Partition of Alkylsulfates of Quaternary Ammonium Compounds: Structure Dependence and Transport Study

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Abstract □ The apparent partition coefficients (log $K_{app.}$, chloroform–water) of 48 alkylsulfates of substituted quinolinium compounds and 19 alkylsulfates of substituted pyridinium derivatives were correlated with Bondi's group contribution to the surface area ($A_w \times 10^9$), Hansch's π constant, and Hammett's σ constant. The surface area of the ring substituent and the alkyl group appears to be the most important factor in governing the apparent partition coefficient. The kinetic study of the dialysis of nicotinic acid *N*-methyl iodide through Visking cellulose membrane showed an effective rate constant of 1.6×10^{-2} min.$^{-1}$ in the first hour and a rate constant of 0.3×10^{-2} min.$^{-1}$ after the first hour. The *in vitro* intestinal absorption of four quaternary ammonium iodides was studied. It was found that the presence of equimolar concentration of sodium decylsulfate inhibited the transfer of the quaternary ammonium compounds.

Keyphrases □ Quaternary ammonium alkylsulfates—apparent partition coefficients □ Partition coefficient correlation—Hansch's π-, Hammett's constants, Bondi's group contribution surface area □ Intestinal absorption, *in vitro*—quaternary ammonium compounds □ Dialysis, kinetics—nicotinic acid *N*-methyl iodide

In 1957–1959, Hogben *et al.* (1, 2) postulated that the gastric mucosa and intestinal blood barrier are essentially lipoid in nature and permit the passive diffusion of the unionized lipid-soluble form of a drug. Schanker (3) suggested that the absorption of organic ions might occur by a specialized transport process analogous to those which operate in transport of certain inorganic cations. He further suggested that the organic ions might penetrate the gastrointestinal blood barrier by the diffusion of the ions in the form of a less polar complex formed with some material normally present in the lumen.

Levine *et al.* have studied the transport of quaternary ammonium compounds extensively (4–9). They attributed the poor absorption to the formation of nonabsorbable complexes with mucin. They also proposed that a phosphatidopeptide fraction allowed a more efficient absorption of certain quaternary ammonium compounds. Other mechanisms in addition to passive diffusion were proposed by Levine (9).

Although hundreds of partition coefficients have been reported for unionized molecules by Hansch *et al.* (10–13), relatively few data on the charged molecules are available in the literature (11, 14). Biles *et al.* showed that partitioning of organic ions into the organic layer from the aqueous layer could be increased by the addition of organic ions of opposite charge and by the addition of water-insoluble proton donor-type molecules to the organic layer (15–17).

The purposes of this report are to analyze quantitatively which physicochemical parameter is most important in governing the partition of the alkylsulfates of pyridinium and quinolinium derivatives, and to explore whether alkylsulfates would enhance the absorption of quaternary ammonium compounds by the small intestine.

EXPERIMENTAL

Synthesis of Quaternary Ammonium Iodides—The appropriate tertiary arylamine was reacted with an excess of methyl iodide to form the quaternary ammonium iodide according to the published methods (18). The precipitated crystals were isolated by filtration and recrystallized from methanol or ethanol. Ethyl ether was used as a washing agent. The melting points were checked for all the compounds synthesized and agreed with those recorded in the literature.

Synthesis of the Alkylsulfates—The alkylsulfates were synthesized either by the method previously described (17) or by the method of Dreger *et al.* (19).

Analysis of the Quaternary Ammonium Compounds—The analysis of the quaternary ammonium compounds was performed either by the method previously described (17) or by UV absorption ($\lambda_{max.}$ 236–322 mμ).

Determination of the Apparent Partition Coefficients—The procedure used was identical with that used for the anticholergic compounds (17). The log $K_{app.}$ values (Tables I and II) were obtained from the following expression (16) using the chloroform–water system:

$$\underset{c_1}{B\text{-}\overset{+}{M}e_{(aq.)}} + \underset{c_2}{SO_3\text{-}\overset{-}{O}R_{(aq.)}} \overset{K_{app.}}{\rightleftharpoons} \underset{c_3}{Me\text{-}B\text{-}SO_3\text{-}OR_{(CHCl_3)}}$$

$$K_{app.} = \frac{c_3}{c_1 c_2} \text{ (l./mole)} \qquad \text{(Eq. 1)}$$

Since the dielectric constant of water is 80.4 and that of chloroform is only 4.8, the ion-pair formation in aqueous phase should be negligible as compared to that in the chloroform phase. It is known that highly polar solvents favor ionization. For example, dilute aqueous solutions of sodium chloride and sodium acetate will have practically 100% ionization. It was felt that the same assumption would be valid in the case of an alkylsulfate of quaternary ammonium compound (a salt of a strong acid and a strong base).

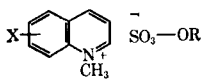
Regression Analysis—The method of least squares was employed to derive the equations using a Honeywell-800 computer. The

Table 1—Equations Correlating log $K_{app.}$ with the Substituent Constants

	n	r	s	Eq.
For *X*-quinolinium-$\overset{+}{\underset{-}{S}}O_3$-OR				
$\log K_{app.} = 0.496\,(A_w \cdot 10^9)_X + 0.345\,(A_w \cdot 10^9)_R - 2.341$	48	0.924	0.272	2
$\log K_{app.} = 0.494\,(A_w \cdot 10^9)_X + 0.345\,(A_w \cdot 10^9)_R + 0.420\,\sigma_X - 2.320$	48	0.931	0.263	3[a]
$\log K_{app.} = 0.536\,\pi_X + 0.931\,\pi_R - 0.582\,\sigma_X - 1.227$	48	0.831	0.401	4
For *X*-pyridinium-$\overset{+}{\underset{-}{S}}O_3$-OR				
$\log K_{app.} = 0.169\,(A_w \cdot 10^9)_X + 0.253\,(A_w \cdot 10^9)_R - 1.366$	19	0.981	0.130	5[a]
$\log K_{app.} = 0.479\,\pi_X + 0.639\,\pi_R + 0.934\,\sigma_X - 0.561$	19	0.967	0.175	6

[a] Equation which is statistically most significant.

Table II—The Apparent Partition Coefficients of the Alkylsulfates of the Quinolinium Derivatives and the Physicochemical Constants Used in the Correlation



Log $K_{app.}$ Obs.	Log $K_{app.}$ Calc.[a]	$A_w \cdot 10^9$ of X	π_X	σ_X	$A_w \cdot 10^9$ of R	π_R	X	R
2.79	2.52	0.78	0.00	0.00[b]	12.92	4.50	H	C_9H_{19}
3.24	2.99	0.78	0.00	0.00	14.27	5.00	H	$C_{10}H_{21}$
3.78	3.45	0.78	0.00	0.00	15.62	5.50	H	$C_{11}H_{23}$
4.20	3.92	0.78	0.00	0.00	16.97	6.00	H	$C_{12}H_{25}$
2.98	3.12	2.12	0.50	−0.14[b]	12.92	4.50	2-CH_3	C_9H_{19}
3.49	3.59	2.12	0.50	−0.14	14.27	5.00	2-CH_3	$C_{10}H_{21}$
3.93	4.05	2.12	0.50	−0.14	15.62	5.50	2-CH_3	$C_{11}H_{23}$
4.35	4.52	2.12	0.50	−0.14	16.97	6.00	2-CH_3	$C_{12}H_{25}$
3.05	3.11	2.12	0.50	−0.17[b]	12.92	4.50	4-CH_3	C_9H_{19}
3.49	3.58	2.12	0.50	−0.17	14.27	5.00	4-CH_3	$C_{10}H_{21}$
3.95	4.04	2.12	0.50	−0.17	15.62	5.50	4-CH_3	$C_{11}H_{23}$
4.42	4.51	2.12	0.50	−0.17	16.97	6.00	4-CH_3	$C_{12}H_{25}$
3.13	3.15	2.12	0.50	−0.08[c]	12.92	4.50	6-CH_3	C_9H_{19}
3.62	3.61	2.12	0.50	−0.08	14.27	5.00	6-CH_3	$C_{10}H_{21}$
4.06	4.18	2.12	0.50	−0.08	15.62	5.50	6-CH_3	$C_{11}H_{23}$
4.58	4.54	2.12	0.50	−0.08	16.97	6.00	6-CH_3	$C_{12}H_{25}$
3.79	3.75	3.46	1.00	−0.22[c]	12.92	4.50	2,6-$(CH_3)_2$	C_9H_{19}
4.20	4.22	3.46	1.00	−0.22	14.27	5.00	2,6-$(CH_3)_2$	$C_{10}H_{21}$
4.66	4.68	3.46	1.00	−0.22	15.62	5.50	2,6-$(CH_3)_2$	$C_{11}H_{23}$
5.13	5.15	3.46	1.00	−0.22	16.97	6.00	2,6-$(CH_3)_2$	$C_{12}H_{25}$
2.98	3.21	2.09	0.86	0.11[c]	12.92	4.50	6-Br	C_9H_{19}
3.48	3.68	2.09	0.86	0.11	14.27	5.00	6-Br	$C_{10}H_{21}$
3.99	4.14	2.09	0.86	0.11	15.62	5.50	6-Br	$C_{11}H_{23}$
4.40	4.61	2.09	0.86	0.11	16.97	6.00	6-Br	$C_{12}H_{25}$
2.86	3.08	1.82	0.71	0.11[c]	12.92	4.50	6-Cl	C_9H_{19}
3.30	3.55	1.82	0.71	0.11	14.27	5.00	6-Cl	$C_{10}H_{21}$
3.78	4.01	1.82	0.71	0.11	15.62	5.50	6-Cl	$C_{11}H_{23}$
4.26	4.48	1.82	0.71	0.11	16.97	6.00	6-Cl	$C_{12}H_{25}$
3.02	3.35	2.66	−0.02	−0.24[c]	12.92	4.50	6-OCH_3	C_9H_{19}
3.56	3.81	2.66	−0.02	−0.24	14.27	5.00	6-OCH_3	$C_{10}H_{21}$
3.98	4.28	2.66	−0.02	−0.24	15.62	5.50	6-OCH_3	$C_{11}H_{23}$
4.52	4.74	2.66	−0.02	−0.24	16.97	6.00	6-OCH_3	$C_{12}H_{25}$
3.31	3.37	2.66	−0.02	−0.20[c]	12.92	4.50	8-OCH_3	C_9H_{19}
3.82	3.83	2.66	−0.02	−0.20	14.27	5.00	8-OCH_3	$C_{10}H_{21}$
4.29	4.30	2.66	−0.02	−0.20	15.62	5.50	8-OCH_3	$C_{11}H_{23}$
4.77	4.76	2.66	−0.02	−0.20	16.97	6.00	8-OCH_3	$C_{12}H_{25}$
3.13	2.77	1.46	−0.67	−0.20[d]	12.92	4.50	8-OH	C_9H_{19}
3.56	3.24	1.46	−0.67	−0.20	14.27	5.00	8-OH	$C_{10}H_{21}$
4.04	3.70	1.46	−0.67	−0.20	15.62	5.50	8-OH	$C_{11}H_{23}$
4.50	4.17	1.46	−0.67	−0.20	16.97	6.00	8-OH	$C_{12}H_{24}$
3.29	3.52	2.51	1.15	0.35[b]	12.92	4.50	2-I	C_9H_{19}
3.79	3.99	2.51	1.15	0.35	14.27	5.00	2-I	$C_{10}H_{21}$
4.21	4.45	2.51	1.15	0.35	15.62	5.50	2-I	$C_{11}H_{23}$
4.65	4.92	2.51	1.15	0.35	16.97	6.00	2-I	$C_{12}H_{25}$
4.65	3.96	3.54[e]	1.24	0.17[b]	12.92	4.50	2,3-$(CH)_4$	C_9H_{19}
4.96	4.42	3.54	1.24	0.17	14.27	5.00	2,3-$(CH)_4$	$C_{10}H_{21}$
5.45	4.89	3.54	1.24	0.17	15.62	5.50	2,3-$(CH)_4$	$C_{11}H_{23}$
5.86	5.35	3.54	1.24	0.17	16.97	6.00	2,3-$(CH)_4$	$C_{12}H_{25}$

[a] Calculated value using Eq. 3. [b] Using Hammett's σ constant from H. H. Jaffé, *Chem. Rev.*, **53**, 191(1953). [c] Estimated value. [d] Calculated from the pKa values of quinoline and 8-hydroxyquinoline, from A. Albert and J. N. Phillips, *J. Chem. Soc.*, **1956**, 1294. [e] Calculated from 4 × 1.08 − 0.78 for $(CH)_4$-H.

log $K_{app.}$ values, Hansch's π constant (10–14), Bondi's group contribution to the surface area (A_w cm.²/mole × 10^9) (20), and Hammett's σ constant used in the analysis are assembled in Tables II and III.

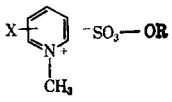
Protein-binding Studies and Kinetic Study of the Dialysis Through Artificial Membrane—The static dialysis method of Matsumoto *et al.* (27) was adapted for these studies. Visking cellulose tubing (Visking Corp., Chicago, average pore size of 24 Å.) was used to carry out the equilibrium dialysis for the binding of *N*-methylacridinium iodide and *N*-methyl-2,6-dimethylquinolinium iodide by bovine serum albumin (2.5×10^{-5} *M*) for a period of 24 hr. Before the binding studies were performed, the Visking tubing was hydrated by soaking it in refrigerated phosphate buffer (pH 6.7) overnight. After soaking, the bag was immediately refilled with 10 ml. of buffer or buffered protein solution and then placed in the bottle which contained 25 ml. of a 6.67×10^{-4} *M* solution of a quaternary ammonium salt in the same buffer. About a dozen assemblies were kept in the refrigerator during the period of dialysis. At specified time intervals, one of the bottles was removed from the refrigerator and the solutions were assayed for the quaternary ammonium compound, so no replacement or correction of the volume was necessary.

Equilibrium time was established by subjecting four compounds (nicotinic acid *N*-methyl iodide, *N*-methyl-2,6-dimethylquinolinium iodide, *N*-methyl-2-chloroquinolinium iodide, and *N*-methylacridinium iodide) to dialysis. It was found that 24 hr. were sufficient for equilibrium to be established.

A kinetic study was done on the dialysis of nicotinic acid *N*-methyl iodide and *N*-methylacridinium iodide for the first 6 hr.

***In Vitro* Intestinal Transport of Some Quaternary Ammonium Compounds**—Preliminary studies were performed on a limited number of *N*-methylquinolinium salts. Fasted, male Sprague Dawley rats weighing 215–307 g. were used. Each rat was anesthesized with ethyl ether. A midline incision was made and the intestine was removed and washed with normal saline solution. The intestine was divided into four segments. The first two segments were considered as the jejunum and the other two as ileal segments. Each segment was everted and attached to the modified Wiseman apparatus previously described by Saltman (21). To the luminal side was added 100 ml. of a 0.001 *M* solution of the quaternary ammonium

Table III—The Apparent Partition Coefficients of the Alkylsulfates of Pyridinium Derivatives and the Physicochemical Constants Used in the Correlation



Log $K_{app.}$ Obs.	Log $K_{app.}$ Calcd.[a]	$A_w \cdot 10^9$ of X	π_X	σ_X[b]	$A_w \cdot 10^9$ of R	π_R	X	R
3.55	3.75	0.78	0.00	0.00	19.67	7.00	H	$C_{14}H_{29}$
3.95	3.97	2.12	0.50	−0.14	19.67	7.00	2-CH_3	$C_{14}H_{29}$
4.46	4.20	3.46	1.00	−0.21	19.67	7.00	2,5-$(CH_3)_2$	$C_{14}H_{29}$
2.70	2.64	4.32	−0.01	0.32	12.92	4.50	3-$COOCH_3$	C_9H_{19}
3.06	2.98	4.32	−0.01	0.32	14.27	5.00	3-$COOCH_3$	$C_{10}H_{21}$
3.36	3.32	4.32	−0.01	0.32	15.62	5.50	3-$COOCH_3$	$C_{11}H_{23}$
3.72	3.66	4.32	−0.01	0.32	16.97	6.00	3-$COOCH_3$	$C_{12}H_{25}$
4.30	4.35	4.32	−0.01	0.32	19.67	7.00	3-$COOCH_3$	$C_{14}H_{29}$
2.97	2.86	5.67	0.49	0.40	12.92	4.50	3-COOEt	C_9H_{19}
3.27	3.21	5.67	0.49	0.40	14.27	5.00	3-COOEt	$C_{10}H_{21}$
3.60	3.55	5.67	0.49	0.40	15.62	5.50	3-COOEt	$C_{11}H_{23}$
3.96	3.89	5.67	0.49	0.40	16.97	6.00	3-COOEt	$C_{12}H_{25}$
4.60	4.57	5.67	0.49	0.40	19.67	7.00	3-COOEt	$C_{14}H_{29}$
3.19	3.32	8.37	1.49	0.40	12.92	4.50	3-COOBu	C_9H_{19}
3.56	3.66	8.37	1.49	0.40	14.27	5.00	3-COOBu	$C_{10}H_{21}$
3.91	4.00	8.37	1.49	0.40	15.62	5.50	3-COOBu	$C_{11}H_{23}$
4.27	4.34	8.37	1.49	0.40	16.97	6.00	3-COOBu	$C_{12}H_{25}$
5.12	5.03	8.37	1.49	0.40	19.67	7.00	3-COOBu	$C_{14}H_{29}$
3.23	3.50	3.34	−1.49	0.28	19.67	7.00	3-$CONH_2$	$C_{14}H_{29}$

[a] Calculated value using Eq. 5. [b] Using Hammett's σ constant in benzene ring system, from H. H. Jaffé, *Chem. Rev.*, **53**, 191(1953).

compound in normal saline; to the serosal side was added 50 ml. of normal saline solution. The system was immersed in a 37° bath, and all solutions were adjusted to 37° before using. The solutions were circulated by bubbling oxygen through the serosal and luminal solutions. Samples were removed at 15, 30, 60, 90, and 120-min. intervals. Two milliliters was removed from the serosal solution and 4 ml. was removed from the luminal solution for each assay. The following quaternary ammonium compounds were studied in this phase of the research: *N*-methylquinolinium iodide, *N*-methyl-6-methoxyquinolinium iodide, *N*-methyl-2-iodoquinolinium iodide, *N*-methyl-6-bromoquinolinium iodide, and *N*-methyl-6-methylquinolinium iodide.

RESULTS AND DISCUSSION

The equations obtained by the method of least squares are listed in Table I. The data used to derive the equations are listed in Tables II and III. In Table I, n is the number of data points used in the regression analysis, r is the correlation coefficient, and s is the standard deviation. From Eqs. 2 and 5, it appears that the surface areas of the substituent on the quaternary ammonium compound as well as that of the alkyl group on the sulfate moiety are the most important factors in governing the apparent partition coefficient (log $K_{app.}$). More than 86 and 96% of the variance in the data (r^2 = 0.86 and 0.96) can be explained by Eqs. 3 and 5, respectively. This reflects the importance of the van der Waals forces (dipole-induced dipole and induced dipole-induced dipole) of the quaternary ammonium–alkylsulfate in the chloroform phase, and the hydrophobic interactions of the alkyl group with the aromatic ring in the aqueous phase. This agrees with the previous finding that the apparent distribution constant of alkylamine salts of tropeolin 00 was governed by the molecular weight and branching of the aliphatic amine, the relative concentration of the amine and dye, and the dielectric constant of the solvent (15). In fact the log $K_{app.}$ of six amine salts of tropeolin 00 reported previously (15) can be correlated with the surface area or the π of the alkyl groups of the amine. This is illustrated by deriving the mathematical expressions by the method of least squares and the equations obtained are expressed (Eqs. 7 and 8).

	n	r	s	
$\log K_{app.} = 0.448\,(A_{wR} \cdot 10^9) - 4.782$	6	0.992	0.150	(Eq. 7)
$\log K_{app.} = 1.177\,(\pi_R) - 2.232$	6	0.994	0.137	(Eq. 8)

Addition of the electronic parameter σ in Eq. 3 gives a better correlation (r = 0.931, s = 0.263). This term is significant at the 95-percentile level ($F_{1,44}$ = 4.02). The positive dependence on σ in Eq. 3 suggests that electron withdrawing groups would enhance the log $K_{app.}$; this is explainable since an electron withdrawer makes the quaternary ammonium ion more positive and attracts the alkylsulfate ion more strongly.

Addition of a σ term to Eq. 5 does not result in an improved correlation. This is probably due to the fact that only two substituents studied have minus σ values and 16 molecules have very close σ values (0.28–0.40). A better selection of the substituents may reveal the role of the electronic effect.

The log $K_{app.}$ values calculated from Eqs. 3 and 5 are in good agreement with the observed values. The calculated and observed values are listed in Tables II and III.

The use of Hansch's π constant has been explored in view of the fact that log P_1 obtained from one solvent system can be related to log P_2 obtained from another system by the linear equation (22): $\log P_1 = a \log P_2 + b$, where a and b are constants. For the quinolinium compounds (Eqs. 2–4) the correlation obtained by using π is not as good as what is obtained by using A_w (r = 0.83 *versus* 0.93), although for the pyridinium compounds (Eqs. 5 and 6) both A_w and π give good correlations (r = 0.98 and 0.97, respectively). This may be due to somewhat different π values of the substituents in the quinolinium system from what were obtained from phenoxyacetic acid system (10).

Equilibrium dialysis studies showed that 24 hr. is sufficient for equilibrium to be established for the compounds studied. Since both solutions were assayed at the same time, it appears that no protein binding occurred with the quaternary compounds investigated. The Student t test revealed that no binding occurred to *N*-methyl-2,6-dimethylquinolinium iodide at P = 0.01 level. The kinetics of the dialysis of nicotinic acid *N*-methyl iodide through Visking cellulose membrane is shown in Fig. 1, using the reversible model (28). In Fig. 1, A_0 is the initial concentration of the drug (5.0×10^{-4} M), A is the outside drug concentration at time t, A_e is the theoretical equilibrium concentration (3.57×10^{-4} M). It is most interesting to note in Fig. 1 that within the 1st hr. the effective rate constant, $k + k'$ (the slope of the regression line) is $(1.62 \pm 0.9) \times 10^{-2}$ min.$^{-1}$, and that following the 1st hr. is $(0.3 \pm 0.15) \times 10^{-2}$ min.$^{-1}$, with the 95% confidence interval

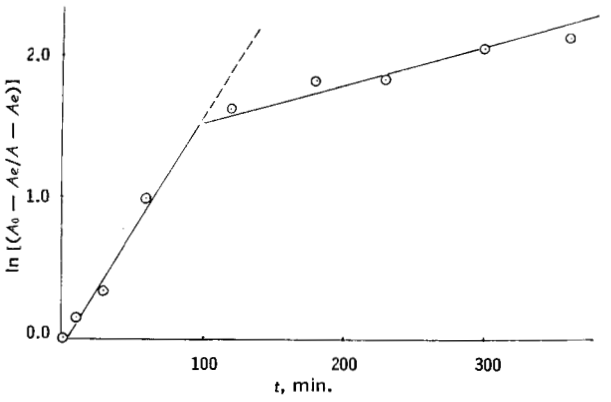


Figure 1—*The kinetic study of the dialysis of nicotinic acid* N-*methyl iodide through Visking cellulose membrane.*

given. The change in the effective rate constant may be due to plugging of some of the smaller pores of the cellulose membrane by the quaternary ammonium compound leaving fewer pores available for transport, and this process appears to be completed within the first hour.

The authors' results on the transport of *N*-methylacridinium iodide showed that this compound might bind on the dialysis membrane since the assay, after a given period of time, resulted in an overall value less than the original value.

The regression lines for the *in vitro* intestinal absorption of some quaternary ammonium salts are given as Eqs. 9–12, where *C* (micromoles) is the amount of quaternary ammonium salt transferred from the mucosal to the serosal side of the intestinal segment, and *t* is time in minutes. Each data point represents the average of four determinations. No transference of *N*-methyl-2-iodoquinolinium iodide was detected. This may be due to steric inhibition because of the presence of the fairly bulky iodo group next to the quaternary ammonium head. The equations expressing the intestinal absorption of the compounds are shown in Table IV.

From the slopes of Eqs. 9–12, it is evident that 6-methylquinoline *N*-methyl iodide and quinoline *N*-methyl iodide were transferred more rapidly. The rate of transfer of 6-bromo-quinoline *N*-methyl iodide and 6-methoxyquinoline *N*-methyl iodide was lower.

The transference of the quaternary ammonium salts was then investigated with the addition of an equimolar concentration of sodium decylsulfate to determine if the ion-ion pair, which is more nonpolar soluble than the iodide salt, occurred at a greater rate. The results showed that no transfer of any of the alkyl salts occurred. This may be due to steric inhibition and/or hydrophobic interactions of the decyl group and the aryl group of the quaternary ammonium moiety with the lipoprotein membrane since it is known that the strength of hydrophobic interaction is about 0.37–1.00 kcal./CH_2 (23–25) and an alkyl group of 10 or more carbon atoms will bind to another hydrophobic counterpart as strongly as an ion pair in the biological system (5 kcal./mole) (26).

Although the apparent partition coefficients of some alkylsulfates of quaternary ammonium compounds were correlated with their molecular structure, it was found that the rate of transfer of these same compounds across the intestinal wall could not be predicted on the basis of their partition coefficients since the presence of equimolar concentration of alkylsulfate inhibited the transfer of the quaternary ammonium compounds. The possible explanations for the failure of absorption of the alkylsulfates of the quaternary ammonium compounds by intestine may be due to: (*a*) steric hindrance because of the attachment of the long alkylsulfate moiety, (*b*) the increased hydrophobic interactions of the alkyl group with the lipoprotein membrane, or (*c*) the absence of the positive charge which is necessary for binding with a carrier.

Table IV—Regression Line Equations Expressing the *In Vitro* Absorption of Some Quaternary Ammonium Salts

Compound	Equation	*n*	*r*	*s*	Eq.
6-Me-quinoline MeI	$\text{Log } C = 6.5 \cdot 10^{-3} t + 0.186$	4	0.99	0.03	9
Quinoline MeI	$\text{Log } C = 5.3 \cdot 10^{-3} t + 1.190$	3	1.00	0.00	10
6-MeO-quinoline MeI	$\text{Log } C = 2.7 \cdot 10^{-3} t + 0.907$	4	0.91	0.05	11
6-Br-quinoline MeI	$\text{Log } C = 2.5 \cdot 10^{-3} t + 1.467$	3	0.98	0.02	12

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