[Contribution from the Central Experiment Station, U. S. Bureau of Mines]

Partition Studies on Phenols. I. Relation between Partition Coefficient and Ionization Constant[1]

By C. Golumbic,[2] M. Orchin[2] and S. Weller[3]

The composition of the complex phenolic mixtures (tar acids) produced during the liquid-phase hydrogenation of coal is being studied by the countercurrent distribution technique. In this procedure a mixture of closely related compounds is distributed between two immiscible solvents in successive countercurrent stages until separation of the components is achieved.[4,5] During this investigation it has been observed that a relationship exists between partition coefficients and ionization constants of phenols, and between these constants and the chemical configuration of phenol homologs. This paper presents the results of the study of 11 phenol homologs.

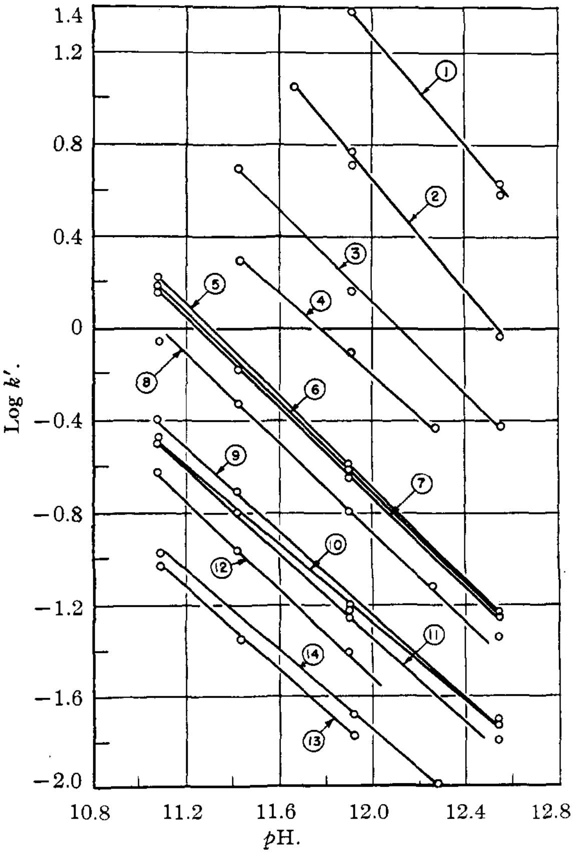

Fig. 1.—Effect of change of *p*H on partition ceofficient: 1, *o*-cyclohexylphenol; 2, *p*-cyclohexylphenol; 3, *o*-phenylphenol; 4, 2,6-xylenol; 5, 2,4-xylenol; 6, 3-methyl-5-ethylphenol; 7, *o*-ethylphenol; 8, 2,5-xylenol; 9, *p*-ethylphenol; 10, *m*-ethylphenol; 11, 3,5-xylenol; 12, *o*-cresol; 13, *m*-cresol; 14, *p*-cresol.

Relation between Partition Coefficient and Ionization Constant.—When a weak acid (HA), such as a phenol, is distributed between a non-ionizing organic phase and an immiscible aqueous phase, the observed partition coefficient, k', is given by equation (1) when no association occurs in either phase.

$$k' = [HA]_0/[HA]_w + [A-]_w \qquad (1)$$

The observed k' is the resultant of two equilibria: (a) the partition of the undissociated acid between the immiscible phases and (b) the ionization of the acid in the aqueous phase.

Analogous to Craig's derivation for weak bases,[6] equation (1) can be converted into an approximate expression, equation (2), relating k' with the partition coefficient, k, of the un-ionized acid, the ionization constant of the acid, K, and the hydrogen ion concentration of the aqueous phase.

$$k' = k/1 + (K/[H^+]) \qquad (2)$$

When the aqueous phase contains a buffer of sufficient alkalinity so that $[H^+] < < K$, the unity term in the denominator of equation (2) becomes negligible in comparison with the other term; hence, equation (2) can be written as

$$k' = k[H^+]/K \qquad (3)$$

or logarithmically

$$\log k' = \log k + \log [H^+] - \log K \text{ or}$$
$$\log k' = -pH + pK + \log k \qquad (4)$$

According to equation (4), a plot of log k' *vs.* *p*H would be a straight line with a slope of −1. Experimental results, represented graphically in Fig. 1, verified this relation. In Fig. 1, the observed partition coefficients of 14 phenols, distributed in the system cyclohexane −0.5 *M* phosphate buffer, are plotted as a function of *p*H. A straight line with a slope, *m*, close to −1 (mean -0.97 ± 0.10) occurred in all instances (Table I). This observation also shows that there was no significant association in the organic phase.

For dibasic acids, the slope of the log k'—*p*H curve should be 1 to 2 when $pK_1 < < pH < < pK_2$, and 2 where $pH > > pK_2$, provided that no association occurs.

Distribution of HA when Association Occurs in the Organic Phase.—If association leads to the formation of dimers according to the reaction: $2\ HA \rightleftarrows (HA)_2$, the total concentration of un-ionized acid in the organic phase, which is shown as $[HA]_0$ in equation (1), becomes $[HA]_0 + 2$

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[4] Craig, *J. Biol. Chem.*, **155**, 519 (1944).

[5] Craig, Golumbic, Mighton and Titus, *ibid.*, **161**, 321 (1948).

[6] Craig, *ibid.*, **150**, 33 (1943).

TABLE I

PARTITION COEFFICIENTS AND IONIZATION CONSTANTS OF PHENOLS^a

Compound	m	k (H_2O)	k at pH 6.65	k' at pH 11.08	pK calculated	pK literature
Phenol		0.19	0.22	0.02	10.0	9.97,^{b} 9.99^c
o-Cresol	0.96	1.34	1.96	.24	10.2	10.20^b
m-Cresol	.92	0.70	1.01	.09	10.0	10.01^b
p-Cresol	.89	.80	1.14	.11	10.1	10.17^b
2,6-Xylenol	.93	19.0	21.7	3.57	10.5^d	10.60,^{b} 10.58^c
2,5-Xylenol	.98	5.85	7.46	1.16	10.3	10.32^b
2,4-Xylenol	1.04	5.71	7.06	1.63	10.4^d	10.47^b
3,5-Xylenol	0.95	3.50	4.02	0.33	10.0	10.09,^{c} 10.18^c
o-Ethylphenol	.97	6.75	10.4	1.45	10.2	
m-Ethylphenol	.88	2.65	4.31	0.31	9.9	
p-Ethylphenol	.92	2.78	4.43	.40	10.0	
3-Methyl-5-ethylphenol	.96	7.77	14.6	1.49	10.1	
o-Phenylphenol	.88			0.39^e		
o-Cyclohexylphenol	1.16			3.81^e		
p-Cyclohexylphenol	1.18			0.92^e		

^{a} All measurements were made at room temperature, 28 ± 2°. ^{b} Boyd, *J. Chem. Soc.*, **107**, 1538 (1915). ^{c} Wheland, Brownell and Mayo, THIS JOURNAL, **70**, 2492 (1948). ^{d} Calculated at pH 11.90. ^{e} k' at pH 12.54.

$[(HA)_2]_0$ or $[HA]_0\ (1 + 2K_a{}^2\ [HA]_0)$ where K_a is the association constant. If Craig's derivation[6] is carried out, a relationship is obtained for the observed partition coefficient, as shown in equation (5)

$$k' = k\,\frac{1 + 2K_a{}^2[HA]_0}{1 + (k/[H^+])} \qquad (5)$$

If dimerization proceeds nearly to completion, the observed partition coefficient, k', is not independent of initial concentration of HA as is the case when no association occurs.

Extractibility of Phenols.—The literature records many instances of failure to extract phenols from an organic phase by aqueous alkali. It is common practice to use alcoholic (Claisen) alkali for extracting such phenols, which have been separately classified as "cryptophenols" or phenols with hidden properties.[7] An examination of equation (4) reveals the probable reason for this phenomenon. Three factors affect the partition of a phenol between the organic and aqueous phase: pH of the aqueous phase, ionization constant of the phenol, and partition coefficient of the un-ionized phenol. When aqueous hydroxide is used for extraction, the pH is about 14. The ionization constant (pK) of phenols in most cases varies within small limits, so that differences in extractibility are seldom due to differences in acid strength. The partition coefficient, k, is then mainly responsible for differences in extractibility. The insolubility in water of the undissociated form of the phenol is the reason why many phenols cannot be extracted from an organic phase. The presence of alcohol in the water increases the solubility of the undissociated phenol in the aqueous phase and hence results in extractibility.

Equation (4) can also be used to calculate the amount of a phenol in an organic phase that can be extracted by aqueous alkali. For example, suppose that *o*-cyclohexylphenol has a distribution coefficient between cyclohexane and water of about 500 and a pK of about 10.8.[8] When 1 N aqueous alkali is used for the extraction, the pH is about 14. Solving equation (4), a value of k' of 0.3 is obtained. This means that 0.3/1.3 × 100 or about 23% of the *o*-cyclohexylphenol can be extracted from cyclohexane solution by one equilibration with an equal volume of aqueous alkali.

Calculation of Ionization Constant from Partition Measurements.—Equation (4) was used for making an approximate evaluation of the ionization constant of each phenol homolog studied. The partition coefficients observed in the systems of cyclohexane–0.5 M phosphate buffers of pH 11.08 and 6.65 (Table I) were used for k' and k, respectively. At pH 6.65, the ionization of a simple phenol is negligible; hence, the observed partition coefficient at this pH measures the distribution of the un-ionized phenol between the organic and aqueous phases. The partition coefficient at pH 6.65 is higher than that observed when the aqueous phase is pure water (Table I, column 3), showing that concentrated buffers produce an appreciable "salting-out" effect. Comparison of calculated ionization constants with literature values (Table I) shows good agreement and further substantiates the validity of equation (4). This method of estimating approximate ionization constants has the advantages of simplicity of measurement and applicability to difficultly soluble phenols.

Relation between Ionization Constant and Molecular Structure.—Introduction of alkyl groups into the nuclear positions of a phenol decreases its acid strength, the effect being most pronounced in ortho and para substitution.[9] This is understandable, since the electron release ef-

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[7] Niederl. *Ind. Eng. Chem.*, **30**, 1269 (1938).

[8] Approximate measurements indicate that the partition coefficients of phenols with cyclohexyl and phenyl substituents are greater than 100 at pH about 7.

[9] Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 185.

fect of alkyl groups in the ortho and para positions can be transmitted to the oxygen of the hydroxyl group, whereby proton removal becomes more difficult and acid strength is decreased. This effect cannot be transmitted when substituents are at the *meta* position and for this reason the meta-substituted phenols in any isomeric series are the strongest acids. Thus, it was not surprising to observe that, in the ethylphenol series, in which no exact ionization constants are available, the calculated pK value of the meta compound is the lowest of the isomers (Table I). Substitution at the ortho position decreases acid strength even more than para substitution because of the special so-called "*ortho*" effect, which is probably electrical in nature.[10] Diortho substitution, of course, magnifies this effect; 2,6-xylenol is the weakest acid, by far, of the xylenols.

Relation between "True" Partition Coefficient (k) and Molecular Structure.—The addition of alkyl groups to a phenol increases the partition coefficient because of the decreasing solubility in the aqueous phase associated with increasing molecular weight. The magnitude of this effect depends on the position of the entering group. An alkyl group introduced into a meta or para position both relatively remote from the solubilizing hydroxyl group, should have a similar effect on the partition coefficient. The data of Table I show that approximately equal partition coefficients are obtained for *m*- and *p*-cresols and also for *m*- and *p*-ethylphenols. However, in each series the ortho isomer has an appreciably higher partition coefficient. An explanation concerning the nature of this type of "ortho" effect can be suggested. Solubility of a phenol in the aqueous phase is probably due partly to hydrogen bonding between the hydroxyl of the phenol and the water molecules. Since the presence of an alkyl substituent in the ortho position would tend to hinder the approach of a solvent molecule to the hydroxyl group, the ortho-substituted phenol would be less hydrogen-bonded than its isomers and, therefore, less soluble. The greater the size of the ortho substituent the more pronounced would be its effect on hydrogen bonding. Coggeshall[11] has shown that the decrease in the magnitude of the shift of the hydroxyl band in the infrared spectrum of a phenol, as a result of ortho substitution, can be used as a criterion of the extent of hydrogen bonding. Bulky alkyl groups produce no appreciable shift, whereas methyl groups do. It is possible that partition coefficients which show an ortho methyl effect are a more sensitive index of the extent of hydrogen bonding than are the reported spectral data. Partition studies on alkylated phenols are under way to test this possibility.

Effect of "True" Partition Coefficient (k), and Ionization Constant on the Observed Partition Coefficient (k').—The above discussion has shown that both the partition coefficient and ionization constant of a phenol are affected by changes in its molecular structure. The observed partition coefficient is a function of both the "true" partition coefficient and the ionization constant. In the alkaline pH region in which equation (4) is valid, the ratio of observed partition coefficients for any two phenols (c and d) is given by the expression

$$\frac{k'_c}{k'_d} = \frac{k_cK_d}{k_dK_c}$$

This ratio is greater than the corresponding ratio in neutral or weakly alkaline regions in those instances in which both k_c/k_d and K_d/K_c are > 1. Thus, the data of Table I show that the ratio of partition coefficients of 2,4- and 2,5-xylenols at pH 11.08 is almost three times that at pH 6.65. For this reason, it is desirable to employ an alkaline buffer as one of the immiscible phases for separating these isomers by a partition method, such as countercurrent distribution.[5] Buffers also allow adjustment of partition coefficients to any desired value, which is a decided advantage when dealing with slightly soluble acids. As will be shown in subsequent publications, these observations find practical application in the separation of isomeric phenols.

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Experimental

Materials.—The *m*-cresol, *p*-cresol and ethylphenols used in this work were obtained from Dr. J. J. McGovern, Koppers Company Fellowship, Mellon Institute. The *m*- and *p*-cresols were said to have a purity of 99%. The 2,5-2,4- and 3,5-xylenols were obtained from Eastman Kodak Company. The 2,6-xylenol was secured from Edcan Laboratories. 3-Methyl-5-ethylphenol was isolated by E. O. Woolfolk from a tar-acid fraction. The *o*-phenylphenol, *o*-cyclohexylphenol and *p*-cyclohexylphenol were samples from the Dow Chemical Company. All crystalline compounds were recrystallized to constant melting point.

Methods.—The organic phase consisted of spectrographic-grade cyclohexane containing 0.5 mg. of phenol per ml. of solution. Twenty ml. of this solution was shaken for two minutes with an equal volume of the aqueous phase, water or 0.5 M phosphate ($Na_2HPO_4 + Na_3PO_4$). Equilibration and phase separation were carried out in 125-ml. centrifuge separatory funnels. Preliminary mutual saturation of the immiscible layers was unnecessary, since it was found to have no effect on the partition coefficient. The initial concentration of 0.5 mg. per ml. was convenient for analysis and also was well below the concentration at which association effects might be expected. Doubling this concentration in a few instances changed the partition coefficient only slightly, within the error of the method.

Measurements of pH were made with the Beckman model M pH meter employing a type E glass electrode. All analyses of the phenol concentration in the distribution layers were made by ultraviolet measurements on a Beckman quartz spectrophotometer. An absorption curve for each phenol was prepared to determine the wave length most suitable for analysis. In order to determine the accuracy of this method, recovery experiments were made in which both immiscible phases were analyzed after distribution. It was found that the sum of the quantities of

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(10) Watson, "Modern Theories of Organic Chemistry," Oxford University Press, Oxford, 1941, pp. 241–243.

(11) Coggeshall, This Journal, 69, 1620 (1947).

phenol in each layer agreed within 5% or less of the original amount. Thereafter, analyses were usually confined to the cyclohexane phase, except in those instances where the partition coefficient was very high or low.

Despite the fact that no close temperature control was maintained during distribution, duplicate partition coefficients, determined at intervals of several days, agreed within 5% of each other in the intermediate range and within 10% in the very high or low range. Since a 30% change in partition coefficient would affect the calculated *pK* value by only a 0.1 unit, it is believed that the calculated values are within about ±0.1 *pK* unit of the exact values.

Summary

The partition coefficients of 14 phenols have been measured in systems composed of cyclohexane–water and cyclohexane–phosphate buffer. A relationship was observed between partition coefficient and *p*H which permitted calculation of approximate ionization constants. Partition coefficients and ionization constants were correlated with molecular configuration of phenols.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT BRANCH, OFFICE OF SYNTHETIC LIQUID FUELS, BUREAU OF MINES]

Partition Studies on Phenols. II. Separation of Isomeric Phenols by Countercurrent Distribution[1]

BY CALVIN GOLUMBIC[2]

Phenolic compounds of wide variety are potentially available in huge amounts from coal-hydrogenation oils.[3] It is therefore of considerable interest to determine the composition of the complex tar-acid fractions in which these phenols are found. Such mixtures are composed largely of homologous and isomeric phenols, and separation by the usual procedures of precise fractional distillation and fractional crystallization is difficult. Since the method of countercurrent distribution[4] has successfully resolved mixtures of isomeric and homologous acidic and basic compounds,[5,6] it appeared to be applicable in isolating individual phenols and testing their purity. Previous partition studies[7] on phenol homologs showed significant relative differences among such compounds, particularly in organic solvent–buffer systems. Alkaline buffer when used as one of the immiscible phases allows adjustment of the partition coefficient to any desired value and frequently increases the partition ratios among groups of closely related phenols. Separation of some isomeric phenols and proof of their homogeneity are described in this manuscript.

Experimental

Materials.—The source and purity of the phenols used in this work have been mentioned previously.[7]

Apparatus.—The countercurrent distribution machine was a stainless steel (8–18), 54-tube instrument manufactured by Otto Post, Maspeth, N. Y. This apparatus differs from Craig's original model[4] principally in the manner of sealing the bottom of the lower drum and top of the upper drum. Plate glass is used instead of steel plates, to permit observation of phase separation. The lower tubes of the instrument hold 10 ml. of solvent; the upper tubes, up to 15 ml.

Procedure.—Before the experiment was started, the organic solvent (cyclohexane or benzene) and 0.5 *M* phosphate buffer ($Na_2HPO_4 + Na_3PO_4$) were mutually saturated at room temperature by shaking in separatory funnels. Sufficient buffer layer was introduced into the lower drum of the countercurrent instrument to fill each tube to its brim; this was followed by addition of 10 ml. of the organic solvent to each upper tube. After inverting the instrument several times to test whether the glass-metal and metal–metal seals were leakproof, the upper phase of tube 0 was replaced with a solution of the entire material to be distributed. Stepwise countercurrent distribution was then conducted as described by Craig.[4] Upon completion of the run, the contents of each tube of the instrument were pipetted into glass-stoppered centrifuge tubes and acidified with 2 ml. of HCl (1:1). These tubes were shaken and centrifuged to clarify the layers. The organic phase was separated and analyzed by means of the Beckman Model DU quartz spectrophotometer. In cases where the analysis indicated the presence of a crystalline component in nearly pure form, a crystalline residue was always obtained by evaporation of the solvent. The amounts, however, were too small for determination of capillary melting points.

Results

Homogeneity Studies.—For this purpose, 53-plate distributions were run in a 54-tube Craig distribution machine[8] employing cyclohexane and 0.5 *M* phosphate buffer as the immiscible phases. Preliminary measurements of the partition coefficient at different *p*H values were made, to select a buffer that would provide a partition coefficient close to one.[7] After distribution, the total amount of phenol in each tube of the distribution machine was determined by ultraviolet measurement at the wave length of maximum absorption.

A typical example of the results is shown in Fig. 1, which represents the distribution of a 50-mg. sample of 3-methyl-5-ethylphenol in cyclohexane–phosphate buffer of *p*H 11.26. Because this compound had been isolated from a tar-acid fraction of a coal-hydrogenation product[3] containing

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(3) Golumbic, Bureau of Mines Rept. Investig., 4467, 56 pp. (1949).

(4) Craig, *J. Biol. Chem.*, **155**, 519 (1944).

(5) Craig, Golumbic, Mighton and Titus, *J. Biol. Chem.*, **161**, 321 (1945).

(6) Warshowsky and Schantz, *Anal. Chem.*, **20**, 951 (1948).

(7) Golumbic, Orchin and Weller, THIS JOURNAL, in press.

(8) Barry, Sato and Craig, *J. Biol. Chem.*, **174**, 221 (1948).