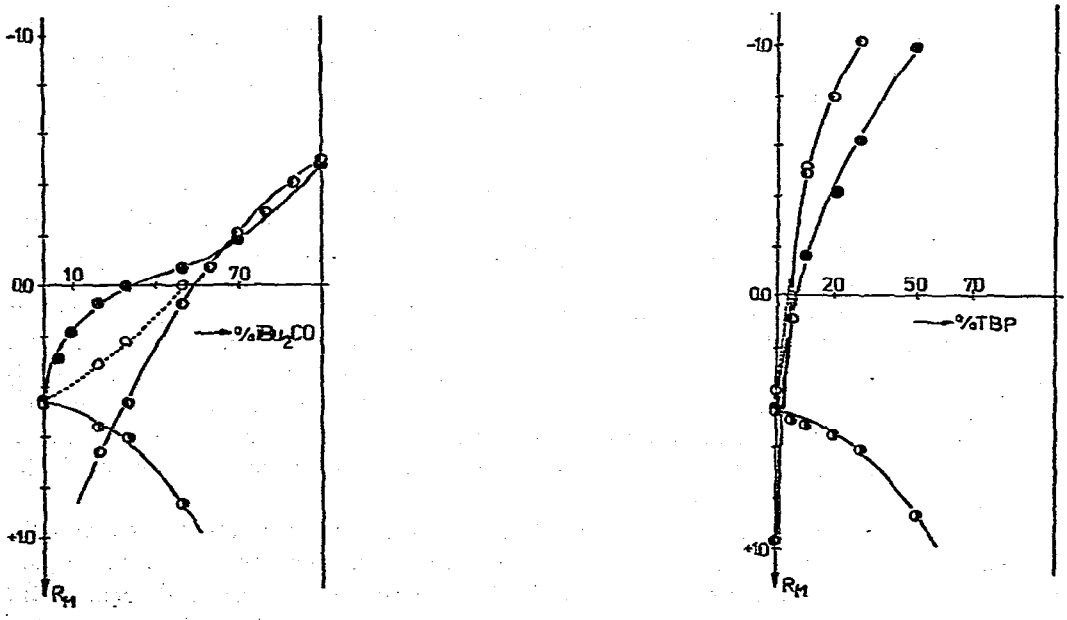


Fig. 4. R_M values of 2-aminopyridine plotted against the concentration (%, v/v) of chloroform and tributyl phosphate. Solvents as in Fig. 2.

Fig. 5. R_M values of 2-aminophenol plotted against the concentration (%, v/v) of chloroform and tributyl phosphate. Solvents as in Fig. 2.

dashed line were calculated from the additivity principle: assuming that the constant in eqns. 2a and 2b can be neglected (*i.e.*, when the solute Z is not extracted by the diluent) we have

$$D_{AB}^{theoret.} \approx D'_A + D'_B \tag{3}$$

where D'_A and D'_B denote distribution coefficients (c_{org}/c_w) obtained for the simpler systems (N + A and N + B, respectively) at compositions corresponding to the binary solvent A + B for which the $D_{AB}^{theoret.}$ value is to be calculated. For instance, distribution coefficients obtained with organic phase containing 40% TBP and 60% $CHCl_3$ (D_{AB}) should be approximately equal to the sum of those obtained with 60% $CHCl_3$ in cyclohexane (D'_A) and 40% TBP in cyclohexane (D'_B). In terms of chromatographic parameters:

$$R_{M(AB)} = \log k'_{AB} = -\log D_{AB}r = -\log (D'_A r + D'_B r) =$$

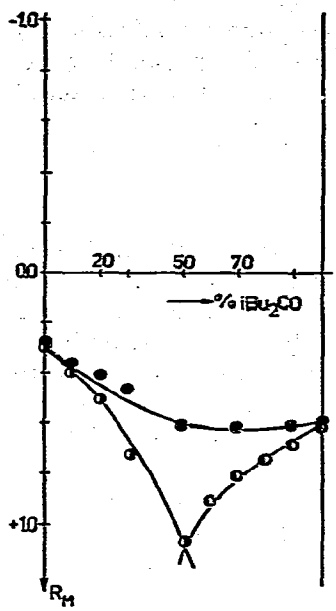
$$= -\log \left(\frac{R_{F(A)}}{1 - R_{F(A)}} + \frac{R_{F(B)}}{1 - R_{F(B)}} \right) \tag{4}$$

where $r = v_{org}/v_w$ = constant and k' is the capacity factor.

In Fig. 3b the partition parameters are given as Dr values, so that the additivity principle is directly apparent; in the remaining plots the ordinate is equivalent to log $Dr = -R_M$, which is convenient in extraction studies. Although for monofunctional solutes, as stated above, $D'_A \approx D_A \cdot \%A \cdot 0.01$ and $D'_B \approx D_B \cdot \%B \cdot 0.01$, for polyfunctional compounds more complex D' *vs.* composition plots may be obtained; in fact, some deviations from linearity are observed for the two simpler systems (half-filled circles) in Fig. 3a. The filled circles denote experimental data obtained for the A + B system, chloroform + TBP. It should be pointed out that TBP, in spite of its low molar concentrations (for pure solvents, $M_{CHCl_3} = 12.4$; $M_{TBP} = 3.6$) is a much stronger extractant of the phenols.

For all solutes the relationships obtained experimentally for the A + B system are markedly lower than the theoretical (dashed) lines predicted from the additivity principle. In some cases (Fig. 3a) the extraction coefficients are even decreased by one R_M unit, i.e., by one order of magnitude. The addition of TBP to the developing solvent should cause stronger extraction owing to the high extraction ability of the solvent. In fact, however, the extraction at first decreases because the relatively small amounts of TBP are bound by the excess chloroform molecules. Only at higher concentrations of TBP does its strong affinity for the phenol group predominate in the molecular interactions and extraction into the organic phase increase. A similar relationship is observed for 2-aminopyridine, although the affinity of TBP for the amino group is weaker (Fig. 4).

In the system chloroform + diisobutyl ketone, the interactions between the solvents are weaker and the R_M *vs.* composition relationships are more regular (Figs. 6–9). Except for 2-aminophenol (Fig. 9), it was not possible to determine the theoretical curves because the partial plots for the N + A and N + B systems could not be determined in wider composition ranges. It was possible to estimate, however, that for this system the A–B interactions play a less significant role, and that the extraction power is contributed by the two solvents roughly in accordance with the



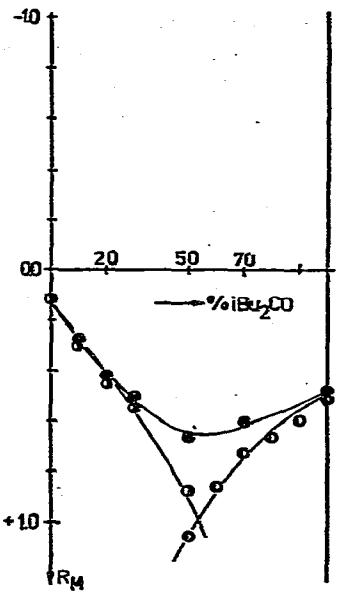
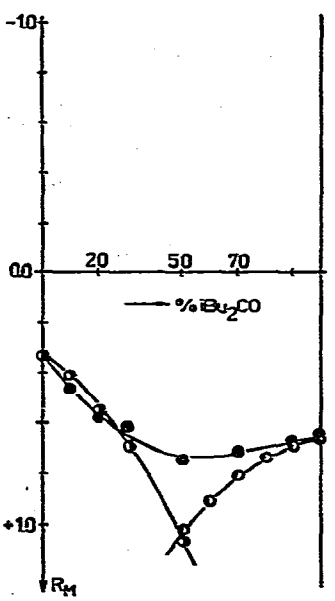


Fig. 6. R_M values of 2,4-dinitrophenol plotted against the concentration (%, v/v) of chloroform and tributyl phosphate in the developing solvent: ◐, cyclohexane + diisobutyl ketone; ●, chloroform + diisobutyl ketone.

Fig. 7. R_M values of 2,4-dinitro-1-naphthol plotted against the concentration (%, v/v) of chloroform and tributyl phosphate. Solvents as in Fig. 6.



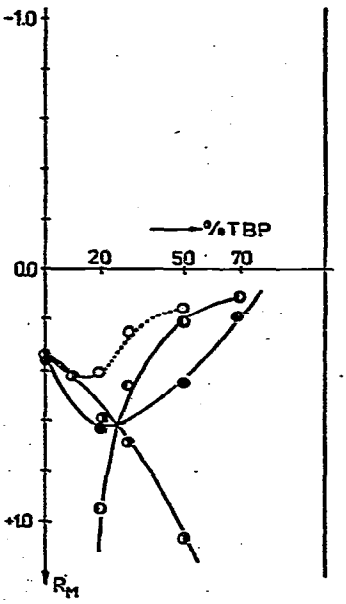


Fig. 8. R_M values of 2-aminopyridine plotted against the concentration (%, v/v) of chloroform and tributyl phosphate. Solvents as in Fig. 6.

Fig. 9. R_M values of 2-aminophenol plotted against the concentration (%, v/v) of chloroform and tributyl phosphate. Solvents as in Fig. 6.

additivity principle. For 2-aminophenol, distinct positive deviations from additivity are observed (Fig. 9) at higher concentrations of chloroform, which could be explained by the formation of a mixed ABZ solvate, or by a tendency to formation of B_2Z solvate or by specific changes of the activity coefficients.

CONCLUSIONS

The extraction strength of mixed interacting solvents can be estimated from the additivity principle only for certain types of mixture, particularly those in which the interactions are relatively weak. The deviations from additive behaviour depend on the solute. The patterns of molecular interactions involved, even assuming a simplified molecular mechanism, become very complex in the case of solutes with several functional groups, *i.e.*, those of special interest in HPLC. A better insight into the mechanism requires the determination of at least some of the solvation constants involved.

Comparison of the results obtained for monofunctional solutes[1] with those presented here shows that the chromatographic behaviour of polyfunctional solutes is more sensitive to molecular interactions in the chromatographic system.

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