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Comparison of Partition Chromatographic Parameters of Lipophilic Organic Electrolytes for Solvents of Various Donor–Acceptor Properties. IV. Quinoline Bases in Systems of the Type Organic Solvent/Formamide + Formic Acid

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Summary

The solvent power of a number of weakly polar solvents is compared for systems of the type organic solvent/formamide solutions of formic acid, using a method elaborated by Rohrschneider for gas-liquid partition chromatography. The characteristics of the weakly polar solvents, determined mainly by their electron acceptor properties, were found to be similar to those obtained in the preceding work for systems containing McIlvaine's buffer solution (Na_2HPO_4 + citric acid) as the polar phase. The solvation of the solutes (quinoline bases) by the polar phase was found to be related to their pK_A values, both in the case of aqueous and formamide systems. Steric hindrance of solvation and molecular size effects were observed, the latter being much more strongly pronounced for aqueous systems.

In the preceding paper of this series (*1*), partition parameters of some quinoline bases were compared for a number of systems of the type weakly polar solvent/water. Assuming one of the bases as the reference solute, the results were presented graphically after the Rohrschneider and Littlewood method (2); in this way, characterization of 20 weakly polar solvents with respect to their solvent power was obtained, the latter being mainly determined by their

proton donor properties, in view of the electron donor character of the solutes studied.

It seemed interesting to investigate if the characterization refers also to nonaqueous partition systems, extensively employed in liquid-liquid partition chromatography. Therefore, in the present work the partition parameters of the quinoline bases were determined in systems of the type weakly polar solvent/formamide which are extensively employed in the chromatography of steroids and alkaloids. To reduce the R_F values to the range of optimal accuracy, formic acid was added to formamide; in this way the partition of quinolines could be shifted in favor of the polar stationary phase as a result of strong interactions between heterocyclic nitrogen and formic acid.

EXPERIMENTAL

Whatman No. 4 paper strips, 7 × 23.5 cm, cut at right angles to the machine direction, were impregnated with 4 to 15 v/v % solutions of formic acid in formamide. To secure a suitable degree of impregnation, the polar solvent was diluted with acetone in the volume ratio 1:4. The strips were immersed in the impregnating solution, blotted between two sheets of filter paper, and allowed to dry in air for several minutes. The impregnation was repeated once more, this time passing the strip through the impregnating solution in the opposite direction. The strips contained ca. 0.5 g (ca. 0.44 ml) of the stationary phase ($HCONH_2$ + HCOOH) per 1 g of dry paper; as determined in an earlier paper (3), the ratio of cross-sectional areas of the mobile and fixed phases ($r = v_{org}/v_{FA}$) under these conditions is ca. 2.5.

The chromatograms were developed in all-glass tanks, 5 × 7 × 22 cm, by the descending technique; the spots were detected with Dragendorff's reagent. The experiments were carried out at room temperature (20 ± 1°C).

RESULTS AND DISCUSSION

Experimental results for solvents of class N and B are presented in Table 1 in terms of $-\log Dr = R_M$ values [$R_M = \log (1 - R_F)/R_F$, i.e., defined after Bate-Smith and Westall]. The stationary phase contained in these experiments 4 v/v % of formic acid.

TABLE 1

	Quinoline (Q)	Isoquinoline (IQ)	2-Methylquinoline (2MQ)	6-Methylquinoline (6MQ)	2,6-Dimethylquinoline (2,6DMQ)	8-Methylquinoline (8MQ)	8-Hydroxyquinoline (8HQ)	Acridine (A)	3-Methylisoquinoline (3MIQ)
Heptane	0.48	0.87	0.87	0.43	0.91	−0.16	0.58	0.69	0.95
Cyclohexane	0.41	0.83	0.83	0.37	0.83	−0.27	0.43	0.60	0.87
Decalin	0.35	0.75	0.75	0.29	0.75	−0.39	0.31	0.55	0.79
Carbon tetrachloride	−0.14	0.31	0.25	−0.21	0.31	−0.69	−0.12	−0.07	0.31
m-Xylene	−0.18	0.29	0.27	−0.23	0.27	−0.79	−0.12	−0.16	0.25
Toluene	−0.19	0.27	0.25	−0.25	0.29	−0.79	−0.18	−0.18	0.23
Benzene	−0.31	0.18	0.16	−0.33	0.19	—	−0.19	−0.23	0.14
Ethylbenzene	−0.12	0.27	0.25	−0.14	0.25	—	−0.10	−0.21	0.23
Chlorobenzene	−0.29	0.10	0.09	−0.37	0.12	—	−0.27	−0.35	0.14
Diisopropyl ether	0.25	0.72	0.69	0.19	0.79	−0.37	0.12	0.43	0.79
Diisoamyl ether	0.37	0.83	0.79	0.33	0.95	−0.31	0.27	0.55	0.95
Methyl isobutyl ketone	−0.25	0.31	0.29	−0.23	0.45	−0.72	−0.19	−0.09	0.33
Chloroform	—	−0.48	−0.50	—	−0.55	—	—	—	−0.55

For solvents of class A, especially for chloroform, most solutes gave R_F values that were too high so that the R_M coefficients could be determined with sufficient accuracy only for isoquinoline, 2-methylquinoline, 3-methylisoquinoline, and 2,6-dimethylquinoline (cf. Fig. 1). Therefore, for solvents of class A the R_M values were determined for a higher content of formic acid in the stationary phase (13 v/v %). The experimental results for solvents of class A are presented in Table 2.

As in the preceding paper (*1*), the experimental data are also presented as R_M-solvent spectra, using the Rohrschneider and Littlewood method. The positions of the solvents on the abscissa are chosen so that the points of the reference solute, 2-methylquinoline, lie on a straight line (dashed lines in Figs. 1–3) connecting the R_M values of the reference solute obtained for heptane and chloroform.

The R_M-solvent spectra for solvents of class N are illustrated in Fig. 1. Comparison with the results obtained for aqueous systems (*1*) shows that the position of the solvents in the scale of solvent power is similar in either system, with the exception of ethylben-

TABLE 2

	Q	IQ	2MQ	6MQ	2,6DMQ	8MQ	8HQ	A	3MIQ
Chloroform	−0.39	0.14	0.12	−0.33	0.12	−0.69	0.10	−0.14	0.10
Trichloroethylene	0.07	0.66	0.57	0.12	0.63	−0.39	0.29	0.31	0.55
1,2,3-Trichloropropane	−0.07	0.50	0.45	0.00	0.54	−0.43	0.16	0.19	0.45
1,1-Dichloroethane	0.09	0.63	0.63	0.07	0.60	−0.23	0.19	0.27	0.55
1,2-Dichloroethane	0.02	0.60	0.55	0.02	0.57	−0.27	0.18	0.21	0.45

zene, which in the case of formamide systems is shifted to the proximity of xylene. Moreover, the slope of the line of the reference solute, determined by the difference of its R_M values for heptane and chloroform, i.e., ΔR_M (C_7H_{16}—$CHCl_3$), is similar to that found for aqueous systems. The ΔR_{M8} value is equal to the R_M value of the reference solute in the hypothetical system chloroform/hep-

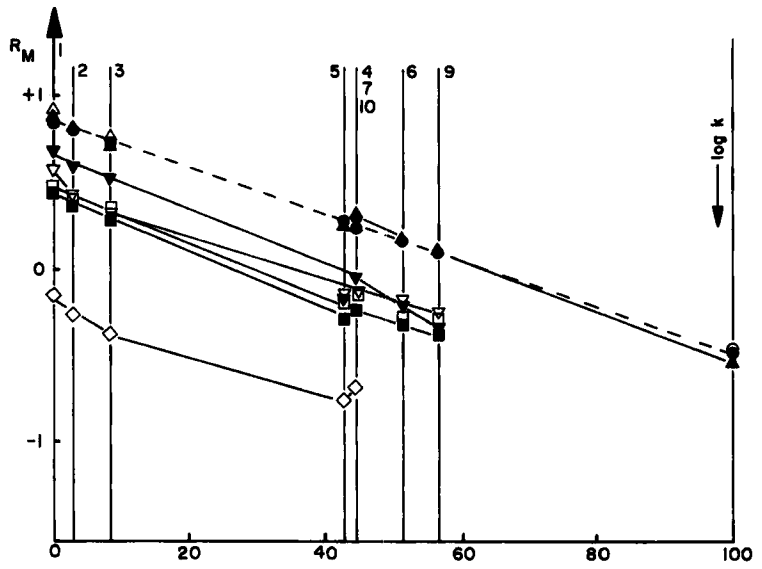

FIG. 1. R_M vs. solvent plot, solvents of class N. 1, Heptane; 2, cyclohexane; 3, decalin; 4, carbon tetrachloride; 5, *m*-xylene; 6, benzene; 7, toluene; 9, chlorobenzene; 10, ethylbenzene. Reference solute: 2-methylquinoline (●, dashed line). The remaining solutes are: ○, isoquinoline; ▲, 2,6-dimethylquinoline; △, 3-methylisoquinoline; ▼, acridine; ▽, 8-hydroxyquinoline; ■, 6-methylquinoline; □, quinoline; ◇, 8-methylquinoline; the first four solutes (●, ○, ▲, △) give almost identical R_F values in most systems. Stationary phase: 4 v/v % formic acid in formamide.

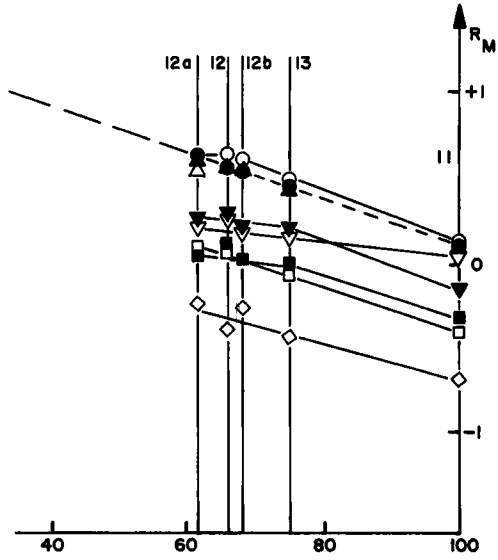

FIG. 2. R_M vs. solvent spectra, solvents of class A. 11, Chloroform; 12, trichloroethylene; 12a, 1,1-dichloroethane; 12b, 1,2-dichloroethane; 13, 1,2,3-trichloropropane. Stationary phase: 13 v/v % formic acid in formamide.

tane and was found to be 1.8 for aqueous systems and 1.4 for formamide systems.

The spectra of the remaining bases are, as in the case of aqueous systems, approximately parallel to the straight reference line, which indicates that the scale of solvent power of the weakly polar solvents refers to all quinoline bases investigated. Also for solvents of class A (Fig. 2) and class B (Fig. 3) the spectra are approximately parallel; only for 8-methylquinoline and 8-hydroxyquinoline are the spectra less steep, which can be explained by weaker solvation of the solutes owing to steric hindrance and formation of an internal hydrogen bond, respectively. The positions of the solvents on the abscissa are similar to those obtained for aqueous systems. The plot for solvents of class A, as stated above, had to be determined for a higher content of formic acid in the fixed phase and is therefore not strictly comparable to Figs. 1 and 3; it was found, however, that R_M values of quinoline bases vary approximately linearly with the percentage of HCOOH in formamide, the slope being similar for the two reference solvents, heptane and chloroform. Since many

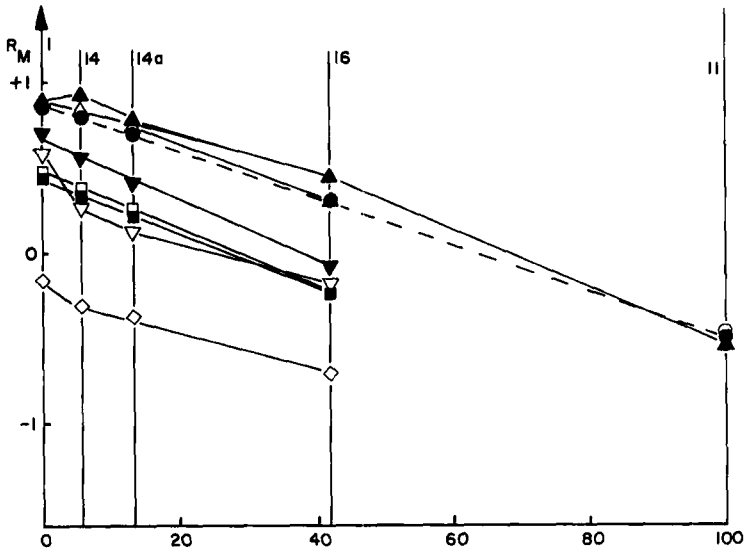

FIG. 3. R_M vs. solvent spectra, solvents of class B. 14, Diisoamyl ether; 14a, diisopropyl ether; 16, methyl isobutyl ketone. Fixed phase: 4 v/v % formic acid in formamide.

solvents of class AB are completely miscible with formamide, this class of solvents was not investigated.

The sequence of R_M values of the solutes is quite different from that observed for aqueous systems, for which the partition coefficients of unionized solutes (C_{org}/C_w) increased in the following sequence: isoquinoline < quinoline, 2-methylquinoline < 6-methylquinoline, 2,6-dimethylquinoline < 8-hydroxyquinoline < 8-methylquinoline < acridine (the sequence of R_F and pH_i values was different in view of the contribution of selective ionization equilibria).

On the other hand, for the formamide systems the partition coefficients usually increase in the following order: isoquinoline, 2-methylquinoline, 2,6-dimethylquinoline < acridine < 8-hydroxyquinoline, quinoline, 6-methylquinoline < 8-methylquinoline.

Undoubtedly, in view of the very weak interactions of quinolines with solvents of class N and B, the main cause of the observed selectivity must relate to the polar phase; the interactions involved may be considered in terms of two opposite tendencies (*4*):

1. Association of the polar solvent, tending to displace the large

molecules of quinoline bases into the nonpolar phase, thus increasing the partition coefficient.

2. Solvation of the solutes (particularly the electron-donor nitrogen atom) by formic acid and formamide, tending to decrease the partition coefficient.

The tendency to "squeeze out" the solute from the polar phase depends on the molecular size, and the introduction of a nonpolar group (=CH_2, another aromatic ring, etc.) should increase the partition coefficient. In the case of formamide, as expected, this effect is much weaker than for aqueous systems (see below and Fig. 4) in view of the weaker association of formamide. Therefore, the introduction of a methylene group has a small effect on partition in formamide systems; in other words, the ΔR_M (ring-attached CH_2) is much smaller than in the case of aqueous systems.

In consequence, in the formamide systems the energy of solvation of quinolines by the polar solvent becomes more important;

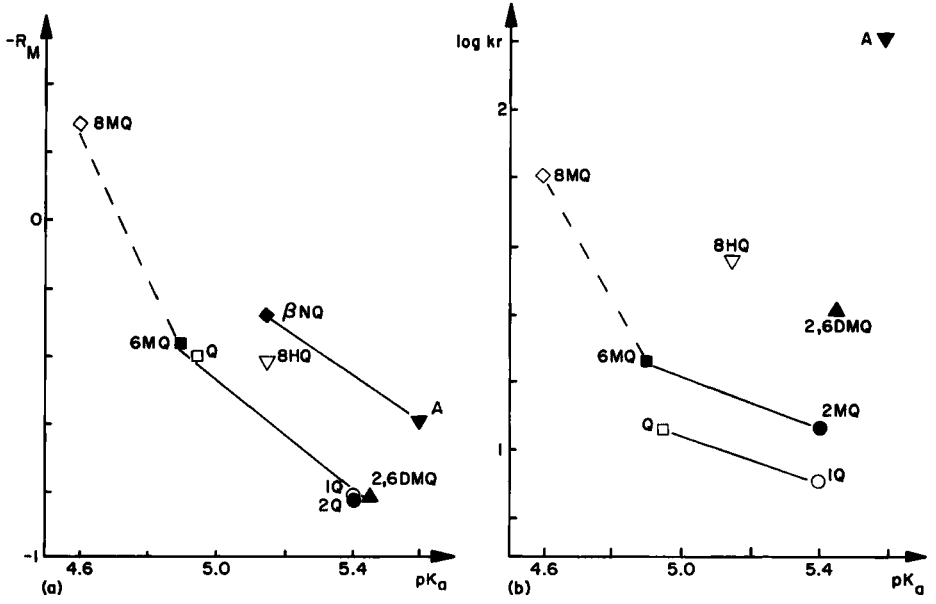

FIG. 4. (a) R_M vs. pK_A plot of some quinoline bases for the system cyclohexane/4% HCOOH in $HCONH_2$. (b) Analogous plot for aqueous systems. The R_M axis is directed downward so that log partition coefficients (c_{org}/c_{polar}) increase upward. For notation of the solutes, see Fig. 1 or Table 1; βNQ = β-naphthoquinoline.

the energy is mainly determined by H-bonding between the molecules of the polar phase and the heterocyclic nitrogen, although some contribution of interactions with π electrons of the aromatic rings cannot be excluded (5). The introduction of a methyl group can influence the solvation by two mechanisms: by changing the electron density on the nitrogen atom, and, in the case of a neighboring position, by shielding the nitrogen atom and thus hindering solvation (6). The first effect, reflected by changes in the pK_A values of the solute, is evident in the case of 2-methyl derivatives of quinoline and the latter in the case of 8-methylquinoline.

To demonstrate the relationship between the R_M coefficient on the one hand and the electron density on the nitrogen atom and the molecular size on the other, in Fig. 4(a) a log *kr* vs. pK_A correlation is presented; unfortunately, the data are too scarce to treat the plot as anything more than an illustration of the theoretical considerations. Nevertheless, the following conclusions can be made.

The points of isoquinoline and quinoline and its methyl and dimethyl substitutes follow a correlation line of a negative slope; thus, for increasing pK_A the partition is shifted in favor of the polar phase, owing to the stronger H-bonding. The following points deviate from the correlation line:

8-Hydroxyquinoline, owing to the formation of an intramolecular H-bond

8-Methylquinoline, owing to the steric hindrance to solvation (it is interesting to note, however, that a methyl group in the 2 position does not seem to affect solvation to a large extent)

Three-ring bases, owing to their markedly larger molecular size

The points of the four solutes lie above the correlation line (higher partition coefficients) owing to the weaker solvation or stronger displacement from the polar phase.

The effect of the pK_A of the basic nitrogen on its solvation by solvents of class AB (or A) may have key importance for the problem of the additivity concept in the case of nitrogen bases; the correlation in Fig. 4(a) seems to suggest that in systems of the type considered, one cannot attribute to the nitrogen atom a constant ΔR_M(N) parameter without taking into account the electron density determining its electron donor properties and characterized by its pK_A value. The correlation suggests that relationships should exist between ΔR_M(N) and pK_A.

The correlation was plotted for the system cyclohexane/HCOOH + $HCONH_2$; for the remaining less-polar solvents similar correlations would be obtained, since the "spectra" are approximately parallel. The R_M-pK_A correlation seems interesting since in some cases it may permit the estimation of the pK_A values of related substances from chromatographic data, taking into account molar volume effects which are relatively small for formamide systems.

To compare molecular volume effects for formamide and aqueous systems, in Fig. 4(b) an analogous R_M vs. pK_A correlation is plotted from data reported in the preceding work for aqueous systems. It can be seen that the pK_A value also influences the partition coefficient of un-ionized solute. The points of methyl and dimethyl substitutes do not form a single correlation line (as is the case for formamide systems), their positions clearly depending on the molecular size; the effect is very marked in the case of acridine, whose point is much higher above the point of isoquinoline (similar pK_A) in comparison to Fig. 4(a). Figure 4(b) seemingly explains the remark made in the preceding paper that the introduction of a methyl group into position 2 does not change the partition coefficient of quinoline bases; incidentally, the effect of increased molar volume is compensated by increased interactions of the heterocyclic nitrogen with the polar phase, owing to increased basicity.

The slope of the R_M vs. pK_A correlation seems to be dependent on the proton-donor activity of the polar solvent. Thus, the line is more steep for formic acid/formamide [Fig. 4(a)] than for water [Fig. 4(b)]; strictly speaking, McIlvaine's buffer solutions contain fair concentrations of citric acid whose carboxyl groups can probably contribute to solvation effects in the aqueous phase, which is thus somewhat analogous to formamide solutions of formic acid and is not strictly comparable to pure water. The concentration of carboxyl groups varies with pH in a series of buffer solutions.

For the hypothetical chloroform/cyclohexane system, the pK_A effect seems to be negligible, probably in view of the relatively weak proton donor properties of chloroform and the narrow range of pK_A values of the quinoline bases studied; only steric effects and intramolecular H-bonding seem to influence solvation: it follows from the data obtained for aqueous systems that the ΔR_{Ms} (cyclohexane/chloroform) values are practically constant (1.70 to 1.75) for most solutes, except for isoquinoline (1.9), 8-methylquinoline (1.15), and 8-hydroxyquinoline (1.35). The higher ΔR_{Ms} value of

isoquinoline may be due to the slightly better accessibility of the nitrogen in the β-position; it can also be supposed, however, that a pK_A effect could be compensated by shielding of the nitrogen atom by the 2-methyl group (cf. above for aqueous phase). Somewhat different results have been obtained for 1,2,3-trichloropropane/cyclohexane system; the ΔR_{Ms} values for quinoline, isoquinoline, 6-methylquinoline, and acridine are constant (1.35 to 1.40); for 2-methylquinoline and 2,6-dimethylquinoline they are somewhat lower (1.15; shielding effect of the 2-methyl group?); for 8-hydroxyquinoline they are 1.10; and for 8-methylquinoline they are significantly lower (0.8). Thus, in the case of class A/class AB solvent systems, the steric effects as well as intramolecular H-bonding in the two phases act in opposite directions in view of weakened solvation in either phase; larger effects and a better selectivity can be expected for class N/class AB systems owing to absence of strong solvation in the nonpolar phase.

In view of the much weaker molecular volume effects in formamide systems, they can give solute sequences and selectivities quite different from those obtained in aqueous systems so that the two types of systems can supplement each other.

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