

# Oxidation of Aldehydes Solubilized in Nonionic Surfactants II

## Oxidation of Benzaldehyde and Methylbenzaldehyde in Aqueous Solutions of Polyoxyethylene Glycol Ethers

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The oxidation of benzaldehyde and *p*-methylbenzaldehyde solubilized in various polyoxyethylene glycol ether nonionic surfactants has been measured manometrically. Evidence is presented to show that rates of oxidation are related to the degree of saturation of the dispersion where this is expressed as the ratio of the amount of aldehyde present to its solubility in the surfactant solution. The effect on oxidation of variation in chain length of the hydrophilic and hydrocarbon parts of the surfactant molecule is discussed.

THE DEVELOPMENT of nonionic surfactants of low toxicity has led to an increase in the use of solubilized preparations in pharmacy. The stability of such preparations toward hydrolysis and oxidation is receiving increased attention (1), and it is apparent that the type and concentration of surfactant used plays an important part in the rate of decomposition.

Using aliphatic aldehydes from *n*-hexanal through *n*-decanal as simple reference compounds, Carless and Mitchell (2) showed that oxidation in aqueous solutions of cetomacrogol 1000 B.P.C.<sup>1</sup> depends on the degree of saturation of the dispersion with aldehyde. The degree of saturation was expressed by

$$R = c/c_s \quad (\text{Eq. 1})$$

where  $R$  is the saturation ratio,  $c$  is the aldehyde concentration, and  $c_s$  its solubility in the surfactant solution. For a given saturation ratio, the rate of oxidation divided by the concentration of reactant was a constant, *i.e.*,

$$\text{rate} = kc \quad (\text{Eq. 2})$$

where from Eq. 1  $c = Rc_s$ .

A relation between saturation ratio and reaction rate also has been shown for the alkaline hydrolysis of *n*-propyl benzoate in nonionic (3), anionic, and cationic surfactants (4) and the bactericidal activity of 4-chloro-3,5-xyleneol in cetomacrogol 1000 (5). The oxidation of aliphatic aldehydes in anionic and cationic surfactants (6) and emulsions of benzaldehyde in ampholytic betaines (7), however, does not appear to depend on the degree of saturation. The present paper reports an investigation into the rela-

tion between degree of saturation and oxidation of benzaldehyde and *p*-methylbenzaldehyde solubilized in aqueous solutions of various polyoxyethylene glycol ethers, with particular reference to the effect of variation in polyoxyethylene and hydrocarbon chain lengths of the nonionic surfactant. Aldehyde solubilities in the nonionic surfactants have been reported previously (1).

### EXPERIMENTAL

**Materials.**—The nonionic surfactants used were Texofors A16, A24, A30, A60, and B23 (Glovers Chemicals Ltd.) and are represented by the general formula  $\text{CH}_3(\text{CH}_2)_m(\text{O}\cdot\text{CH}_2\cdot\text{CH}_2)_n\cdot\text{OH}$ . For the A series,  $m$  is approximately 15 and  $n$  approximately 16, 24, 30, or 60; for B23,  $m$  and  $n$  are approximately 11 and 23, respectively. For convenience, Texofors in the A series are designated C16, C24, C30, and C60. Similarly, Texofor B23 is designated L23. These materials and the aldehydes have been described in the previous paper (1).

**Measurement of Oxidation.**—Measurements of oxygen uptake were made at a temperature of  $25^\circ \pm 0.01^\circ$  using a Braun model VL-85 Warburg apparatus. In this model, each of 14 reaction flasks is mounted above a 40-w. tungsten filament lamp which moves together with the flask during the shaking motion. The intensity of illumination, measured from the surface of the water during stirring, was 425–450 lux. The reaction was found to be highly light-sensitive. Hence, the whole apparatus was enclosed within a light-proof box to exclude extraneous light. Access for reading the manometers was through an open side covered with a black cloth. The rate of oxygen uptake was independent of agitation above a shaking rate of 88 strokes/min., but unlike aliphatic aldehydes (2), was dependent on both reactant and flask volumes. Constant rates could be obtained for different reactant and flask volumes by keeping the ratio of flask volume to reactant volume constant; but generally 2-ml. samples were used in  $13 \pm 1$ -ml. conical flasks without side arm or center well. Cupric sulfate ( $1 \times 10^{-4} M$ ) was included as catalyst

Received September 22, 1964, from the Department of Pharmaceutics, University of Singapore, Singapore, Malaysia. Accepted for publication December 29, 1964.

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<sup>1</sup> Corresponding to C24 in this paper.

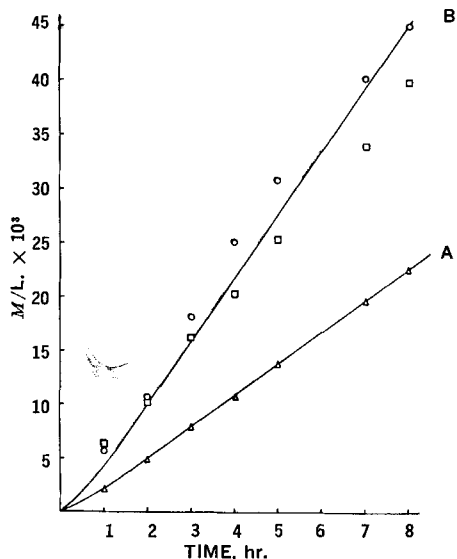


Fig. 1.—Analytical results for the oxidation of benzaldehyde (0.179 *M*) in C24 (0.04 *M*) at 25°. Key: curve A, oxygen uptake; curve B, theoretical amount of benzaldehyde reacted and benzoic acid formed calculated from oxygen uptake, assuming the reaction  $2 \text{C}_6\text{H}_5\text{CHO} + \text{O}_2 \rightarrow 2 \text{C}_6\text{H}_5\text{COOH}$ ; O, aldehyde reacted; □, benzoic acid formed; Δ, oxygen uptake.

in aqueous solutions and  $1 \times 10^{-4}$  *M* cupric stearate in cetane solutions. Readings were started after an equilibration period of 5 min. Measurements were made in duplicate and the results averaged. Preliminary investigations on a large number of replicates showed that the rates were reproducible within 3%.

**Benzoic Acid Estimation.**—Samples of the reactant mixture were taken at suitable time intervals and diluted 1 in 25 with freshly boiled and cooled distilled water. The amount of benzoic acid present was estimated by potentiometric titration with carbon dioxide-free 0.01 *N* sodium hydroxide using a Pye tropical pH meter and a lithium glass-calomel electrode system. Nitrogen was bubbled through the solution during the titration.

**Peroxide Estimation.**—Samples were assayed for peroxide by the iodometric method of Liebhafsky and Sharkey (8).

**Benzaldehyde Estimation.**—The amount of benzaldehyde remaining after varying periods of oxygen uptake was determined gravimetrically as the 2,4-dinitrophenylhydrazone according to the method of Iddles and Jackson (9). Assay of known amounts of aldehyde under the same conditions gave not less than 99.8% recovery.

## RESULTS

**Oxidation in Surfactant Solutions.**—Aldehydes autooxidize by a free radical chain reaction to form carboxylic acid through intermediate steps involving peroxide formation (10). Carless and Nixon (11) claimed that the amount of benzoic acid formed during the oxidation of benzaldehyde in aqueous solutions of cetomacrogol 1000 accounted for only half of the oxygen taken up and suggested that the remainder was used in the peroxidation of the cetomacrogol. Moreover, Coates and co-workers

(12) reported that polyethylene glycols had oxidizing activity thought to be due to peroxides which could be destroyed by catalase. Hence, it was necessary to determine whether measurement of oxygen uptake using a manometric method was a valid means of measuring the rate of aldehyde oxidation in the systems studied. Solutions of the surfactants plus copper catalyst did not take up oxygen on the Warburg apparatus, and peroxides were not detected in stock solutions of surfactant without added catalyst after storage for over 1 year. The amount of benzoic acid formed during the oxidation of surfactant solutions containing solubilized benzaldehyde was slightly greater in the early stages and less in the later stages of the reaction than the theoretical amount expected from oxygen uptake, assuming the over-all reaction  $2 \text{C}_6\text{H}_5\text{CHO} + \text{O}_2 \rightarrow 2 \text{C}_6\text{H}_5\text{COOH}$  (Fig. 1). Perbenzoic acid was detected, but the amount was too small for quantitative estimation. Analysis for remaining benzaldehyde during the course of the reaction showed reasonable agreement between the amount reacted and the amount expected from oxygen uptake (Fig. 1). Hence, measurement of oxygen uptake is a valid method for estimating the oxidation rate of solubilized aldehyde.

The general form of the oxygen-uptake curve showed three well-defined regions: (a) an initial autocatalytic phase during which the rate of uptake increases, (b) a linear period, and (c) a gradual falling off in rate. Figure 2 shows the results of a typical experiment. By conversion of oxygen absorption to aldehyde reacted, it is possible to obtain linear first-order plots of log remaining aldehyde against time for about the first 10–12% of the reaction. However, apparent zero-order uptake of oxygen was maintained until approximately 40–50% of the aldehyde had reacted. Therefore, the rate of reaction was taken as the slope of the linear portion of the oxygen-uptake curve calculated as mole

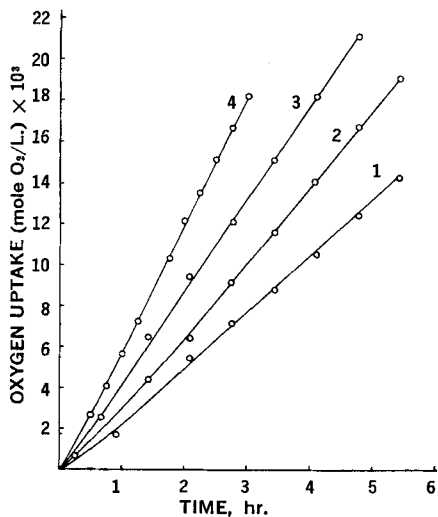


Fig. 2.—Oxygen uptake of benzaldehyde in C24 at 25°. (Saturation ratio = 1.0.) Key: 1, 0.04 *M* C24 and 0.179 *M* benzaldehyde; 2, 0.06 *M* C24 and 0.238 *M* benzaldehyde; 3, 0.08 *M* C24 and 0.296 *M* benzaldehyde; 4, 0.126 *M* C24 and 0.436 *M* benzaldehyde.

TABLE I.—OXIDATION RATE CONSTANTS OF BENZALDEHYDE AND METHYLBENZALDEHYDE IN SEVERAL NONIONIC SURFACTANT SOLUTIONS AT 25° (SATURATION RATIO = 1.0)<sup>a</sup>

Surfactant Concn., Molar	Aldehyde Concn., Molar				Rate Constant, $k \times 10^3$ (mole O <sub>2</sub> /mole ald./hr.)			
	C16	C24	C30	C60	C16	C24	C30	C60
<b>Benzaldehyde</b>								
0.010	0.087	0.092	0.096	0.105	9	10	10	10
0.020	0.116	0.121	0.127	0.146	12	14	13	12
0.040	0.170	0.179	0.186	0.226	15	15	14	14
0.050	0.198	0.209	0.218	...	16	16	15	..
0.060	0.226	0.238	0.247	...	15	16	15	..
0.080	0.281	0.296	0.308	...	16	16	15	..
0.108	0.357	0.380	0.392	...	15	16	15	..
0.126	0.407	0.436	0.448	...	15	15	15	..
<b>Methylbenzaldehyde</b>								
0.010	0.038	0.040	0.045	0.051	18	19	17	20
0.020	0.056	0.058	0.065	0.074	21	22	20	22
0.040	0.093	0.098	0.105	0.121	22	24	23	25
0.050	0.112	0.117	0.125	...	22	24	23	..
0.060	0.130	0.137	0.146	...	23	25	25	..
0.080	0.166	0.176	0.186	...	23	25	25	..
0.108	0.217	0.230	0.242	...	23	24	25	..
0.126	0.250	0.266	0.278	...	23	24	25	..

<sup>a</sup> Each solution in this and subsequent tables contained  $1 \times 10^{-4} M$  copper ion.

TABLE II.—OXIDATION RATE CONSTANTS OF BENZALDEHYDE AND METHYLBENZALDEHYDE IN AQUEOUS SOLUTIONS OF C24 AT 25° (SATURATION RATIO = 1.0)

C24 Concn., Molar	Aldehyde Concn., Molar		Micellar Ald. <sup>a</sup> Total Ald. (%)		Mole Micellar Ald. Mole Surfactant		Rate Constant, $k \times 10^3$ (mole O <sub>2</sub> /mole ald./hr.)		Micellar Rate Constant, $k_m \times 10^3$ (mole O <sub>2</sub> /mole micellar ald./hr.)	
	Benz.	MeBenz.	Benz.	MeBenz.	Benz.	MeBenz.	Benz.	MeBenz.	Benz.	MeBenz.
0.000	0.062	0.019	0.00	0.00	0.0	0.0	2.3	2.5	0.0	0.0
0.001	0.064	0.023	3.3	19	2.0	4.1	3.2	9.2	32	40
0.002	0.067	0.025	8.2	24	2.5	3.1	5.0	11	38	37
0.005	0.078	0.029	21	34	3.2	2.0	8.4	14	32	36
0.006	0.081	0.030	24	38	3.3	1.9	8.8	15	30	37
0.008	0.088	0.035	30	46	3.3	2.0	10	17	27	34
0.010	0.092	0.040	33	52	3.0	2.1	10	19	25	34
0.020	0.121	0.058	49	68	3.0	1.9	14	22	26	32
0.040	0.179	0.098	66	81	2.9	2.0	15	24	22	29
0.060	0.238	0.137	74	86	2.9	2.0	16	25	21	28
0.080	0.296	0.176	79	89	2.9	2.0	15	25	20	27
0.108	0.380	0.230	84	92	3.0	2.0	16	24	18	26
0.126	0.436	0.266	86	93	3.0	2.0	15	24	16	25

<sup>a</sup> Micellar aldehyde/total aldehyde (per cent) =  $\left(\frac{c_m - c_w}{c_m}\right) \times 100$ , where  $c_m$  = solubility of aldehyde in surfactant solution and  $c_w$  = solubility of aldehyde in water.

O<sub>2</sub>/L./hr. Although individual oxygen-uptake curves followed apparent zero-order kinetics after the initial acceleration period, marked differences were found in the rates when varying initial aldehyde concentrations and different surfactant concentrations were used. The various systems studied were compared on the basis of oxidation rate constants,  $k$ , calculated as mole O<sub>2</sub>/mole aldehyde/hr. (Tables I-V).

**Oxidation in Water and Other Solvents.**—Rate constants for the oxidation of solutions containing varying amounts of benzaldehyde and *p*-methylbenzaldehyde in water, 50% ethyl alcohol, 60% w/v dioxane, 70% w/v polyethylene glycol 600, and cetane are given in Table VI.

## DISCUSSION

It is apparent from the results in Table I that when the saturation ratio,  $R$  (as defined in Eq. 1) = 1.0, the rate of oxidation per mole of solubilized

aldehyde is a constant,  $k$  (Eq. 2), above about 0.04  $M$  surfactant. The rate constant,  $k$ , is independent not only of aldehyde and surfactant concentration but also of polyoxyethylene chain length. Below about 0.04  $M$  surfactant, the rate constants decrease and finally reach a value comparable with that of a saturated solution of aldehyde in water (Table II). According to McBain and Hutchinson (13), the solubility of water-insoluble materials in aqueous solutions of surface-active agents can be regarded as a distribution phenomenon in which the dissolved material is distributed between the true aqueous phase and the micelles. When  $R = 1.0$ , both micelles and true aqueous phase are fully saturated with aldehyde. It has been shown previously (1) that solubility curves of benzaldehyde and *p*-methylbenzaldehyde in dilute solutions of C24 approach the solubilities of the aldehydes in water. It can therefore be assumed that the solubility of aldehyde in the true aqueous phase is the same as in water and is not affected by the presence of the surfactant.

TABLE III.—OXIDATION RATE CONSTANTS OF BENZALDEHYDE AND METHYLBENZALDEHYDE IN L23 AND C24 AT 25° (SATURATION RATIO = 1.0)

Surfactant Concn., Molar	Aldehyde Concn., Molar				Rate Constant, $k \times 10^4$ (mole O <sub>2</sub> /mole ald./hr.)			
	Benz.		MeBenz.		Benz.		MeBenz.	
	L23	C24	L23	C24	L23	C24	L23	C24
0.04	0.179	0.179	0.092	0.098	15	15	19	24
0.05	0.209	0.209	0.109	0.117	16	16	18	24
0.06	0.238	0.238	0.127	0.137	15	16	19	25
0.08	0.296	0.296	0.163	0.176	15	16	19	25

TABLE IV.—OXIDATION RATE CONSTANTS OF BENZALDEHYDE AND METHYLBENZALDEHYDE IN SEVERAL NONIONIC SURFACTANT SOLUTIONS AT 25° (SATURATION RATIO = 0.5)

Surfactant Concn., Molar	Aldehyde Concn., Molar				Rate Constant, $k \times 10^4$ (mole O <sub>2</sub> /mole ald./hr.)			
	C16	C24	C30	C60	C16	C24	C30	C60
<b>Benzaldehyde</b>								
0.010	0.044	0.046	0.048	0.053	5	3	5	5
0.020	0.058	0.062	0.064	0.073	6	6	6	6
0.040	0.085	0.089	0.093	0.113	7	9	7	7
0.050	0.099	0.105	0.109	...	7	9	8	..
0.060	0.113	0.119	0.124	...	7	9	8	..
0.080	0.140	0.149	0.154	...	8	10	9	..
0.108	0.179	0.190	0.196	...	8	10	9	..
0.126	0.204	0.218	0.224	...	8	10	9	..
<b>Methylbenzaldehyde</b>								
0.010	0.019	0.020	0.023	0.025	13	16	12	14
0.020	0.028	0.029	0.032	0.037	14	17	17	16
0.040	0.046	0.049	0.053	0.060	17	21	18	17
0.050	0.056	0.058	0.063	...	17	21	18	..
0.060	0.065	0.068	0.073	...	18	22	20	..
0.080	0.083	0.088	0.093	...	18	22	20	..
0.108	0.109	0.115	0.121	...	19	22	20	..
0.126	0.125	0.133	0.139	...	19	22	20	..

TABLE V.—DEPENDENCE OF OXIDATION OF SOLUBILIZED BENZALDEHYDE ON SURFACTANT CONCENTRATION AT 25° (BENZALDEHYDE CONCENTRATION, 0.226 M)

Surfactant Concn., Molar	Saturation Ratio, R			Rate Constant, $k \times 10^3$ (mole O <sub>2</sub> /mole ald./hr.)		
	C16	C24	C30	C16	C24	C30
0.060	1.00	0.950	0.915	15	14	12
0.080	0.810	0.762	0.734	13	12	11
0.108	0.634	0.596	0.577	11	10	9
0.126	0.555	0.519	0.504	9	9	8

TABLE VI.—OXIDATION OF BENZALDEHYDE AND METHYLBENZALDEHYDE IN WATER AND OTHER SOLVENTS AT 25°

Aldehyde Concn., Molar	Solvent	Rate Constant, $k \times 10^3$ (mole O <sub>2</sub> /mole ald./hr.)	
		Benz.	MeBenz.
0.0189	Water	...	2.5
0.0329	Water	0.0	...
0.0617	Water	2.3	...
0.10	Alcohol, 50%	0.0	1.1
0.10	PEG 600, 70%	3.2	4.7
0.10	Dioxane, 60%	0.4	1.8
0.10	Cetane	5.4	5.5

Hence, for saturated solutions the amount of aldehyde in the micelles,  $c_m$ , is given by

$$c_m = c_s - c_w \quad (\text{Eq. 3})$$

where  $c_s$  = solubility of aldehyde in the surfactant solution and  $c_w$  = solubility of aldehyde in water.

For fairly water-soluble materials, such as benzaldehyde and *p*-methylbenzaldehyde, the proportion in the micelles decreases markedly as the concentration of Texofor is decreased (Table II). This is accompanied by a decrease in the rate constant when the amount of aldehyde in the micelles relative to that in the true aqueous phase falls below about 60%. This contrasts with the findings of Carless and Mitchell (2) for the behavior of aliphatic aldehydes like *n*-octanal and *n*-decanal, in which for a given saturation ratio the rate constant is independent of surfactant concentration. *n*-Octanal and *n*-decanal are relatively water insoluble, and the amount in the true aqueous phase is negligible compared with that in the micellar phase. Oxidation of aldehydes proceeds by a free radical chain reaction (14, 15), and it is likely that in the solubilized state the main site of reaction will be in the micelles. These provide high local concentrations of aldehyde in which it should be possible for the chain reaction to proceed rapidly. The low oxidation rate constants shown by benzaldehyde and

*p*-methylbenzaldehyde in dilute surfactant solutions are probably because much of the aldehyde is dispersed in the true aqueous phase where the molecules cannot enter readily into a chain reaction.

Evidence for the above suggestions is provided by the low rates of oxidation found in water and mixtures of water with ethyl alcohol, dioxane, and polyethylene glycol (Table VI). These findings conflict with those of Carless and Nixon, who gave a figure of 3.49 Gm./L. (0.0329 *M*) for the water solubility of benzaldehyde at 25° (16) and claimed that the oxidation rate of a saturated solution of benzaldehyde in water was slightly above the rate of benzaldehyde solubilized in cetomacrogol (C24). They concluded that oxidation took place almost exclusively in the true aqueous phase (11). The authors have found that the water solubility of benzaldehyde is 6.55 Gm./L. (0.0617 *M*) (17) and that the oxygen uptake of a solution in water containing 0.0329 *M* benzaldehyde was zero, while for a saturated solution of benzaldehyde in water the oxidation rate constant was still less than the most dilute surfactant solution studied. (See Tables II and VI.)

Assuming that the main reaction site is in the micelles, then the rate constant for the micellar reaction,  $k_m$ , should be given by

$$k_m = \frac{\text{rate}_m}{c_m} = \frac{\text{rate}}{c} - \frac{\text{rate}_w}{c_w} \quad (\text{Eq. 4})$$

where  $\text{rate}_w$  is the rate of oxidation of aldehyde,  $c_w$ , in the true aqueous phase. Table II shows the rate constants,  $k_m$ , for benzaldehyde and *p*-methylbenzaldehyde when  $R = 1.0$ . Under these conditions,  $c_m$  is given by Eq. 3; it is assumed that  $\text{rate}_w$  is the same as that for a saturated solution of aldehyde in water. Over the range 0.001 to 0.126 *M* surfactant,  $k_m$  decreases gradually,<sup>2</sup> showing that the relationship between the measured rate of oxygen uptake and the rates of reaction in the micelles and true aqueous phase is not a simple one. Nevertheless, it is apparent that oxidation of solubilized aldehyde takes place mainly within the micelles.

Since aldehydes oxidize by a free radical chain process, the rate of reaction in the micelles may be expected to depend on the proximity of aldehyde molecules to one another. When  $R = 1.0$ , *i.e.*, when the micelles are fully saturated with aldehyde, the mole micellar aldehyde/mole surfactant ratio<sup>3</sup> is approximately constant, an indication of a similar packing of aldehyde molecules within the micelles at each surfactant concentration (Table II).

The effect of variation in the hydrocarbon part of the surfactant at constant saturation ratio depends on the aldehyde. The rate constants when  $R = 1.0$  for benzaldehyde in L23 and C24 are the same, while for *p*-methylbenzaldehyde, the rate constants are greater in the surfactant with the longer hydrocarbon chain (Table III). These results can again be interpreted in terms of oxidation taking place mainly within the micelles. On the basis of solubility and ultraviolet absorption data, it was sug-

gested earlier (1) that benzaldehyde was solubilized in the polyoxyethylene region of the micelle, while *p*-methylbenzaldehyde was distributed between both hydrophilic and hydrocarbon regions. The higher value of the oxidation rate constant of *p*-methylbenzaldehyde in the surfactant with the longer hydrocarbon chain is due probably to the increase in proportion of aldehyde located in the center of the micelle. The aldehyde molecules will be more closely packed, and the interior of the micelle provides a nonpolar hydrocarbon environment which appears to favor the oxidation process. [Compare rate constants in cetane with rate constants in polar solvents (Table VI).]

Saturation ratio values of less than 1.0 can be obtained either by decreasing the concentration of aldehyde or by increasing the concentration of surfactant. Table IV shows the rate constants,  $k$ , when  $R = 0.5$ . It was not possible to estimate the rate constants for the micellar reaction,  $k_m$ , since the distribution of aldehyde between the micelles and the true aqueous phase was not known for undersaturated solutions. Attempts to estimate this distribution are being made using the dialysis technique developed by Kostenbauder (18–20). However, for equimolar surfactant concentrations, the rate constant,  $k$ , is similar for surfactants of different polyoxyethylene chain length, and above surfactant concentrations of about 0.05 *M*, the rate constant becomes independent of the concentrations of aldehyde and surfactant.

The effect of increasing surfactant concentration on the oxidation rate constant of a solution containing a fixed amount of aldehyde is shown in Table V. An increase in the concentration of surfactant and thereby the number of micelles can be expected to reduce the amount of aldehyde in each micelle. If, as suggested above, the oxidation of aldehydes proceeds by a chain reaction within the micelles, then it is reasonable to conclude that a decrease in the number of reactant molecules per micelle is responsible for the observed decrease in rate constant. For a fixed aldehyde concentration and equimolar concentrations of the different surfactants, the rate constant decreases with an increase in the number of ethylene oxide units. This is related to the decrease in saturation ratio. It is possible to consider from these results the effect of variation in hydrophilic chain length on the rate of reaction. A survey of the literature (21–24) concerning the effect of variation in polyoxyethylene chain length on micellar weight and size indicates that micellar weight and aggregation number decrease with increase in polyoxyethylene chain length, while the micellar radius remains approximately the same. Therefore, for equimolar concentrations of surfactants of varying polyoxyethylene chain lengths, there should be an increase in the number of micelles present in the system as the hydrophilic chain length is increased.

As discussed earlier (1), the solubilization of benzaldehyde appears to take place in the polyoxyethylene region of the micelle. As the polyoxyethylene chain becomes longer, it is likely that in dispersions containing equimolar amounts of benzaldehyde the aldehyde molecules will be distributed over a greater number of ethylene oxide units and also between a larger number of micelles. This would result in a decrease in oxidation rate

<sup>2</sup> Any errors in the measured rate of oxygen uptake or deviation from the assumed values of  $\text{rate}_w$  and  $c_w$  will have a relatively greater effect on the calculated values of  $k_m$  for dilute surfactant solutions than for concentrated solutions.

<sup>3</sup> In calculating the ratio of aldehyde to surfactant molecules within the micelle, a correction should be made for the concentration of nonmicellar surfactant. However, the CMC is sufficiently low (1) for this correction to be neglected.

since the chance of collision between reactive species is reduced.

It has been shown previously (2) that dispersions containing aliphatic aldehydes in excess of their solubility, *i.e.*, emulsions, have similar rate constants, provided the saturation ratio is the same. With benzaldehyde and *p*-methylbenzaldehyde, however, agreement between rate constants in dispersions having the same saturation ratio is confined to the solubilized state. With emulsions, the rate constant falls progressively with increase in surfactant concentration. Carless and Swarbrick (7) have reported a similar pattern for the oxidation of emulsions of benzaldehyde in betaines. They pointed out that the term "emulsion" is used to cover all forms of dispersion in which oil is present in excess of its solubility in a surfactant and that in a ternary system the nature of the separating phase or phases may vary in composition with the concentration of each component, even though the saturation ratio is the same.

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## Effect of Particle Size on Gastrointestinal Absorption of Sulfisoxazole in Dogs

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After oral administration of sulfisoxazole to dogs, the blood level is affected by the particle size of the drug. Equations which describe this change in the range of experimental testing were derived empirically. Statistical evaluations and probabilities of error are given. The effect of particle size on the blood level of sulfisoxazole in dogs is due largely to the dissolution rate of the drug in the gastrointestinal tract of the animal. The possibility of controlling blood level by controlling the particle size content of a single dose is evident. Faster and higher blood levels of sulfisoxazole can be obtained by reduction of particle size. The proportion of the dose which is absorbed does not change; however, the rate at which this proportion is absorbed does change with a change of particle size.

THE PARTICLE size of some medicaments has been observed to affect their biological activity (1, 2). A reduction of the particle size of a drug increases the specific surface area and usually results in an increase in both the dissolution rate and the solubility. The logical assumption follows that if more of a medicament is in

solution and if solution is effected at a faster rate in the gastrointestinal tract, a more rapid rate of absorption will result (1-3). It is reasonable to expect that those drugs which are practically insoluble present a case in which reduction of particle size may be advantageous. Such has proved to be the case with griseofulvin (4). There is also the possibility that sustained-release medication can be produced by increasing the particle size of some medicaments.

In view of the fact that most of the studies regarding the effects of particle size in biological systems have been brief, a carefully controlled statistically analyzed study of this phenomenon

Received September 3, 1964, from the School of Pharmacy, University of Mississippi, University.

Accepted for publication December 29, 1964.

Presented to the Scientific Section, A.Ph.A., Detroit meeting, March 1965.

Abstracted from a dissertation submitted by Julian H. Fincher to the Graduate School, University of Connecticut, Storrs, in partial fulfillment of Doctor of Philosophy degree requirements.

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