Synthesis and CMC Determination of a Series of Aliphatic Diamines

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Abstract □ Fifteen aliphatic diamines substituted with one long alkyl chain (C_{10}–C_{18}), a varying number of methylene groups separating the nitrogens (two to six), and various aliphatic substituents were synthesized and their CMC's were determined. While the length of the long alkyl chain plays a dominant role in influencing the CMC, the other *N*-alkyl substituents as well as the length of the methylene chain separating the two nitrogens of the diamine are significant factors.

Keyphrases □ Diamines, aliphatic—synthesis, determination of CMC values, effect of long alkyl and methylene chains on surface activity □ CMC—determined for 15 aliphatic diamines with one long alkyl chain and varying methylene chain

The bactericidal activity of aliphatic monoamines and diamines was shown to depend largely on their surface activity (1). This has been established in numerous model systems which have correlated antibacterial activity with surface tension lowering (2), critical micelle concentration (CMC) (3, 4), and penetration into monolayers (5). While the length of the aliphatic chain is the predominant factor in determining surface activity, the smaller but significant effects of changes at the protonated nitrogen have been noted (6).

To explore further the effect of structural variation on surface activity, a series of aliphatic diamines was synthesized and their CMC values were determined. This series allows variation of not only the length of the long alkyl chain (R_1) and the other nitrogen substituents (R_2, R_3, and R_4) but also the number of methylene groups *(n)* separating the two amino nitrogens.

EXPERIMENTAL[1]

***N,N*-Dimethyldiamine Dihydrochlorides (I–VIII and X–XIV)**—The appropriate acyl chloride was added to a stirred solution of the appropriate *N,N*-dimethyldiamine (1 equivalent) and triethylamine (1 equivalent) in benzene. The reaction mixture was refluxed for 2 hr, cooled, and filtered. The filtrate was washed with 5% $NaHCO_3$ and a saturated solution of sodium chloride and dried (sodium carbonate). The residue from the evaporation of the benzene was recrystallized from benzene–isopropanol to give the desired amide.

The amide was placed in an erlenmeyer flask connected to a three-necked round-bottom flask with a length of rubber tubing. From this container, the amide was added over 2 hr to a suspension of lithium aluminum hydride (twofold excess) in ether under dry nitrogen. After stirring for 12 hr at 25°, the reaction mixture was worked up in the usual method (7). The resulting filtrate was dried (sodium carbonate) and filtered. Then a saturated solution of dry hydrogen chloride in ether was added to the filtrate until no more salt precipitated. The precipitated salt was washed with ether and recrystallized from a mixture of ethyl acetate and methanol. IR spectra of the final compounds and intermediates were compatible with the structural assignments. The 2-hydroxyethyl derivatives, VII and XIV, were synthesized from V and XIII, respectively, using ethylene oxide in ether (8).

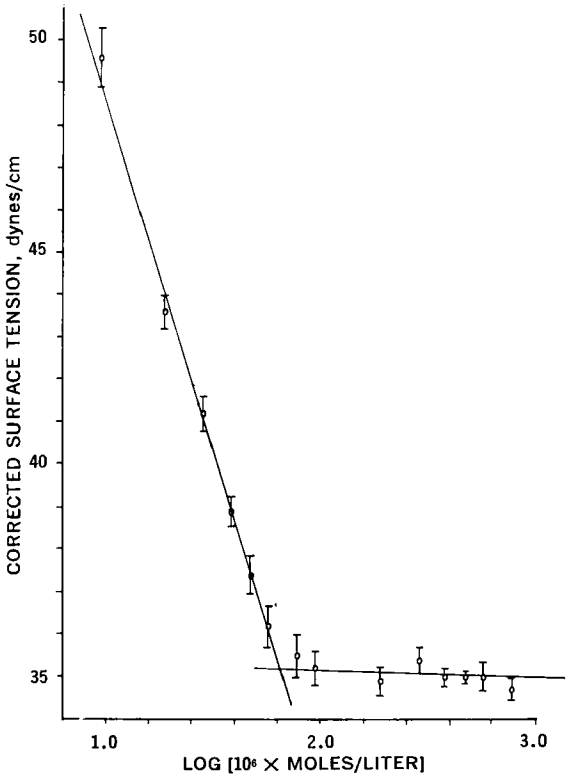


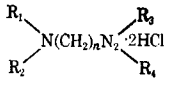
Figure 1—*CMC determination for* N′*-hexadecyl*-N,N-*dimethylbutanediamine dihydrochloride, XII. Vertical bars indicate the standard deviation* (n = 5).

***N*-Octadecyl-1,3-propanediamine Dihydrochloride (XV)**—3-Bromopropionyl chloride (18.6 mmoles, 3.18 g) was added dropwise to a cold (5–10°) solution of octadecylamine (18.6 mmoles, 5 g) and triethylamine (2.58 ml) in benzene (200 ml). The reaction mixture was allowed to warm to 25° and was stirred for 72 hr, during which time a product precipitated. The benzene was evaporated and the residue was washed well with water. The residue was recrystallized from methanol to give 5.1 g of the amide as white crystals, mp 90–91°. The IR spectrum was consistent with the structural assignment.

N-Octadecyl-3-bromopropionamide (12.4 mmoles, 4.0 g) and potassium phthalimide (13.6 mmoles, 2.29 g) were slurried in dimethylformamide (60 ml) and refluxed for 3 hr. The reaction mixture was cooled and poured into water, and the slurry was acidified with concentrated hydrochloric acid. The mixture was extracted with chloroform, the organic layer was dried (sodium sulfate), and the chloroform was removed. The white residue was washed with 2 *N* NaOH and recrystallized from methanol to give 2.5 g of the *N*-octadecyl-3-phthalimidylpropionamide as white crystals, mp 140–141°. The IR spectrum was consistent with the structural assignment.

The phthalimide (1.0 g) was dissolved in a refluxing solution of 95% ethanol (10 ml) and 85% hydrazine hydrate (0.5 ml). The reac-

[1] Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. NMR spectra were determined in $CDCl_3$ (tetramethylsilane internal standard) solution on a Varian A-60A analytical spectrometer or a Hitachi-Perkin-Elmer 60-MHz spectrometer. IR spectra were determined on a Perkin-Elmer model 257 spectrophotometer.

Table I—Melting Points, CMC's, and Elemental Analyses for a Series of Alkyl Diamine Dihydrochlorides 

Compound	R_1	R_2	R_3, R_4	n	Melting Point	CMC (log concentration $\times 10^6$)	Analysis, % Calc.	Found
I	$C_{10}H_{21}$	H	CH_3	2	225–226°	—[a]	C 55.80	56.05
							H 11.37	11.43
							Cl 23.53	23.97
							N 9.30	9.45
II	$C_{12}H_{25}$	H	CH_3	2	216–219°	3.87	C 58.34	58.31
							H 11.63	11.54
							Cl 21.53	21.46
							N 8.50	8.49
III	$C_{14}H_{29}$	H	CH_3	2	212–215°	2.83	C 60.48	60.35
							H 11.84	11.68
							Cl 19.84	19.86
							N 7.84	7.90
IV	$C_{14}H_{29}$	H	CH_3	3	236–238°	2.94	C 61.43	60.99
							H 11.94	12.23
							Cl 19.09	18.98
							N 7.54	7.70
V	$C_{16}H_{33}$	H	CH_3	2	220–222°	1.65	C 62.31	62.12
							H 12.03	11.87
							Cl 18.39	18.48
							N 7.27	7.37
VI[b]	$C_{16}H_{31}O$	H	CH_3	2	69–70°	1.61	C 73.56	73.96
							H 12.96	13.27
							Cl —	—
							N 8.58	8.65
VII	$C_{16}H_{33}$	C_2H_4OH	CH_3	2	210–212°	1.49	C 61.51	61.93
							H 11.73	12.43
							Cl 16.51	16.21
							N 6.52	7.00
VIII	$C_{16}H_{33}$	H	CH_3	4	254° dec.	1.82	C 63.89	63.76
							H 12.18	12.56
							Cl 17.41	16.99
							N 6.77	6.62
IX	$C_{16}H_{33}$	H	CH_3	6	182–183°	2.10	C 65.27	65.25
							H 12.33	12.27
							Cl 16.06	16.12
							N 6.34	6.23
X	$C_{18}H_{37}$	H	CH_3	2	182–183°	1.72	C 63.89	63.79
							H 12.18	12.17
							Cl 17.14	17.18
							N 6.77	6.80
XI	$C_{18}H_{37}$	H	CH_3	3	190° dec.	1.98	C 64.61	64.53
							H 12.26	12.46
							Cl 16.58	16.38
							N 6.55	6.27
XII	$C_{18}H_{37}$	H	CH_3	4	210° dec.	1.80	C 65.27	65.49
							H 12.33	12.27
							Cl 16.06	16.12
							N 6.34	6.23
XIII	$C_{18}H_{37}$	H	C_2H_4OH	3	66–67°	1.36	C 61.58	61.73
							H 11.58	11.69
							Cl 14.54	14.44
							N 5.74	5.83
XIV	$C_{18}H_{37}$	C_2H_4OH	C_2H_4OH	3	88–90°	1.26	C 60.99	60.74
							H 11.37	11.82
							Cl 13.34	13.14
							N 5.27	5.50
XV	$C_{18}H_{37}$	H	H	3	212–214° dec.	0.96	C 63.13	63.25
							H 12.11	12.17
							Cl 17.74	17.58
							N 7.01	7.20

[a] No CMC was found below 10^{-2} *M*. [b] Palmitamide derivative, melting point and analysis are of the free base; hydrochloride, mp 120–121°.

tion mixture was refluxed for 12 hr and then cooled. The ethanol was evaporated and the residue was recrystallized from ethyl acetate to give 0.34 g of *N*-octadecyl-3-aminopropionamide, mp 108–110°. The IR spectrum was consistent with the spectral assignment.

The *N*-octadecyl-3-aminopropionamide (0.35 g) was added to a slurry of lithium aluminum hydride (0.5 g) in ether. The mixture was stirred overnight and worked up in the usual manner (7). The resulting ether solution was dried (sodium carbonate), and a saturated solution of anhydrous hydrogen chloride in ether was added. The precipitated dihydrochloride salt was recrystallized from a mixture of isopropanol–ethyl acetate to give 0.3 g of crystals, mp 214° dec. The IR spectrum was consistent with the structural assignment.

***N,N*-Dimethyl-*N'*-hexadecyldiaminohexane (IX)**—Caprolactone (30 ml, 0°) and cold (0°) dimethylamine (100 g) were added to a Parr bottle. The bottle was sealed and allowed to warm to 25° and then to stand for 1 week at 25°. The reaction vessel was cooled to 0° and the stopper was removed. Nitrogen was bubbled through the mixture to evaporate the excess dimethylamine. The

residue was distilled to give 30 g of oil (bp 188–190°/11 mm). IR and NMR indicated that it was pure *N,N*-dimethyl-6-hydroxyhexamide.

N,N-Dimethyl-6-hydroxyhexamide (5 g) and purified tosyl chloride (14 g) (9) were dissolved in dry pyridine (distilled from barium oxide) and stored for 3 days at 5°. The reaction mixture was poured into water (200 ml), and the resulting slurry was extracted with chloroform (2 × 150 ml). The combined chloroform solutions were washed with 1 *N* H_2SO_4 (3 × 100 ml), 5% $NaHCO_3$ (3 × 100 ml), and a saturated solution of sodium chloride. The chloroform solution was dried (magnesium sulfate), and the chloroform was evaporated to give an oil (7.7 g). NMR and IR indicated that it was >90% pure. This product was used without further purification.

N,N-Dimethyl-6-tosylhexamide (15.9 mmoles, 5 g) and potassium phthalimide (17.5 mmoles, 3.25 g) were slurried in dimethylformamide, and the mixture was refluxed for 3 hr. The reaction mixture was cooled and poured into water (150 ml), and the slurry was extracted with chloroform (3 × 100 ml). The chloroform was washed with 5% NaOH (2 × 100 ml), the organic layer was dried (magnesium sulfate), and the solvent was evaporated. The residual oil (2.5 g) was dissolved in 95% ethanol (25 ml), and 85% hydrazine hydrate (1 ml) was added. Then the mixture was refluxed for 12 hr. The ethanol was evaporated, and the residual oil was distilled through a short column to give 1 g of a clear oil. IR and NMR indicated that it was the desired *N,N*-dimethyl-6-aminohexamide.

A mixture of *N,N*-dimethyl-6-aminohexamide (4.74 mmoles, 750 mg), triethylamine (0.7 ml), and palmitoyl chloride (4.74 mmoles, 1.30 g) was refluxed for 2 hr in benzene and then allowed to stand for 12 hr at 25°. The reaction mixture was washed with water and a saturated solution of sodium chloride and dried (magnesium sulfate). Evaporation of the benzene gave a white residue (1.3 g). Then 1 g of this residue was reduced with lithium aluminum hydride and converted to the dihydrochloride salt in ether. The precipitate was washed with ether and recrystallized from ethyl acetate–methanol, mp 182–183° (yield 700 mg).

CMC Determinations—The CMC's were determined by the du Nouy ring method (10) in isotonic saline at 25° using a surface tensiometer[2]. The corrected surface tension, *S*, was calculated as $S = P \times (0.7250 + aP + b)$ dynes/cm, where *P* is the apparent surface tension (dial reading), $a = 4.0333 \times 10^{-4}$, and $b = 0.01378$ (11, 12). A minimum of 14 concentrations, five replicates each, were measured for each amine. The CMC was designated as the intercept of the linear segments from a plot of surface tension *versus* log (amine concentration). A typical plot is shown in Fig. 1.

RESULTS AND DISCUSSION

To determine the effect of changes in the length of the long alkyl chain (R_1) and the number of methylene groups separating the two nitrogens on the CMC, a series of *N,N*-dimethyl (R_3 and R_4) diamines was synthesized. These compounds were synthesized by converting the long chain carboxylic acid (commercially available in high purity) to the corresponding acyl chloride. The acyl chloride was then allowed to react with the appropriate *N,N*-dimethyldiamine. The resulting amide was reduced to the desired diamine by adding it, as a dry powder, to lithium aluminum hydride in ether. The addition of the amide as a dry powder was found to be more convenient than the soxhlet method recommended by Wilson and Stenberg (13) for amides of low solubility in ether.

It was necessary to synthesize the *N,N*-dimethylhexanediamine to obtain the hexamethylenediamine (IX). In contrast to the opening of γ-butyrolactone with amines, which gives a mixture of products (14), the opening of ε-caprolactone with dimethylamine gave a near quantitative yield of ω-hydroxy-*N,N*-dimethylhexamide. This compound was converted to the tosylate and then, by the Gabriel synthesis, to the corresponding 6-amino compound, which was acylated with palmitoyl chloride and reduced to the desired diamine with lithium aluminum hydride.

[2] Fisher.

The CMC decreased with increases in chain length from C_{10} to C_{16} as expected (Table I). The CMC's of C_{16} and C_{18} derivatives with the same substituents were similar (compare V and X and VIII and XII).

Increasing the N–N separation on the palmitoyl series (V, VIII, and IX) gave a consistent increase in CMC. This finding is in contrast to that with the stearoyl series (X, XI, and XII) which does not vary consistently. While this series does not contain a sufficient number of compounds to make definite conclusions on the effect of N–N separation, it appears that the CMC's vary in the order $n = 2 < n = 4 < n = 3 < n = 6$. This order perhaps reflects the ability of the compounds to form the hydrophilic shell of the micelle. In the case of the hexamethylene derivative, the *N'*-nitrogen must be in the center of the micelle or the hydrophobic hexamethylene chain must be on the surface of the micelle. Both of these possibilities appear to be unfavorable because they require a hydrophilic group in a lipoid region or a lipophilic group in an aqueous region.

Perhaps the most unexpected aspect of the data in Table I is the fact that the palmitamide derivative, VI, and the corresponding diamine, V, have essentially the same CMC. It is surprising that the second ionium ion in V does not have a more significant effect on the CMC. Substitution of the 2-hydroxyethyl substituent at R_2 resulted in a slight (20–25%) decrease in the CMC.

In comparing the CMC's of dimethyl-substituted, bis(2-hydroxyethyl)-substituted, and unsubstituted octadecylpropylenediamines (XI, XIII, and XV, respectively), the CMC increases as the *N*-substituent becomes more lipophilic. This order of increasing CMC is reasonable because increasing the polarity of the onium head and decreasing its steric bulk should make the formation of the hydrophilic shell of the micelle more favorable. In comparing the derivatives where R_2 is either H or C_2H_4OH (*i.e.*, V and VII and XIII and XIV), the more lipophilic hydroxyethyl substituent decreases the CMC. That is, increasing the lipophilicity of the internal amine makes the amine behave as if it has a longer alkyl chain.

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