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Partition Studies. VII. Molecular Complex Formation in Fractional Extraction. Silver and Cineole Complexes of Cresols

BY CALVIN GOLUMBIC AND SOL WELLER

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The formation of silver and cineole molecule complexes of the isomeric cresols has been demonstrated, and the equilibrium constants for these reactions have been determined by a partition method. Equations relating partition coefficients and equilibrium constants for different types of complexes were derived in order to investigate the applicability of complex formation in separations by fractional extraction. The conditions under which complex formation enhanced separability of compounds were defined mathematically.

The possibility of utilizing molecular complexes for separation of organic compounds by the various fractional extraction procedures¹ has hitherto received little attention. In this communication, the results of such an investigation are reported. The conditions under which the use of complex formation aids in the separation of closely related compounds have been defined in terms of partition coefficients and equilibrium constants. The validity of the theoretical treatment was tested by the measurement of the partition coefficients of the isomeric cresols in the presence of cineole and silver ion. From these data, the equilibrium constants for the formation of the complexes were calculated.

These reagents and the solvent system (cyclohexane-water) were chosen because they permitted adjustment of partition coefficients to values near unity. This is important because maximum separation of a pair of components by countercurrent extraction is obtained when the geometric mean of their partition coefficients is one.^{2,3}

$$k_{B \text{ opt.}} = \sqrt{1/R} \quad (1)$$

$$\sqrt{k_{A \text{ opt.}} k_{B \text{ opt.}}} = 1 \quad (2)$$

Relation between Partition Coefficient and Equilibrium Constant of Complex Formation.—Equations relating equilibrium constants and partition coefficients for several types of complexes were derived by the method described in detail below for a 1:1 complex. Although expressions equivalent to equations 3, 8 and 9 were derived previously by Winstein and Lucas,⁴ the present treatment demonstrates particularly the effect of complex formation on partition properties and hence is more useful for predicting the separability of compounds.

Case A: Formation of a 1:1 Complex.—It is assumed that the simple distribution law is valid and that a complexing agent, Y, reacts with a substance, X, in either an aqueous phase (I) or an immiscible non-polar organic phase (II) to

(1) (a) T. G. Hunter and A. W. Nash, *Ind. Eng. Chem.*, **27**, 836 (1935); (b) B. Williamson and L. C. Craig, *J. Biol. Chem.*, **166**, 687 (1947); (c) L. C. Craig and D. Craig, in Weissberger, ed., "Technique of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1950, Vol. III, Ch. IV; (d) M. T. Bush and P. M. Densen, *Anal. Chem.*, **20**, 121 (1948); (e) A. E. O'Keeffe, M. A. Dolliver and E. T. Stiller, *THIS JOURNAL*, **71**, 2452 (1949); (f) C. Golumbic, *Anal. Chem.*, **23**, 1210 (1951).

(2) (a) W. J. D. van Dijck and A. Schaafsma, U. S. Patent 2,245,945 (1941); (b) S. Stene, *Arkiv Kemi Mineral. Geol.*, **18B**, No. 18 (1944).

(3) This relationship also applies to countercurrent distribution. In that procedure, position *N* of the maximum of a distribution band is governed by partition coefficient *k*, and the total number of transfers *n*, according to the equation,^{1b} $N = nk/k + 1$. The optimum choice of partition coefficients for maximum separation of a pair of compounds, A and B, whose $k_A/k_B = R$ is determined as

$$\Delta N = N_A - N_B = n[k_A/(k_A + 1) - k_B/(k_B + 1)] = n[Rk_B/(Rk_B + 1) - k_B/(k_B + 1)]$$

$$(d\Delta N/dk_B)_{\max} = nR/(Rk_B + 1)^2 - n/(k_B + 1)^2 = 0$$

(4) S. Winstein and H. J. Lucas, *THIS JOURNAL*, **60**, 836 (1938).

form a complex XY. The following notations are employed for the instance in which the complexing agent is soluble only in the aqueous phase:

$$C_{II} = X_{II} = \text{molar concentration of X in phase II}$$

$$C_x = X_I + (XY)_I = \text{total molar concentration of X (free and combined) in phase I}$$

$$C_y = Y_I + (XY)_I = \text{total molar concentration of Y (free and combined) in phase I}$$

$$k = \frac{X_{II}}{X_I} = \frac{C_{II}}{X_I} = \text{partition coefficient of free X}$$

$$K = \frac{(XY)_I}{X_I \cdot Y_I} = \text{complex formation constant}$$

The apparent partition coefficient, k' , which is measured in the presence of the complexing agent will then be

$$k' = \frac{C_{II}}{C_x} = \frac{X_{II}}{X_I + (XY)_I} = \frac{X_{II}}{X_I + KX_I Y_I} = \frac{k}{1 + KY_I}$$

$$k' = \frac{k}{1 + K(C_y - C_x + \frac{C_{II}}{k})} \quad (3)$$

When $C_y \gg (XY)_I$ or $Y_I \gg (XY)_I$, equation (3) is reduced to

$$k/k' - 1 = KC_y \quad (4)$$

Accordingly, a plot of $k/k' - 1$ as a function of C_y should be a straight line passing through the origin, if a 1:1 complex is formed in the presence of excess complexing agent. The slope of this line gives the value of K , which is independent of the concentration of the complexing agent.

If Y is soluble only in non-aqueous phase II instead of phase I, the term k/k' of equation 4 is inverted. If, in addition, X is a weak acid, the equilibria involved in the distribution are further complicated by ionization in the aqueous phase. Under these circumstances, it may be readily shown that the following equation applies

$$k'/k[1 + K_1/(H^+)] - 1 = KC_y \quad (5)$$

in which K_1 is the ionization constant of the acid. If K_1 is known, and if the hydrogen ion concentration is fixed by a buffer, K may be readily determined. If the pH of the buffer is sufficiently high so that the acid is essentially completely ionized, then equation 5 is reduced to

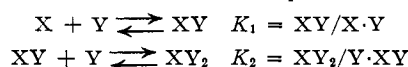
$$[k'K_1/k(H^+)] - 1 = KC_y \quad (6)$$

Case B: Simultaneous Formation of 1:1 Complexes with Different Complexing Agents.—If, in addition to the reaction $X + Y \rightleftharpoons XY$ in phase I, a second, independent complexing reaction takes place in phase II, $X + Z \rightleftharpoons XZ$, the partition coefficient, k' , measures the quotient

$$k' = \frac{[X_{II} + (XZ)_{II}]/[X_I + (XY)_I]}{k(1 + K'Z_{II})/(1 + KY_I)} \quad (7)$$

where K' represents the equilibrium constant for the formation of XZ. Y_I and Z_{II} of equation 7 may be replaced by C_y and C_z , respectively, when $C_y \gg (XY)_I$ and $C_z \gg (XZ)_{II}$.

Case C: Formation of 1:2 and 2:1 Complexes in One Phase.—If the value of K calculated by equation 4 increases with increasing values of C_y , the formation of a 1:2 complex is indicated in addition to the 1:1 complex



From material balance considerations, it can be shown that

$$(1/Y_1)(k/k' - 1) = K_1 + K_1K_2F_1 \quad (8)$$

if the complexing reaction is confined to phase I. If $Y_1 \sim C_y$, K_1 and K_2 may be evaluated from a plot of $\frac{1}{C_y} \left(\frac{k}{k'} - 1 \right)$ vs. C_y ; otherwise, a method of successive approximations may be employed.

Conversely, when the calculated value of K decreases with increasing concentration of C_y , a 2:1 complex is indicated



and equation 9 applies.

$$(1/Y_1)(k/k' - 1) = K_1 + 2X_1K_1K_2' \quad (9)$$

K_1 and K_2' may be calculated in a manner similar to that for K_1 and K_2 in equation 8.

Silver Complexes of Cresols.—The data presented in Table I show the effect of increasing concentration of silver ion on the distribution of the isomeric cresols in the system cyclohexane–water. In all distributions, the silver ion concentration was much greater than the total concentration of phenol (0.00463 *M*). The k values are the partition coefficients of the cresols for distribution between cyclohexane and 1 molar potassium nitrate solution. Ionic strength of the silver nitrate solutions was maintained at unity by addition of appropriate amounts of potassium nitrate. Plots of the data according to equation 4 demonstrated that each cresol formed a 1:1 complex with silver ion over the concentration range studied. The equilibrium constants derived from the slopes (m) of these curves are summarized in Table I.

TABLE I

DISTRIBUTION OF CRESOLS BETWEEN CYCLOHEXANE AND WATER IN THE PRESENCE OF SILVER NITRATE AT 25°^a

C_y , moles/ liter	o-Cresol		K	m-Cresol		K	p-Cresol		K
	k^b	k'		k^b	k'		k^b	k'	
0	1.82	0.81	0.83
0.25	..	1.10	2.60	..	0.53	2.12	..	0.60	1.53
.50	..	.76	2.80	..	.39	2.16	..	.47	1.54
.75	..	.58	2.85	..	.31	2.15	..	.39	1.54
1.00	..	.46	2.95	..	.26	2.12	..	.32	1.59
	$m = 2.8$			$m = 2.1$			$m = 1.5$		

^a In each distribution, the total concentration of cresol in the system was 0.00463 mole per liter. ^b The aqueous phase was 1 molar potassium nitrate.

complexes are largely determined by the relative inductive effects of nuclear substituents. A strong steric factor is also manifest among benzene derivatives containing large, bulky groups or many small ones,⁷ possibly because the silver ion, as demonstrated by Mulliken,⁸ is located in a position intermediate between the plane of the ring and its six-fold symmetry axis.

Both steric and electronic effects appear to be needed to explain the relative stability of the silver complexes of the cresols. Winstein and Lucas⁴ found that the argentation constant of phenol was 2.19 at 25°. The greater stability of the *o*-cresol complex may be attributed to slight enhancement of the basicity of the ring by the electron-releasing methyl group. A meta methyl group would be expected to be more effective; however, meta and para alkyl substituents may offer a progressively greater barrier to the approach of the silver ion to the benzenoid nucleus and thereby decrease the tendency for complex formation. An apparently related observation has been made with the xylenes⁹; *p*-xylene has a smaller argentation constant than *o*-xylene, *m*-xylene and toluene.

Cineole Complexes.—The effect of increasing concentrations of cineole on the distribution of cresols between cyclohexane and water is shown by the results presented in Table II. The k values are the partition coefficients measured in the absence of cineole. Since ionization in the aqueous phase is negligible, these values essentially represent the distribution constants of the un-ionized phenols. In columns 5–7 of Table II, data are presented for the distribution of *o*-cresol between cyclohexane and a phosphate buffer of pH 11.08. The k values for this series are those obtained in the distribution of the cresols between cyclohexane and a slightly acidic phosphate buffer.¹⁰

Plots of the experimental data showed that cineole formed a complex of the 1:1 type with each cresol. The equilibrium constants for the formation of the cineole complexes are given in Table II.

Cineole contains a strongly basic oxygen atom¹¹ and is known to form complexes with a large variety of proton donors. Its complexing action

TABLE II

DISTRIBUTION OF CRESOLS BETWEEN CYCLOHEXANE AND WATER IN THE PRESENCE OF CINEOLE AT 25°^a

C_y , mole/liter	o-Cresol		K	o-Cresol ^b		K	m-Cresol		K	p-Cresol		K
	k	k'		k	k'		k	k'				
0	1.26	2.05 ^c	0.66	0.68
0.10	..	2.97	13.6	..	0.56	13.4
.25	..	5.41	13.2	..	1.06	13.8	..	3.35	16.3	..	3.55	16.8
.50	..	9.87	13.7	..	1.79	13.0	..	6.14	16.6	..	6.35	16.7
.75	..	13.7	13.2	9.42	17.7	..	9.00	16.3
1.00	..	17.5	12.9	12.2	17.5	..	12.2	17.0
	$m = 13$			$m = 13$			$m = 17$			$m = 17$		

^a In each distribution, the total concentration of cresol in the system was 0.00463 mole per liter. ^b Unless otherwise noted, the aqueous phase was 0.5 *M* phosphate buffer of pH 11.08. ^c The aqueous phase was phosphate buffer of pH 6.65.

Silver complexes of aromatic compounds appear to be formed by a Lewis acid–base interaction in which the π -electrons of the aromatic ring function as electron donors to the silver ion.⁵ According to Andrews and Keefer,⁶ the relative stabilities of the

with cresols may be assumed to be a Lewis acid–base interaction, with a hydrogen bond serving as the actual linkage between the molecules. The

(5) R. S. Mulliken, *THIS JOURNAL*, **72**, 600 (1950).

(6) L. J. Andrews and R. M. Keefer, *ibid.*, **72**, 3113 (1950).

(7) L. J. Andrews and R. M. Keefer, *ibid.*, **72**, 5034 (1950).

(8) R. S. Mulliken, *J. Chem. Phys.*, **19**, 514 (1951).

(9) L. J. Andrews and R. M. Keefer, *THIS JOURNAL*, **71**, 3644 (1949).

(10) C. Golumbic, M. Orchin and S. Weller, *ibid.*, **71**, 2624 (1949).

(11) S. Searles and M. Tamres, *ibid.*, **73**, 3704 (1951).

relative stabilities of the complexes are in accord with the relative hydrogen bonding tendencies of the phenols,⁹ namely, $o < p, m$.

It is noteworthy that the *o*-cresol complex, which is least stable, is the one easiest to prepare in the pure state. This complex crystallizes from a mixture of isomeric cresols and can be used for the quantitative determination of *o*-cresol.¹²

Molecular Complexes in the Separation of Compounds.—In order to separate any pair of substances (A and B) by extraction, the ratio of their partition coefficients, or β -values, must be different from unity. In the presence of a complexing agent, the ratio of observed partition coefficients, k'_A/k'_B is given by the expression

$$k'_A/k'_B = k_A(1 + Y_1K_B)/k_B(1 + Y_1K_A) \quad (10)$$

for the case where a 1:1 complex is formed in phase I. Without loss of generality, let $k_A > k_B$. The ratio k'_A/k'_B is greater than the corresponding ratio k_A/k_B when $(1 + Y_1K_B)/(1 + Y_1K_A) > 1$. (The latter term is inverted if complexing occurs in phase II.) The ratio k'_A/k'_B changes with increase in concentration of complexing agent and approaches the limiting value given in the equation

$$k'_A/k'_B = k_AK_B/k_BK_A \quad (11)$$

The limiting expression, if complete complexing in phase II is accompanied by complete ionization in phase I, is

$$k'_A/k'_B = k_AK_A(K_1)_B/k_BK_B(K_1)_A \quad (12)$$

Thus, the β -value, k_A/k_B , of 1.03 for a mixture of *p*- and *m*-cresol can be increased to a maximum of $(0.83) \times (2.1)/(0.81) \times (1.5) = 1.44$ by complexing with silver ion. The separation of these isomers now becomes feasible by a fractional extraction procedure, such as countercurrent distribution,^{1b} provided that $C_Y \gg XY$. This latter requirement should be fulfilled in order to maintain a linear partition isotherm which is desirable in countercurrent distribution. For a mixture of *o*-cresol with *m*- or *p*-cresol, it can be shown similarly that complexing with silver decreases the β -value and is thus useless for separation of these pairs of isomers.

Similarly, the formation of cineole complexes does not increase separation of the cresols and actually nullifies in part the increase in β -value that results from ionization alone.⁹

It is of interest to examine possibilities for separation when the substances being extracted react with a different complexing agent in each phase (case B). The limiting expression for the β -value under these conditions is given by the equation

$$k'_A/k'_B = k_AK'_AK_B/k_BK'_BK_A \quad (13)$$

where K and K' represent the equilibrium constants for the formation of complexes in phase I and II, respectively. A calculation of k'_A/k'_B according to this equation shows that simultaneous com-

plexing with cineole and silver ion is no better and may be less effective than complexing with either reagent alone. This conclusion was verified by determining the partition coefficients of the individual cresols when distributed between 1 molar silver nitrate solution and cyclohexane containing different concentrations of cineole. The partition ratios to be expected under these circumstances can be calculated by means of equation 7. As shown by the results summarized in Table III, excellent agreement was obtained between theory and experiment.

TABLE III
EFFECT ON PARTITION COEFFICIENT OF SIMULTANEOUS FORMATION OF CINEOLE AND SILVER COMPLEXES OF CRESOLS

AgNO ₃ , M	Cineole, M	<i>o</i> -Cresol		<i>m</i> -Cresol		<i>p</i> -Cresol	
		$k'_{\text{obsd.}}$	$k'_{\text{calcd.}}$	$k'_{\text{obsd.}}$	$k'_{\text{calcd.}}$	$k'_{\text{obsd.}}$	$k'_{\text{calcd.}}$
1.0	0.25	1.9	2.0	1.4	1.4	1.7	1.7
1.0	.50	3.4	3.6	2.4	2.5	3.2	3.2

Experimental

Materials.—The source and purity of the cresols used in this work are described elsewhere.⁹ The cineole was a commercial product which was purified by means of the resorcinol complex.¹³ The silver nitrate and potassium nitrate were of reagent-grade quality. Spectrographic-grade cyclohexane was employed as the organic base.

Methods.—The distributions were carried out in centrifuge separatory funnels by the technique described previously.^{10,14} A standard solution of the cresol (0.5 mg. per ml.) was added to an equal volume of the aqueous phase in a 125-ml. separatory funnel and immersed in a water thermostat maintained at $25.00 \pm 0.02^\circ$. The phases were mixed by vigorous hand shaking for two-minute periods. The establishment of equilibrium was checked by the method of Barry, *et al.*¹⁵ The measurements of concentration were made by ultraviolet spectroscopy at 280 $m\mu$ with the Beckman quartz spectrophotometer. The partition coefficient was determined by the relation $k = C/C_0 - C$ where C_0 and C are the concentration of phenol in the cyclohexane before and after the equilibration. For the runs employing the highest cineole concentrations, the absorbance had to be corrected for the slight contribution of cineole. Pure cineole exhibits only slight general absorption in the ultraviolet region. Cineole is very sparingly soluble in water (0.2%) and is almost completely removed from aqueous solution by extraction with cyclohexane.

In the concentration range involved in this work, the partition coefficients of the cresols are known to be essentially independent of their concentration.¹⁶ To determine the accuracy of the partition measurements, recovery experiments were made in which both immiscible phases were analyzed after equilibration. The sum of the quantities of cresol in each layer thus obtained was always within 1% of the original amount. However, the accuracy of the equilibrium constants is no greater than about 10–15% because a small variation in partition ratio is reflected in a proportionally much greater change in the calculated equilibrium constant.

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(13) Schimmel & Co., report of October, 1907, p. 31; Beilstein, "Handbuch der organischen Chemie," 17, 24 (1933).

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(16) C. Golumbic, *THIS JOURNAL*, 71, 2627 (1949).

(12) F. M. Potter and H. B. Williams, *J. Soc. Chem. Ind.*, 51, 59T (1932).