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On the Parallelism of Solubility and Chromatographic Behaviour in Partition Chromatography. I. Chromatography of Some Barbiturates in the System: Ethyl Ether/Dimethyl Sulphoxide + Water

O analogii rozpuszczalności i parametrów chromatograficznych w chromatografii podziałowej. I. Chromatografia barbiturowców w układzie: eter etylowy/dwumetylosulfotlenek + woda

О параллелизме растворимости и хроматографического поведения в распределительной хроматографии. I. Хроматография барбитуратов в системе: этиловый эфир/диметилсульфоксид + вода

The choice of optimal chromatographic systems aims at an appropriate distribution of the spots along the chromatogram. In partition chromatography this is effected by the control of the partition coefficients of the solutes between the two liquid phases. The methods most frequently employed for the regulation of partition coefficients involve variation of the composition of the mixed phase, or in the case of lipophilic organic electrolytes, variation of the pH of the aqueous phase. Assuming certain simplifications and a constant composition of one of the phases, it may be expected that a variation of the composition of the other phase (or its pH), changing the partition coefficient of the solute, entails also a parallel change of its solubility in the second phase (cf. [1]). This rule can only be considered as an approximation for the same reasons for which the partition coefficient usually differs from the ratio of solubilities of the solute in the two liquid phases [2]. Nevertheless, it seems that chromatographic data may often provide qualitative if not semi-quantitative information concerning the effect of the composition

of one of the phases on the solubility of the solute. This conclusion is substantiated, among others, by the linear R_M vs. pH relationship of organic electrolytes [3] (slope $+1$ or -1, depending on the basic or acidic character of the electrolyte); similar variation of solubility of electrolytes with pH is known from literature and has been utilized for the determination of ionization constants of weak electrolytes [4]. It should be pointed out that in investigations of this type the coefficient R_M is more directly analogous to partition and solubility, as in the idealized case (partition coefficient equal to ratio of solubilities of the solute in the two phases):

$$R_M = \text{const} - \log K = \text{const'} \pm \log C_s$$

where K is the partition coefficient (c_{org}/c_w, at equilibrium) and C_s is the solubility of the solute in one of the phases (w/v concentration units).

In the present communication we shall report a parallelity of R_M values and solubilities found for a solvent system of the type: ethyl ether/dimethyl sulphoxide $+$ water. The main purpose of the work was to determine the solubilities of two barbiturates (veronal, luminal) in dimethyl sulphoxide-water mixtures, and to elaborate a rapid method of chromatographic analysis of barbiturates. The advantages of dimethyl sulphoxide as the fixed phase have been reported earlier by Swedish workers, e. g. [5]; the possibility of controlling the migration rates by addition of water to dimethyl sulphoxide has also been reported, linear relationship being found between the R_M value and the volume composition of the mixed phase [6]. Mixed solvents are not only interesting when modifying the solubility of solutes purified by crystallization, but also in separation methods depending on fractional precipitation.

The problem of solubility of substances in mixed solvents has been recently discussed by M i k h a i l o v [7, 8] (cf. also [9]) who has also reviewed the literature on the subject. It follows from his considerations that in the idealized case, the logarithm of the solubility should be linearly dependent on the composition of the mixed phase, provided that both the concentration of the saturated solution and the composition of the mixed solvent are expressed in m o l e f r a c t i o n s (similar remark has been made by K e m u l a, B u c h o w s k i and T e p e r e k in relation to partition coefficients, cf. [10]). For practical reasons this concentration is rarely used, the solubility of the substance being expressed in weight per volume scale, and the composition of the mixed solvent in volume fractions. In these cases it may be expected that the deviations from linearity caused by the change of the concen-

tration scale will be more pronounced when the difference of the molar volumes of the component solvents is greater, and/or in the case of marked solubility of the solute in one of the two solvents. Additional deviations from linearity can be contributed by non-ideality of the solvent mixture, and, perhaps, by stronger interaction of the solute with one of the component solvents. Therefore, a strictly linear relationship between the solubility of the substance (in w/v concentration) and the volume composition of the mixed solvent can be only rarely expected.

EXPERIMENTAL

In order to give better characteristics of the purity of the solvents used, their refraction coefficients and densities have been measured (Table 1).

Table 1. Physico-chemical data of solvents used

Solvent	d_{20} measured	d_{20} reported	n_D^{20} measured	n_D^{20} reported
DMSO	1.100	1.100	1.4782	1.4783
EG	1.1139	1.1136	1.4290	1.4318
Ethyl Ether	0.7180	0.7135	1.3540	1.3528

Whatman No 1 paper strips were used, 5×23.5 cm, cut at right angles to the machine direction and impregnated with polar liquids; 1 gram of dry paper contained ca. 0.5 ml of stationary phase, which was controlled by weighing (DMSO + water mixtures, cf. [6]; the concentration of DMSO approximately doubled as a result of drying), or by the concentration of the non-volatile liquid in acetone (DMSO + glycol mixtures).

The barbiturates were spotted as solutions in DMSO, the chromatograms developed with ethyl ether, by the descending technique, in glass tanks $6 \times 14 \times 21$ cm. The spots of the barbiturates were revealed by spraying with a modified mercury-diphenylcarbazone reagent [11]*, and suspending in ammonia vapours.

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* 0.5 g of diphenylcarbazone dissolved in 20 ml of 90 % ethanol, 1 ml of 5 % HgCl₂ and 5 drops of 30% acetic acid added, the solution diluted to 30 ml with 95% ethanol, and finally diluted with 4 volumes of ethanol.

The results of the chromatographic experiments are presented in Figs. 1 and 2 as R_F and R_M vs. volume composition plots (R_M values were calculated according to B a t e - S m i t h and W e s t a l l [12], i. e.,

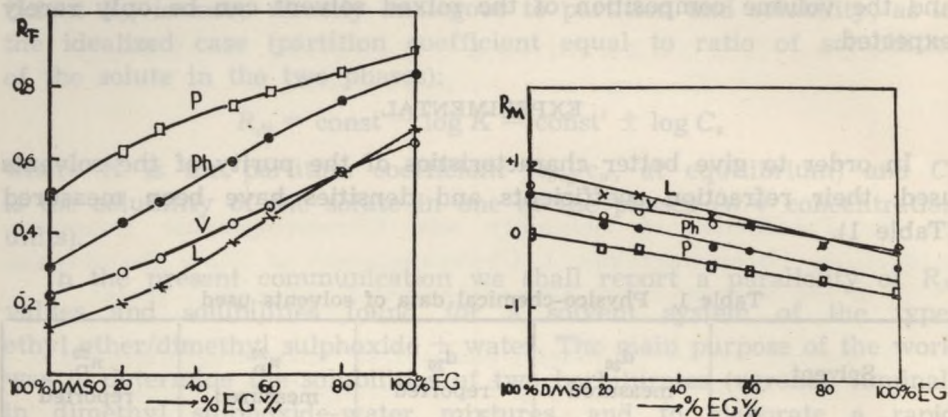$$R_M = \log \frac{1 - R_F}{R_F} = - \log Kr,$$ where r is the ratio of volumes of the non-polar and polar phase).

Fig. 1. a — R_F vs. composition plot; mobile phase: ethyl ether; stationary phase: mixtures of DMSO and ethylene glycol (EG); b — same data, R_M vs. composition plot; P — prominal, Ph — phanodorm, V — veronal, L — luminal

The solubilities of two barbiturates, veronal and luminal, in DMSO-water mixtures of various composition were also determined. The substances were shaken for 10 min. with the mixed solvents and
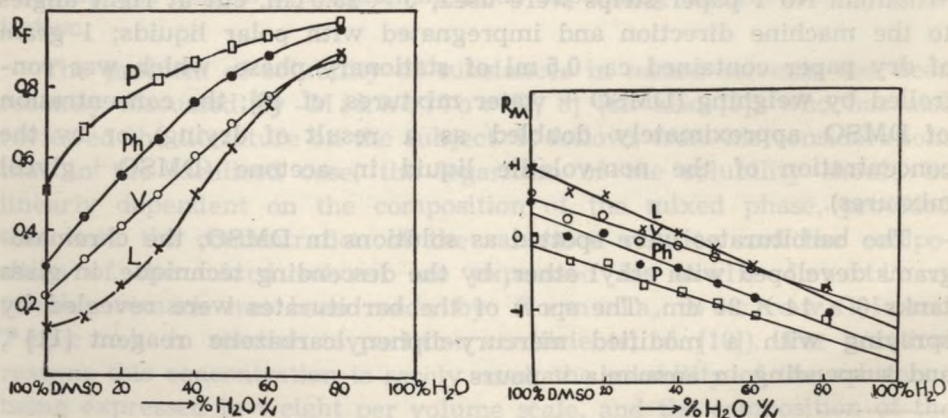

Fig. 2. R_F and R_M vs. composition plots. Stationary phase: mixtures of DMSO and water; for symbols cf. Fig. 1

kept in a thermostat (20°C) for 24 hours. After centrifuging the solid residue, the concentration of the saturated solution was determined by titration with 0.1 N NaOH using phenolftalein as indicator (cf. Polish

Table 2. Solubilities of veronal and luminal in mixtures of water and DMSO

VERONAL		LUMINAL	
v/v % DMSO	C_s g/100 ml	v/v % DMSO	C_s g/100 ml
0	0.66	0	0.116
2	0.662	5	0 230
5	0.736	10	0.230
10	0.810	19	0.279
20	0.957	33.3	1.045
30	1.147	40	1.440
37.7	1.510	50	4.528
45	2.484	55	9.752
50	3.818	70	53.173
60	9.200		
65	14.168		
70	13.800		

Pharmocopea III). The solubility data obtained are given in Table 2 and presented graphically as log C_s — volume composition plots (Fig. 3).

DISCUSSION AND RESULTS

1. Solvent systems of the type: ethyl ether/DMSO + glycol, or ethyl ether/DMSO + water, in view of their marked selectivity, are suitable for the rapid identification and analysis of the substances investigated (preparation of paper strips and development takes ca. 1 hour). Taking

into account the possibility of elution of DMSO from the paper, it seems
that the optimal results are obtained with paper strips impregnated
with DMSO containing 20—30 % of glycol, or 10—20 w/v % of water.
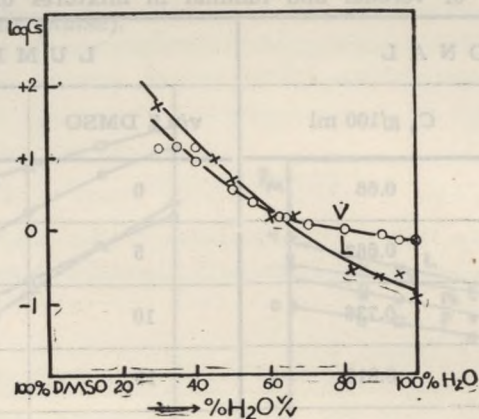

Fig. 3. Solubilities of veronal and luminal in water-DMSO mixtures. Ordinate:
logarithm of solubility (g/100 ml). Abscissa: volume composition of mixed solvent;
for symbols cf. Fig. 1

2. Approximately linear relationship between the R_M value and the
volume composition of the stationary phase was found (cf. [6]). Slight
positive deviations are observed for mixtures rich in DMSO, e. g., con-
taining ca. 10 % of water. These deviations are probably caused by
elution of DMSO from the paper by the mobile solvent. Only larger
proportions of water or ethylene glycol cause the formation of a two-
-phase system (Fig. 4). These deviations could be also contributed by
non-ideality of the DMSO-water and DMSO-glycol mixtures. R_F coef-
ficients are related to the composition of the mixed stationary phase
in a more complex way.

3. A parallelity of R_M values and logarithm of the solubility of the
solutes in the fixed phase is evident (compare Fig. 3 and Fig. 2 b).
A decrease in the solubility of the substance in the stationary phase,
brought about by addition of water (Fig. 3), causes also a decrease
in the R_M value (Fig. 2 b), i. e., a shift of the partition equilibrium in
favour of the mobile phase (Fig. 2 a). R_M — composition lines for both
substances have slopes similar to the corresponding log C_s — composition
lines, in the range of highest accuracy of both series of experiments,
that is to say, for mixtures containing 40—70% of water; moreover, on
both diagrams (Figs. 2 a and 3) the two lines cross at water content
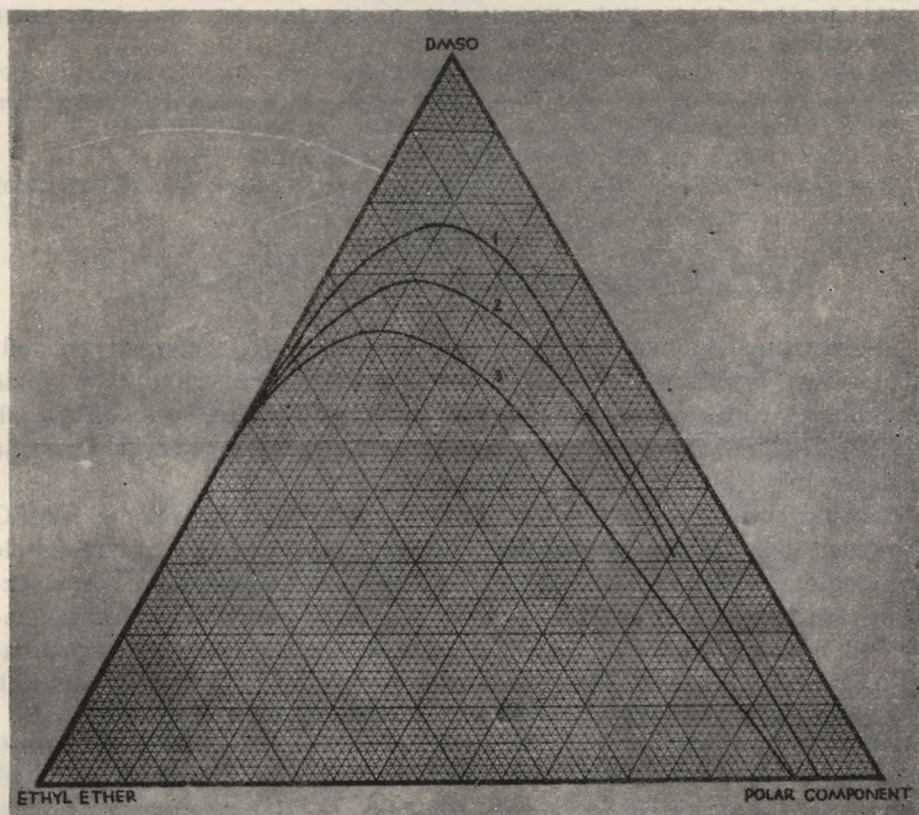
Fig. 4. Immiscibility areas of water (1), glycerol (2) and ethylene glycol (3) with ethyl ether and DMSO

in the fixed phase of ca. 60% (in view of the similar molecular weight of the two solutes, their solubilities could be expressed simply in gram/volume concentration scale).

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STRESZCZENIE

Stwierdzono liniową zależność współczynnika R_M czterech pochodnych kwasu barbiturowego od zawartości wody (lub glikolu) w fazie nieruchomej, której drugi składnik stanowił dwumetylosulfotlenek (DMSO). Badane układy wykazywały dość dobrą selektywność i nadają się do szybkiej analizy chromatograficznej.

Rozpuszczalność dwóch substancji w mieszaninach wody i DMSO (wyrażona jako logarytm stężenia roztworu nasyconego) zmieniała się równolegle ze współczynnikiem R_M, zgodnie z oczekiwaniami teoretycznymi; nachylenie linii $log\ C_s$ — skład v/v, było bardzo zbliżone do nachylenia odpowiednich linii R_M — skład rozpuszczalnika mieszanego i nawet przecięcie linii dla obu substancji przypadało na obu wykresach przy zbliżonych stężeniach wody w fazie nieruchomej (ryc. 2 b, 3).

РЕЗЮМЕ

Была найдена линейная зависимость коэффициентов R_M четырех производных барбитуровой кислоты от количества воды (или гликола) в стационарной фазе, содержащей диметилсульфоксид (DMSO) в качестве второго компонента. Исследованные системы обладают довольно хорошей селективностью и пригодны для быстрого хроматографического анализа.

Растворимость двух веществ в смесях воды и DMSO (выраженная как логарифм концентрации насыщенного раствора) изменялась параллельно коэффициенту R_M, в согласии с теоретическими рассуждениями; наклон линии $log\ C_s$ — состав очень близок наклону соответствующих линии R_M — состав смешанного растворителя и даже пересечение линии для обоих веществ происходит при близких концентрациях воды в неподвижной фазе (рис. 2б, 3).