Table I—Values of Krafft Point and CMC for Sodium Soaps and Sodium Alkyl Sulfates in Water

n^a	Krafft Point[b]	CMC[c], moles/l. × 10^3
	$C_nH_{2n+1}OSO_3Na$	
10	8°	33.1 (25°)
12	20°	8.1 (25°)
14	33°	2.2 (40°)
16	46°	0.5 (40°)
18	58°	—
	$C_nH_{2n+1}COONa$	
7	—	340 (25°)
9	—	94 (25°)
11	36°	24.4 (25°)
13	53°	7.1 (50°)
15	62°	—
17	71°	—

[a] Number of carbon atoms in the normal alkyl chain. [b] From *Reference 8.* [c] From *Reference 9.*

for the concentration of nonassociated surfactant molecules is the solubility limit at temperatures below the Krafft point and the CMC above it. The solubility at the Krafft point is equal to the CMC (7). The monomer activity of aqueous surfactant solutions increases only slightly after the overall concentration has been raised above the CMC because the bulk of the surfactant added in excess of the CMC forms micelles. CMC values and Krafft points for two homologous series of anionic surfactants are assembled in Table I.

As the alkyl chain length increases on ascending a homologous series, there is a monotonic decrease in the maximum concentration of single or nonmicellar surfactant species owing to a decrease in solubility or in the CMC. This effect is responsible for the downturn in the curves of Figs. 1 and 2. This reasoning is only valid if, at temperatures above the Krafft point, the surfactant concentrations in the aqueous phase are equal to or exceed the CMC values.

Conclusion—With the oil–water partition coefficient increasing and the limiting monomer concentration decreasing on ascending a homologous series, a maximum surfactant concentration in the "oil" (collagen, skin, muscle tissue, or erythrocyte membrane) phase is found at an intermediate chain length. As a result, a surfactant of intermediate chain length has the greatest irritant, toxic, or hemolytic effectiveness.

It is to be expected that the chain length for maximum effectiveness within each homologous series depends on the hydrophilicity of the polar headgroup, being greater for the more hydrophilic groups. The $—O—SO_3^-\ Na^+$ group is more hydrophilic than the $—COO^-\ Na^+$ group. The most active alkyl sulfate was found to be the dodecyl ester ($m = n = 12$), whereas sodium laurate ($m = 12$ but $n = 11$) was the most active soap. Unfortunately, only surfactants with even numbers m of carbon atoms were investigated in the two homologous series, making the most effective member among the alkyl sulfates the one with $n = 12 \pm 1$ and among the soaps the one with $n = 11 \pm 1$; n is the number of carbon atoms in the alkyl chain.

Since the increase in P and the decrease in the CMC as a function of n are of comparable magnitude, the ascending and descending branches of curves like the ones of Figs. 1 and 2 should have slopes of comparable absolute values though of opposite signs, as long as the experimental temperatures exceed the Krafft points.

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Enhancement of Intestinal Absorption of a Quaternary Ammonium Compound by Salicylate and Trichloroacetate

Keyphrases ☐ Quaternary ammonium compounds—enhancement of intestinal absorption by salicylate and trichloroacetate ☐ Ammonium compounds, quaternary—enhancement of intestinal absorption by salicylate and trichloroacetate ☐ Absorption, intestinal—effect of salicylate and trichloroacetate on *N,N*-bis(phenylcarbamoylmethyl)dimethylammonium chloride absorption ☐ Salicylate effect—intestinal absorption of a quaternary ammonium compound ☐ Trichloroacetate effect—intestinal absorption of a quaternary ammonium compound

Sir:

The possibility of increasing the GI absorption of poorly permeable, charged drug molecules by formation of lipoid-soluble ion-pairs with various counterions has received a good deal of attention (1–7). The present report concerns the influence of certain anions on the intestinal absorption of *N,N*-bis(phenylcarbamoylmethyl)dimethylammonium chloride (I), a quaternary ammonium compound with antiarrythmic activity[1].

The purity of the drug[2], tritium-labeled on an *N*-methyl group (specific activity 14.5 μc./mg.) as well as

[1] Personal communication, Astra Pharmaceutical Products, Inc., Worcester, Mass.
[2] Provided by Astra Pharmaceutical Products, Inc.

Table I—Effect of Salicylate and Trichloroacetate on the Absorption of I from the Rat Intestine

Minutes	Percent Remaining[a] Control	Salicylate	Trichloroacetate
5	93.5 ± 12.9	75.5 ± 13.1	70.8 ± 8.6
10	84.4 ± 7.3	54.9 ± 5.0	48.5 ± 4.4
15	81.0 ± 8.4	48.7 ± 3.6	39.6 ± 4.0

[a] Mean of five experiments ± one standard deviation.

Table II—Effect of Anions on the Plasma Level and Apparent Partition Coefficient of I

	Plasma Concentration at 30 min.[a], mcg./ml.	Butanol–Water Partition Coefficient
Control	0.24 ± 0.13	23
Salicylate	1.37 ± 0.67	58
Trichloroacetate	—	97

[a] Mean of five rats ± one standard deviation.

unlabeled, was verified by high-voltage electrophoresis. All other chemicals were reagent or scintillation grade. Tritium-labeled I and sufficient unlabeled drug were dissolved in isotonic buffer to give a concentration of 0.4 mg./ml. The buffer (pH 7.4) contained sodium bicarbonate (26 m*M*), potassium chloride (5 m*M*), potassium acid phosphate (1 m*M*), and either sodium chloride, sodium salicylate, or sodium trichloroacetate (122 m*M*). Trichloroacetate solutions were prepared by dissolving equimolar quantities of sodium hydroxide and trichloroacetic acid in water. The molar ratio of anion (*i.e.*, salicylate or trichloroacetate) to drug was about 90:1.

Male Sprague–Dawley rats, weighing about 300 g. and fasted for 24 hr., were anesthetized with ethyl carbamate (1.3 g./kg. i.p.) and prepared as described by Doluisio *et al.* (8) for studying drug absorption from the *in situ* small intestine. Seven milliliters of drug solution was placed in the intestine, and 0.1-ml. samples were removed at 5-min. intervals for 15 min. The volume of the luminal solution was maintained constant by adding buffer immediately prior to sample removal. In a second series of experiments, the renal pedicles as well as the bile duct were ligated, and loss of drug from the intestinal lumen was followed for 30 min. At the end of the absorption period, blood was collected by cardiac puncture and centrifuged for 10 min. at 575 × *g* to obtain the plasma.

Tritium levels were determined by liquid scintillation spectrometry[3]. Scintillation fluid was prepared by dissolving 0.28 g. 1,4-bis[2-(5-phenyloxazolyl)]benzene, 9.46 g. 2,5-diphenyloxazole, and 142 g. naphthalene in 946 ml. dioxane and 50 ml. water. Two-tenths-milliliter samples of plasma were added to 15 ml. scintillation fluid and counted for 100 min.; raw counts were 500–2000 above background. Half-milliliter samples of diluted intestinal perfusate were counted in 15 ml. of scintillation fluid to 10^5 counts. Tritiated water was used as an internal standard; the efficiency of the system was 32% for tritium in buffer, plasma, and intestinal solution.

The results of the absorption studies are summarized in Table I. Both salicylate and trichloroacetate significantly enhance the disappearance of I from the intestinal lumen. Both anionic agents exert their greatest influence on the initial absorption rate of the drug and, thereafter, the effect tends to decline with time. Throughout the experiment, trichloroacetate was slightly more effective than salicylate in enhancing the absorption of I. Determination of tritium levels in the plasma immediately after the 30-min. absorption studies (Table II) clearly showed that the enhanced loss of I from the intestinal perfusate containing salicylate results in substantially higher apparent drug levels in the body. Salicylate concentration in the plasma at the same time averaged about 1.1 mg./ml. Since most of the apparent drug in whole blood is associated with the nonserum fraction, there was some concern that the elevated levels of I in plasma containing salicylate might be due to displacement of the quaternary ammonium compound from the formed elements of the blood. This possibility was ruled out by demonstrating equal concentrations of I in the plasma of whole blood spiked with drug and of whole blood spiked with both drug and salicylate.

The absorption and plasma level data are in general agreement with equilibrium partitioning data (Table II). Both salicylate and trichloroacetate significantly increase the apparent butanol–water partition coefficient of I, with trichloroacetate being somewhat more effective. The results of our investigations are quite encouraging and offer the possibility of substantially improving the bioavailability of quaternary ammonium compounds and other highly ionized drugs.

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[3] Packard Tricarb model 2111.