Effect of Chain Length on Critical Micelle Formation and Protein Binding of Quaternary Ammonium Compounds

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The micelle formation tendency (log 1/CMC) of a series of alkyldimethylbenzylammonium compounds is shown to be linearly dependent on the alkyl chain length, indicating no curling of the side chain up to C_{19}. Protein binding of these charged molecules on the primary binding site for sulfaethiodole is shown to be parabolically dependent on the chain length with an optimal chain length around C_{16}.

One uncertainty, usually encountered in quantitative structure–activity relationship (QSAR) studies using additive–constitutive parameters, is the validity of assuming a constant increment in physical constants upon the addition of one methylene group. This may be of particular importance when one is dealing with molecules with long side chains, since there exists a possibility of having "curling" or "balling" of the nonpolar side chain in the aqueous solution by hydrophobic interactions. Furthermore, if one is studying surfactants, micelle formation may further complicate the picture as the concentration goes beyond the critical micelle concentration (CMC). It would also be important to know if the CMC decreases regularly as one increases the length of the side chain gradually.

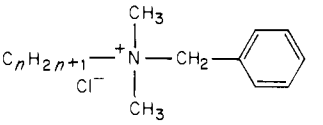
Dunn and Hansch have reported that the hydrophobic interactions of organic compounds with the same species (in micelles) or with macromolecules in many cases are a linear function of the hydrophobicity as represented by log P, where P is the 1-octanol–water partition coefficient.[1] Earlier work by Ross et al. on CMC determinations[2] using dye titration showed a break in the curve at $n = 12$ for a series of even chain homologues of alkylbenzyldimethylammonium chlorides. This was later attributed to mixed micelle formation with the dye molecules by Cutler et al.,[3] since in their surface tension measurement of the odd and even chain homologues a straight line was obtained for 11 molecules on a semilog plot of CMC vs. the chain length. This is clearly evidenced by the extremely high correlation obtained between log 1/CMC and n as well as log 1/CMC and log (surface area) (Table I, eq 1 and 2 of Table II). The high degree of correlation between log $1/C$ and n as well as log SA indicates that there is no detectable deviation from linearity in CMC for the series of alkyldimethylbenzylammonium compounds with side chains from C_8 to C_{19}. This is also supported by the partition coefficient data available. From the unpublished log P values of Soderberg and Hansch[4] on six quaternary ammonium compounds with n from 2 to 16, a reasonably good correlation is obtained between log P and n (eq 3 in Table II and Table III). The relatively high standard deviation of 0.37 may be due to the difficulties involved in measuring the partition coefficients of these surfactants. Substitution of eq 3 into eq 1 give

$$\log 1/\mathrm{CMC} = 0.820 \log P_{\mathrm{oct}} + 11.349$$

It is interesting to note that this equation has a slope very close to that reported by Dunn and Hansch[1] for the binding of alkyl sulfate by BSA at pH 6.1 (0.82 vs. 0.83) although the intercepts are quite different (11.349 vs. 3.92).

An important phenomenon affecting drug action is plasma protein binding. Hansch and his co-workers reported that, in most cases, binding of various drugs appeared to be linearly dependent upon log P.[1,5-8] Recently, Perrin and Nelson employed circular dichroism (CD) to study the displacement of bound sulfaethidole from bovine serum albumin (BSA) by a series of alkyldimethylbenzylammonium chlorides.[9] They reported that the displacement capability, as reflected by the binding constant K, is a function of the chain length. The effect rose to a maximum with $n = 14$–16.

Table I. Critical Micelle Formation and Protein Binding Data and the Physical Constants Used in the Correlations



Chain length n	Log 1/CMC (mol/l.) Obsd[a]	Log 1/CMC (mol/l.) Calcd[b]	Log K Obsd[c]	Log K Calcd[d]	Log SA[e]
8	0.67	0.70	−4.82	−5.18	1.35
10	1.47	1.44	−5.00	−4.57	1.40
11	1.85	1.81	−4.55	−4.32	1.42
12	2.16	2.18	−4.26	−4.11	1.45
13	2.57	2.55	−3.85	−3.93	1.47
14	2.92	2.92	−3.51	−3.79	1.49
15	3.22	3.28	−3.57	−3.69	1.50
16	3.62	3.65	−3.49	−3.62	1.52
17	4.00	4.02	−3.55	−3.60	1.54
18	4.48	4.39	−3.66	−3.60	1.56
19	4.74	4.76	−3.80	−3.65	1.57

[a] From ref 3. [b] Calculated from eq 1. [c] From ref 8. [d] Calculated from eq 5. [e] Surface area A_w, $cm^2/mol \times 10^9$, from A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

When regression analysis is applied to the data (Table I) eq 4–7 (Table II) are obtained. An F test indicates that the n^2 term in eq 5 is statistically significant at the 95 percentile level. A parabolic equation of log SA, on the other hand, not only has a lower correlation coefficient r but also a higher standard deviation s. This may be due to the fact that a very narrow range of log SA is involved. Nonlinear function has also been found for the displacement of series acidic drugs from serum albumin.[10,11] Higuchi and Davis[12] have proposed a pseudoequilibrium model to account for the nonlinearity, while other possible explanations have also been suggested by Hansch and Clayton.[13]

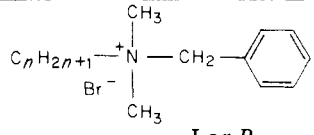
The fact that a parabolic equation of n gives the best correlation for protein binding involving only the primary binding site on BSA ($K = 2.1 \times 10^5$ l. mol^{-1} for sulfaethidole) with an optimum n of ca. 17 for maximum binding suggests that the hydrophobic area for binding is

Table II. Equations Correlating the Micelle Formation Tendency, Partition Coefficient, and Protein Binding Constant with the Chain Length and the Surface Area

Eq		n^a	r^b	s^c	F	Sign. level, %
	Micelle Formation					
1	Log 1/CMC = 0.369 (±0.009)[d] n − 2.251 (±0.134)[d]	11	0.999	0.045	$F_{1,9}$ = 7968	99.99
2	Log 1/CMC = 18.425 (±1.386) log SA − 24.372 (±2.052)	11	0.995	0.134	$F_{1,9}$ = 904	99.99
3	Log P_{oct} = 0.450 (±0.093) n − 4.094 (±0.832)	6	0.989	0.374	$F_{1,9}$ = 179	99.95
	Protein Binding					
4	Log K = 0.133 (±0.067) n − 5.857 (±0.963)	11	0.830	0.328	$F_{1,9}$ = 19.9	99.5
5	Log K = −0.019 (±0.017) $(n)^2$ + 0.640 (±0.466) n − 9.117 (±3.077)	11	0.910	0.259	$F_{1,8}$ = 6.37	95.0
6	Log K = 6.902 (±3.107) log SA − 14.214 (±4.601)	11	0.859	0.301	$F_{1,9}$ = 25.3	99.9
7	Log K = −33.963 (±84.724) $(\log SA)^2$ + 107.049 (±248.43) log SA − 87.549 (±181.811)	11	0.611	0.494		N.S.

[a] The number of data points used in the correlation. [b] The correlation coefficient. [c] The standard deviation of the correlation. [d] 95% confidence limit.

Table III. Octanol-Water Partition Coefficients and the Chain Length of Quaternary Ammonium Compounds



Chain length n	Log P Obsd[a]	Log P Calcd[b]
2	−3.38	−3.19
4	−1.85	−2.29
6	−1.53	−1.39
8	−0.29	−0.49
10	−0.08	0.41
16	3.28	3.11

[a] From ref 4. [b] Calculated from eq 3.

not unlimited. Since there is a collinearity between log P and n (see eq 3), a similar parabolic equation should be obtained if one uses log P instead of n. Due to the lack of reliable experimental log P values for the quaternary ammonium compounds examined, we elect to use n for the correlation. When less discriminatory techniques like dialysis are used, additional secondary sites may also be taken into account and the cut-off point may then be moved upward. This may consequently give rise to the linear equation frequently observed for drug–albumin interactions. It has been shown that differences in solution conditions and in albumin purity may affect the binding data significantly.[14,15]

Fatty acids[16,17] and long-chain alkyl sulfates and sulfonates[18,19] also show a maximum in their binding energies following interaction with bovine serum albumin.

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A Potential Amphetamine Antagonist, Adamantanamine Derivative of Fluphenazine[1]

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Fluphenazine adamantylcarbamate was prepared and tested for antagonism of amphetamine-induced increase in spontaneous motor activity and shock avoidance response in rats. This compound exerts weaker antiamphetamine action than fluphenazine.

Neuroleptic drugs can effectively inhibit the agitation and stereotyped gnawing behavior induced in rats by amphetamine.[2] The antagonism of amphetamine hyperthermia by several neuroleptic drugs in rats[3a] and more specifically by pimozide in rabbits[3b] has been reported. An undesirable side effect of neuroleptic drugs is the production of extrapyramidal, Parkinson-like symptoms which probably arise from drug action on the corpus striatum.[4]