Study on the Interaction in Mixed Adsorbed Films at the Water/Air Interface. I. Phenol and Its *para*-Derivatives

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This paper presents a method for determination of the parameter β related to the molecular interaction between two surface active compounds in the mixture. The co-adsorption of phenol *para*-derivatives, which are well known in medicine and pharmacy as commonly used antiseptic drugs, was investigated. The surface properties of *p*-methylphenol, *p*-chlorophenol and *p*-bromophenol, as well as their mixtures, studies on the basis of surface tension measurements, have been related to their pharmacological action.

Keywords   phenol derivative; mixed monolayer; adsorbed film, interaction parameter; water/air interface; surface tension

Phenol and its derivatives are well known not only in the chemical industry, but also in medicine and pharmacy as antiseptic and bacteriostatic agents.[1] Phenol had been introduced by Lemaire in 1860, was next applied vigorously by Lister in surgery, and still has a place in current chemotherapy. Phenol is bacteriostatic in a concentration of approximately 0.2%, bactericidal above 1% and fungicidal above 1.3%.[2] Phenol can form a complex with proteins of the bacterial wall, and locally in high concentration is a protein precipitant. These properties, however, appear to be unrelated to its antiseptic action.[1] It is supposed that the antimicrobial action of phenol derivatives depends on their amphipathic structure and their surface activity. It is believed that molecules of this bacteriostatic drug undergo adsorption and are anchored with their hydrophilic groups to the bacterial cell wall,[1] which for most bacteria has a hydrophilic character.[3] Since they strongly decrease the interfacial tension,[4] they influence the permeability of the cell membrane, eventually causing the distruction of the cell.[5] Chemical modification which increases the surface activity of phenol, such as halogenation or allegation, tends to increase its bacteriostatic properties.[6] For example, cresol is about three times as active as phenol, and thymol (4-isopropyl-*m*-cresol) is *ca.* 30 times as active as cresol.[1] However, the introduction of an additional hydrophilic group to the phenol molecule lowers its surface activity as well as its bacteriostatic properties.

Mixed systems, containing two or more physiologically active compounds, are of interest in medicine and pharmacy and are very popular in practical clinical use. It is well known that in mixture form they may interact with each other to produce either favourable or unfavourable effects *in vivo*. Generally, four types of interaction are known, *i.e.* synergy, antagonism, additivity and indifference. If these drugs possess some surface activity and if their pharmacological action can be related to their surface behaviour, it would be interesting to check whether the same kind of interaction observed at the free water surface exists *in vivo* as well. The surface activity of alkylphenols is very high: however, they are known to be very toxic in comparison to halogenophenols, which possess almost the same surface activity as phenol alkyl-derivatives. Therefore it is interesting to investigate the properties of mixed films formed by molecules of alkyl- and halogeno-derivatives to find out if any interaction between the molecules occur at

the water/air interface. The nature of these interactions can be helpful in formulating mixed drug systems with antiseptic properties.

Adsorbed Monolayers at the Water/Air Interface—Theoretical Backgrounds Numerous organic compounds have dipolar character and so-called amphipathic structure. They consist of a polar—hydrophilic head and a nonpolar—hydrophobic tail. After being dissolved in water they adsorb to the surface and form a monolayer. Thus they change both the surface tension, σ, and electric surface potential, ΔV, of water. The adsorption of an organic compound at the free surface of water always causes a decrease in surface tension, while the electric surface potential may either decrease or increase, depending on the chemical character and structure of the adsorbed compound.[7] For example, for a phenol/water system, the surface tension decreases with phenol added, indicating in this way that the surface is selectively enriched by phenol molecules. According to Gibbs approach,[8] there is an excess of adsorbed molecules at the surface in comparison to their concentration in the bulk phase. Quantitatively, surface excess, Γ, of the adsorbed component can be expressed by the following formula:

$$\Gamma = -1/RT(d\sigma/d\ln a) \tag{1}$$

where a is the activity of the organic component in the bulk water. The above formula is valid for a two-component system, assuming that the surface excess of water molecules $\Gamma_{H_2O} = 0$. By fitting surface tension changes with activity to a polynomial, and differentiating the fitted function, one can calculate the Gibbs surface excess for a particular system.[9]

The above equation for the Gibbs surface excess was derived for monolayers formed by organic molecules of the same kind. However, in the case of monolayers formed by the adsorption of molecules of two or more different components, the situation is more complex because of a possible interaction that may exist between molecules of the adsorbed compounds. For example, in the three component system consisting of water molecules and molecules of two different surface active compounds, either a decrease or increase in the surface activity of a mixed monolayer in comparison to the monolayers formed by molecules of one kind can be observed. Thus the mixture can show either synergism or antagonism between molecules of the adsorbed compounds. Quantitatively,

this phenomenon can be described using the parameter β which was originally derived for mixed micellar systems by Rubingh[10] and next extended for mixed surfactant systems adsorbed at the water/air interface by Rosen.[11-13] Using a regular solution theory,[14] it is possible to apply the equations for the surface activity coefficients (γ^S) of two surface active agents, i and j, as a funcion of their surface concentration, expressed in the mole fraction, X:

$$\gamma_i^S = \exp\beta[(1 - X_{i,s})^2] \tag{2}$$

$$\gamma_j^S = \exp\beta X_{i,s}^2 \tag{3}$$

In the above equations, β is the parameter of interaction which is the measure of the nature and the extent of interactions between two surfactants in the mixed film. The negative value of the parameter β is evidence of the attraction forces which occur between molecules, the positive value proves the presence of the repulsion forces.[11] When no interaction between adsorbed molecules occurs, $\beta = 0$. The greater the value of β, the stronger the interaction in the mixture. In the above equation, $X_{i,s}$ is the molar fraction of component i at the surface, defined as:

$$X_{i,s} = \Gamma_i/(\Gamma_i + \Gamma_j) \tag{4}$$

Values of Γ_i and Γ_j can be calculated from the adsorption equation for a three-component system, which has the form:

$$d\sigma = -RT\Gamma_i d(\ln a_i) - RT\Gamma_j d(\ln a_j) \tag{5}$$

Assuming that $\Gamma_{H_2O} = 0$, it is possible to calculate the surface excess for the individual components i and j:

$$\Gamma_i = -1/RT(d\sigma/d\ln a_i)a_j \tag{6}$$

$$\Gamma_j = -1/RT(d\sigma/d\ln a_j)a_i \tag{7}$$

For mixed adsorbed films formed by two different surface active compounds, the surface molar fraction ($X_{i,s}$) can also be estimated by solving the following equation[11,12]:

$$[(X_{i,s})^2 \ln(a_i/a_i^\circ X_{i,s})] : [(1 - X_{1,s})^2 \ln(a_j/a_j^\circ(1 - X_{i,s}))] = 1 \tag{8}$$

wherein a_i (a_j) is the activity of component i (j) in the bulk solution in the mixture required to produce the same surface pressure as a solution containing only substance i (j), for which the activity equals $a_i^\circ = c_i^\circ \cdot \gamma_{i,s}$ ($a_j^\circ = c_j^\circ \cdot \gamma_{j,s}$). Knowing the value of $X_{i,s}$, the parameter β can be estimated from the equation[11,12]:

$$\beta = \ln(a_i/a_i^\circ X_{i,s}) : (1 - X_{i,s})^2 \tag{9}$$

For the determination of the parameter β, one has to measure the surface tension of aqueous solutions of individual components (i and j) with their bulk concentration ($\sigma = f(c_i)$ and $\sigma = f(c_j)$), as well as the surface tension of the mixtures containing both components ($\sigma = f(c_i, c_j)$). Since β can be estimated based on surface tension measurements, its value depends on temperature. β decreases with an increase in temperature, in part because the area per molecule at the interface increases as temperature increases, weakening the interaction between adjacent molecules.[11]

Experimental

The measurements of the surface tension of the aqueous solutions of p-cresol (p-methylphenol), p-chlorophenol, and p-bromophenol (p.a., produced by The British Drug Houses, England) were performed at $20\,°C \pm 0.1\,°C$, using a drop-weight method with a 20 s drop life-time.

The time of the drop formation was empirically established. For a period longer than 10 s no changes in surface tension were observed. The radius of the stalagmometer tip was 0.003521 m. The accuracy of the measurements was ± 0.1 mN/m. All phenol $para$-derivatives were used without further purification. Water was distilled four times and boiled down to two-thirds of the primary volume to remove steam volatile traces of organic impurities.
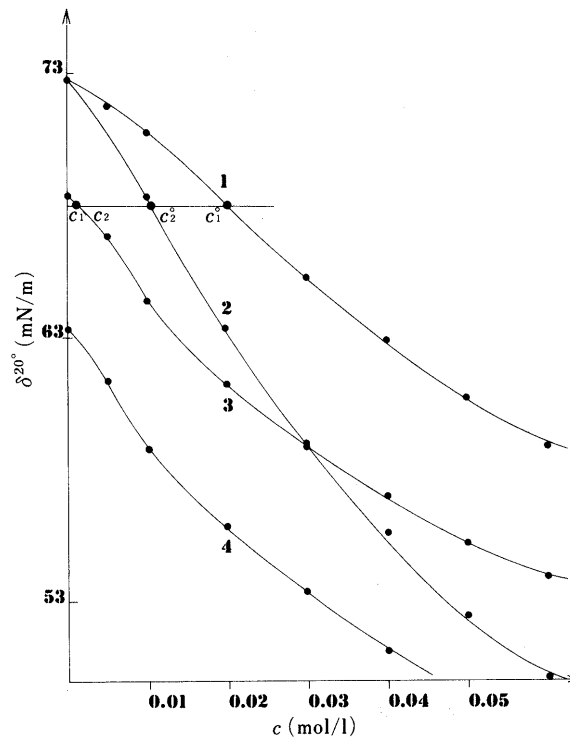

Fig. 1. Surface Tension (σ) of Aqueous Solutions of p-Chlorophenol (1), p-Cresol (2), and Mixtures p-Chlorophenol/p-Cresol at a Constant Concentration of p-Cresol Being 0.01 M (Curve 3) and 0.02 M (Curve 4)

Fig. 2. Surface Tension (σ) of Aqueous Solutions of p-Bromophenol (1), p-Cresol (2), and Mixtures p-Bromophenol/p-Cresol at a Constant Concentration of p-Cresol Being 0.01 M (Curve 3) and 0.02 M (Curve 4)
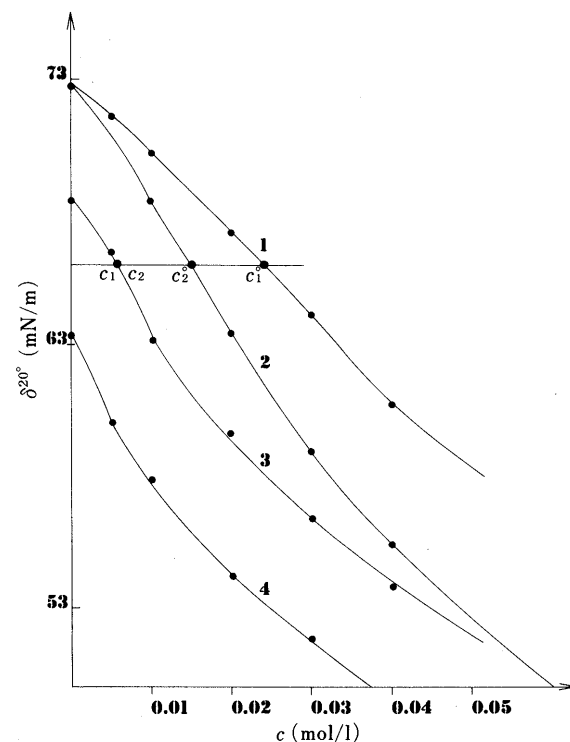
TABLE I. Parameters of Interaction for Mixed Films of p-Chlorophenol/p-Cresol and p-Bromophenol/p-Cresol Adsorbed at the Water/Air Interface

p-Chlorophenol (1)/p-cresol (2)					
c_1^o	c_2^o	c_1	c_2	$X_{1,s}$	β
		(mol/l)			
0.0200	0.011	0.00125	0.01	0.088	-0.411
0.0276	0.015	0.00660	0.01	0.303	-0.486
0.0350	0.019	0.01130	0.01	0.409	-0.683
0.0430	0.023	0.01800	0.01	0.493	-0.634
0.0430	0.023	0.02000	0.02	0.116	-1.175
0.0537	0.027	0.00760	0.02	0.227	-0.800
				$\beta_{average}=$	-0.698

p-Bromophenol (1)/p-cresol (2)					
c_1^o	c_2^o	c_1	c_2	$X_{1,s}$	β
		(mol/l)			
0.02375	0.01450	0.00575	0.01	0.289	-0.354
0.03000	0.01825	0.00875	0.01	0.386	-0.751
0.03625	0.02275	0.01300	0.01	0.465	-0.908
0.03625	0.02275	0.00200	0.02	0.111	-0.887
0.04250	0.02725	0.01850	0.01	0.529	-0.885
0.04250	0.02725	0.00500	0.02	0.225	-1.078
0.05000	0.03200	0.02420	0.01	0.575	-0.930
0.05000	0.03200	0.01000	0.02	0.313	-0.954
				$\beta_{average}=$	-0.843

Results and Discussion

Figures 1 and 2 show the experimental data of the surface tension (σ) of aqueous solutions of p-cresol, p-chlorophenol, p-bromophenol, and mixtures p-cresol/p-chlorophenol and p-cresol/p-bromophenol as a function of their bulk concentration. Values of c_i^o and c_i causing the same decrease in surface tension were determined directly

from the graphs. The values of parameter β for investigated mixed films are compiled in Table I. In the case of investigated systems, parameter β has a negative sign which proves the synergetic properties of the mixtures of p-cresol with phenol p-halogenoderivatives. Taking into consideration the average value of parameter β, stronger interactions occur in mixtures with p-bromo- than p-chlorophenol. Considering the analogy between the surface activity of phenol and its antiseptic and bacteriostatic properties, p-cresol mixtures with p-chloro- and p-bromophenol should possess stronger antiseptic properties as it is more surface active in mixed films at the free surface of water.

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