Micellar Solubilization of Barbiturates II: Solubilities of Certain Barbiturates in Polyoxyethylene Stearates of Varying Hydrophilic Chain Length

M. WAFIK GOUDA*, A. A. ISMAIL†, and M. M. MOTAWI†

Abstract □ A study has been made of the solubilities of a series of 5,5-disubstituted barbituric acid derivatives in aqueous solutions of polyoxyethylene stearates of varying polyoxyethylene chain length. Except for phenobarbital, which forms an insoluble precipitate complex with the solubilizers, all other barbiturates studied were micellarly solubilized. On a molar basis, solubility increases with an increase in hydrophilic chain length but decreases if solubility is expressed in terms of the amount solubilized per ethylene oxide unit. A possible explanation for such a pattern was given. The partition coefficient, K, of the drug molecules between a micellar pseudophase and an aqueous phase was found to be dependent on both the polar effect and the number of carbon atoms of the substituents on the 5-position. The formation of an insoluble precipitate complex by phenobarbital was attributed to the presence of the aromatic phenyl group in the molecule.

Keyphrases □ Barbiturates, 5,5-disubstituted—solubility □ Micellar solubilization—barbiturates □ Solubilization, barbiturates—polyoxyethylene stearates □ Hydrophilic chain length, polyoxyethylene stearates—barbiturates solubilization

The micellar solubilization of certain barbiturate drugs in polysorbates 20, 40, 60, and 80[1] was previously reported (1). These polysorbates have the same hydrophilic portion in their molecule but differ in the length of the carbon atom chain of their lipophilic portion. This investigation was undertaken to study the effect of the hydrophilic group of nonionic solubilizers and the chemical structure of solubilizates on the degree of solubilization. Polyoxyethylene stearates are nonionic surfactants used as solubilizing agents in the same manner as polysorbates (2). Polyoxyl 40 stearate was official in USP XVII as a pharmaceutic aid. A group of four polyoxyethylene stearates[2] was chosen as the solubilizing agents for this study. Since these solubilizers are all of one chemical type, differing only in ethylene oxide content, they serve as a good model to compare solubilization of the barbiturates as a function of hydrophilic chain length.

EXPERIMENTAL

Materials—The following surfactants[2] were used as received: polyoxyethylene 30 monostearate, polyoxyethylene 40 monostearate, polyoxyethylene 50 monostearate, and polyoxyethylene 100 monostearate.

The barbiturates used and their melting points[3] were: phenobarbital, 5-ethyl-5-phenylbarbituric acid, m.p. 173–174°; barbital, 5,5-diethylbarbituric acid, m.p. 185–187°; amobarbital, 5-ethyl-5-isoamylbarbituric acid, m.p. 153–155°; diallylbarbituric acid, 5,5-diallylbarbituric acid, m.p. 169–170°; and cyclobarbital, 5-(1-cyclohexenyl)-5-ethylbarbituric acid, m.p. 89–91°.

[1] Tween 20, 40, 60, and 80, Atlas Chemical Industries, Inc., Wilmington, DE 19899

[2] Myrj 51, 52, 53, and 59, Atlas Chemical Industries, Inc., Wilmington, DE 19899

[3] Uncorrected melting points determined with a Thomas-Hoover Unimelt.

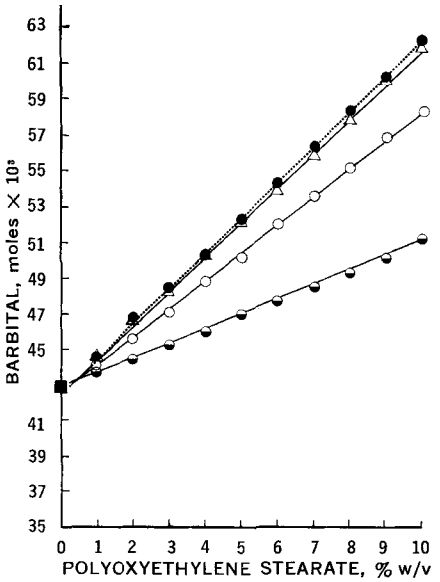

Figure 1—*Solubility of barbital in polyoxyethylene stearate solutions at 30°. Key: ■, solubility in water; ●, polyoxyethylene 30 stearate; △, polyoxyethylene 40 stearate; ○, polyoxyethylene 50 stearate; and ◒, polyoxyethylene 100 stearate.*

Assay Procedure—The differential UV procedure of Walker *et al.* (3), using a Unicam SP 500 spectrophotometer, was used to assay for the barbiturates.

Solubility Determinations—The solubilities of the barbiturates in solutions of polyoxyethylene stearates in 0.003 N sulfuric acid at 30° were determined by the procedure described earlier (1). Equilibrium solubility was attained after 24 hr.

RESULTS AND DISCUSSION

The solubilization of barbital, diallylbarbituric acid, cyclobarbital, amobarbital, and secobarbital in the polyoxyethylene stearate surfactants is shown in Figs. 1–5. The concentrations of the polyoxyethylene stearates used were well beyond their CMC (4). All of these barbiturate drugs showed a linear increase in solubilities in the presence of the solubilizers characteristic of micellar solubilization of such polar solubilizates.

To compare the solubilizing power of the different homologs of solubilizer, the slopes of the solubilization isotherms were calculated using the method of least squares. Table I shows the solubilization capacities expressed as moles drug per gram solubilizer, moles drug per mole solubilizer, and moles drug per equivalent of ethylene oxide in the surfactant. The latter values are the slopes of the solubilization isotherms if the moles of solubilizate were to be plotted against the surfactant concentration in equivalents of ethylene oxide per liter. The solubilizing power of the solubilizers, expressed on a molar basis, is found to increase slightly but gradually as the polyoxyethylene chain increases. However, when the solubilizing power of the surfactants is expressed in terms of moles drug per gram surfactant or moles drug per ethylene oxide equivalent, the

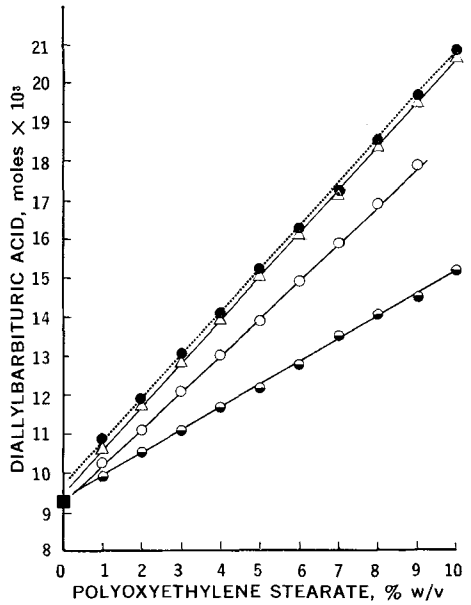

Figure 2—*Solubility of diallylbarbituric acid in polyoxyethylene stearate solutions at 30°. Key: ■, solubility in water; ●, polyoxyethylene 30 stearate; △, polyoxyethylene 40 stearate; ○, polyoxyethylene 50 stearate; and ◒, polyoxyethylene 100 stearate.*

efficiency of solubilization decreases with the increasing length of the polyoxyethylene chain.

Other authors have reported a similar pattern for the solubilization of benzoic acid derivatives in the same polyoxyethylene stearate surfactants (5) and for the solubilization of benzaldehyde and *p*-methyl benzaldehyde in polyoxyethylene ethers of varying hydrophilic chain length (6). No explanation for such a pattern was given. A possible explanation could be forwarded, however, on the basis of the study of Schick *et al.* (7) of the effect of the polyoxyethylene chain length of polyoxyethylene ethers on the micellar weight and the number of surfactant molecules per micelle. From light-scattering measurements, these authors found that, for polyoxyethylene ethers of branched nonylphenol and *n*-decanol having a hydrophobic chain of 10.5 and 12 carbon atoms, respectively, both the aggregate number (number of molecules per micelle) and the aggregate molecular weight of the micelles decrease as the polyoxyethylene chain increases from 10 to 50 ethylene oxide units. However, for *n*-octadecanol ethers with a hydrophobic chain of 18 carbon atoms, the increase in ethylene oxide units from 14 to 100 resulted in a decrease of the aggregate number but an increase of the aggregate molecular weight of the micelle. This increase in micellar weight was also found to be associated with increase in the micellar size. Such an increase in both micellar weight and micellar size was not linearly parallel to the increase in ethylene oxide units. For example, the aggregate molecular weight for the *n*-octadecanol ether surfactants with 14 ethylene oxide units was found to be 330,000; while for the surfactant with 100 ethylene oxide units, it was found to be 465,000. This means that the micellar size per ethylene oxide equivalent will actually be seen to decrease with the increasing length of the polyoxyethylene chain. Since the authors here are dealing with surfactants having the same 18 carbon atom hydrophobic chain length, it seems reasonable to expect that if the solubilization efficiency is expressed on a molar basis, it will increase with the hydrophilic chain length due to formation of larger micelles which could accommodate more solubilizate. On the other hand, if the solubilization efficiency is expressed in terms of number of moles solubilized per ethylene oxide equivalent, then it is expected to decrease as the hydrophilic chain increases.

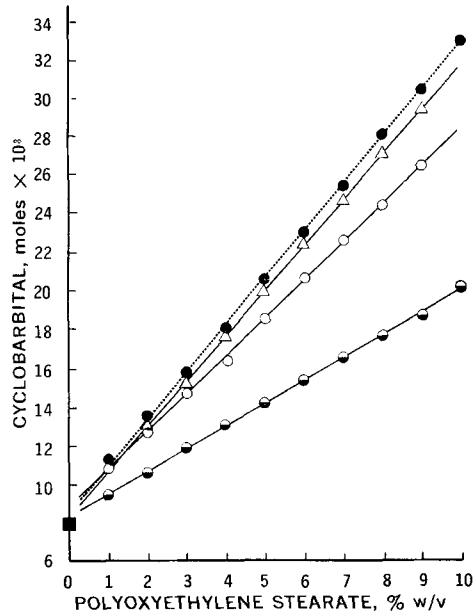

Figure 3—*Solubility of cyclobarbital in polyoxyethylene stearate solutions at 30.° Key: ■, solubility in water; ●, polyoxyethylene 30 stearate; △, polyoxyethylene 40 stearate; ○, polyoxyethylene 50 stearate, and ◒, polyoxyethylene 100 stearate.*

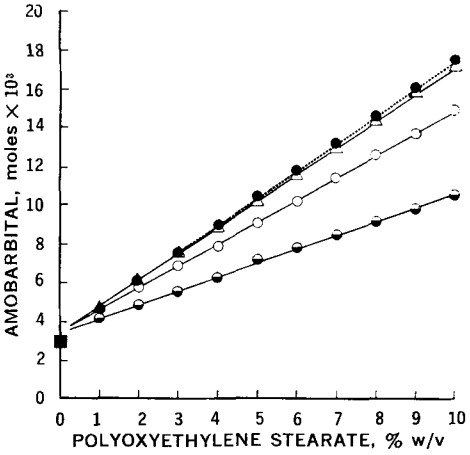

Figure 4—*Solubility of amobarbital in polyoxyethylene stearate solutions at 30°. Key: ■, solubility in water; ●, polyoxyethylene 30 stearate; △, polyoxyethylene 40 stearate; ○, polyoxyethylene 50 stearate; and ◒, polyoxyethylene 100 stearate.*

The effect of the chemical structure of the solubilizate on the degree of solubilization was determined by regarding the solubilization

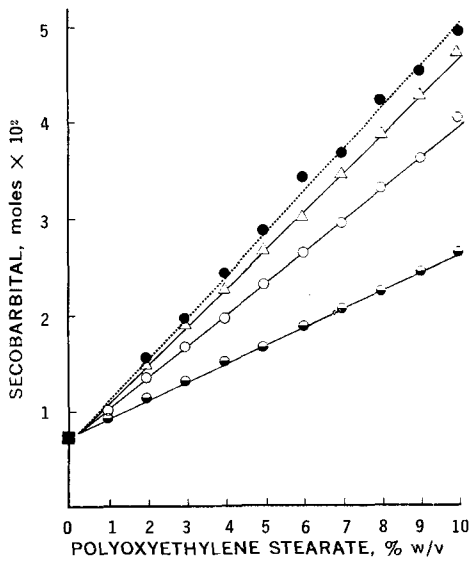

Figure 5—*Solubility of secobarbital in polyoxyethylene stearate solutions at 30°. Key: ■, solubility in water; ●, polyoxyethylene 30 stearate; △, polyoxyethylene 40 stearate; ○, polyoxyethylene 50 stearate; and ◒, polyoxyethylene 100 stearate.*

Table I—Solubilities and Partition Coefficients of Barbiturates in Polyoxyethylene Stearate Solutions at 30°

Drug	Surfactant	Solubility: mole Drug/ g. Surfactant × 10^4	Solubility: mole Drug/ Ethylene Oxide equiv.[a] × 10^2	Solubility: mole Drug/ mole Surfactant[b] × 10^2	Partition Coefficient K [micelles]/[water] × 10^{-2}
Barbital	Polyoxyethylene 30 stearate	1.95	1.07	31.2	4.04
	Polyoxyethylene 40 stearate	1.93	1.00	39.4	5.09
	Polyoxyethylene 50 stearate	1.60	0.79	39.8	5.15
	Polyoxyethylene 100 stearate	0.85	0.40	39.8	5.15
	Polysorbate 60[c]	—	—	25.1	3.17
Diallylbarbituric acid	Polyoxyethylene 30 stearate	1.13	0.62	18.2	10.89
	Polyoxyethylene 40 stearate	1.12	0.58	22.9	13.72
	Polyoxyethylene 50 stearate	0.96	0.47	23.9	14.32
	Polyoxyethylene 100 stearate	0.59	0.28	27.8	16.62
	Polysorbate 60[c]	—	—	17.3	10.48
Cyclobarbital	Polyoxyethylene 30 stearate	2.42	1.33	38.8	27.11
	Polyoxyethylene 40 stearate	2.24	1.17	45.7	31.99
	Polyoxyethylene 50 stearate	1.97	0.97	49.0	34.26
	Polyoxyethylene 100 stearate	1.18	0.55	55.1	38.53
	Polysorbate 60[c]	—	—	33.8	23.97
Amobarbital	Polyoxyethylene 30 stearate	1.42	0.78	22.8	43.29
	Polyoxyethylene 40 stearate	1.38	0.72	28.2	53.76
	Polyoxyethylene 50 stearate	1.15	0.56	28.5	54.36
	Polyoxyethylene 100 stearate	0.72	0.34	33.6	64.07
	Polysorbate 60[c]	—	—	—	—
Secobarbital	Polyoxyethylene 30 stearate	4.33	2.37	69.2	54.88
	Polyoxyethylene 40 stearate	4.01	2.09	81.9	65.03
	Polyoxyethylene 50 stearate	3.31	1.63	82.2	65.27
	Polyoxyethylene 100 stearate	1.88	0.88	87.8	69.71
	Polysorbate 60[c]	—	—	—	—

[a] Percentages of ethylene oxide per surfactant molecules are: polyoxyethylene 30 stearate, 80.0% w/w; polyoxyethylene 40 stearate, 84.5% w/w; polyoxyethylene 50 stearate, 89.5% w/w; and polyoxyethylene 100 stearate, 94.0% w/w (5). [b] Calculations are based on the following molecular weights: polyoxyethylene 30 stearate, 1604; polyoxyethylene 40 stearate, 2044; polyoxyethylene 50 stearate, 2484; and polyoxyethylene 100 stearate, 4684. [c] The molar solubilities and partition coefficients of the drugs in polysorbate 60 were obtained from *Reference 1*.

as a partition between a micellar phase and a water phase. The partition coefficient, K, associated with this process was calculated using the equation reported previously (1). Table I lists the values of K for the various barbiturates in the different polyoxyethylene stearates. The values of K for the same drugs in polysorbate 60, polyoxyethylene 20 sorbitan monostearate, is also included for comparison. The order (decreasing) of the partition coefficients for the mentioned barbiturates between the micellar pseudophase and the aqueous phase was: secobarbital > amobarbital > cyclobarbital > diallylbarbituric acid > barbital. This same order was found for the partition coefficients of the same barbiturates between the polysorbate micellar phase and the aqueous phase (1). It is also the order of their distribution coefficients between 1-octanol and water (8). As expected, the value of K is dependent on the lipophilic character, as well as the inductive effect of the substituents on the 5-position of the barbituric acid molecule. The extent of solubilization, as expressed by K, was found to be higher for the polyoxyethylene stearate solubilizers than for polysorbate 60. Both types of solubilizers have a stearate hydrophobic chain length but the former has more ethylene oxide units. The higher solubilizing power of the polyoxyethylene stearates is considered to be due to their larger size micelles.

The results obtained for these barbiturates indicate that their solubilization in the polyoxyethylene stearate solutions is essentially a micellar solubilization and similar in mechanism to their solubilization in polysorbate solutions. The solubilization mechanism appears to be essentially an inclusion within the micelles. For nonionic surfactants containing polyoxyethylene chains, the micelle may be considered to consist of two parts, an inner core of hydrocarbon tails and an outer shell of hydrated polyoxyethylene (9). The position of the solubilizate molecule inside the micelle cannot be determined with certainty from these results. However, it seems reasonable to expect that the lipophilic character of the substituents on the 5-position of the barbiturate molecule, as well as their influence on the rest of the molecule, will determine whether the solubilizate molecule is predominantly within the hydrocarbon core or the polyoxyethylene shell of the micelles.

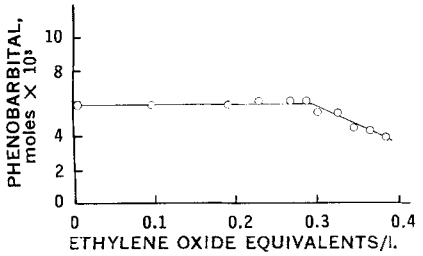

Figure 6—*Interaction of phenobarbital with polyoxyethylene 40 stearate at 30.°*

The interaction of phenobarbital with the polyoxyethylene stearate surfactants resulted in the formation of an insoluble precipitate. The effect of varying polyoxyethylene 40 stearate concentrations, expressed as ethylene oxide equivalents per liter, on the solubility of phenobarbital is shown in Fig. 6. The results are typical of the solubilization curves obtained with all the solubilizers studied. This phase diagram shows a plateau region, indicating that phenobarbital interacts strongly with the surfactant and forms an insoluble precipitate complex. The stoichiometric ratios of the phenobarbital–surfactant complex formed in the plateau region could be calculated from the phase diagrams (10). Analysis of this region shows that 1 molecule of phenobarbital reacts with 3 equivalents of ethylene oxide. This stoichiometric ratio of 1:3 was obtained for all the surfactants studied. Because of the heterogenicity of the surfactants, this value is regarded as an approximation.

Higuchi and Lach (10) found that while pentobarbital and barbital do not interact with polyethylene glycols, phenobarbital forms an insoluble complex with a stoichiometric ratio of 1:2 phenobarbital-PEG. Chakravarty *et al.* (11) showed that polyoxyethylene 40 stearate interacted with phenol and resorcinol to form insoluble complexes. Saito and Shinoda (12) reported that benzene mixes with the polyoxyethylene shell of polyoxyethylene nonylphenyl ethers and depresses the cloud points of their solution to below 0°. Such a depression results in turbidity and separation into two phases at any temperature above the cloud point. The strong interaction of phenobarbital with the surfactants is attributed to the presence of the aromatic ring in the molecule, the phenyl group causing an increased interaction between the barbiturate molecule and the polyoxyethylene chain of the surfactant resulting in the formation of an insoluble precipitate complex.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 23, 1970, from the **School of Pharmacy, University of Montana, Missoula, MT 59801*, and the *†College of Pharmacy, University of Alexandria, Alexandria, U.A.R.*

Accepted for publication May 22, 1970.

* To whom all inquiries should be directed.

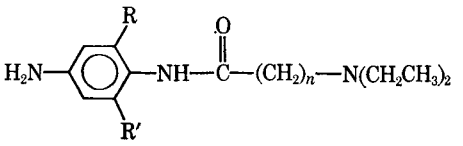
Potential Antiarrhythmic Agents II: Effects of Amide Reversal and *ortho*-Methylation on Activity of Procaine Amide

D. K. YUNG, M. M. VOHRA, and I. CHU

Abstract □ Substitution of a methyl group at one or both of the *ortho*-positions of the benzene ring in procaine amide and procaine provides analogs that are more active in prolonging the refractory period of isolated rabbit atria than procaine amide itself. These analogs, however, fail to abolish ouabain-induced ventricular and aconitine-induced atrial arrhythmias in cats. On the other hand, analogs like 2-diethylamino-4′-amino-2′,6′-dimethylacetanilide dihydrochloride monohydrate, 4-amino-*N*-(2-diethylaminoethyl)-2′,6′-dimethylbenzamide, 2-diethylaminoethyl 4-amino-2-methylbenzoate, and 2-diethylaminoethyl 4-amino-2,6-dimethylbenzoate produce a significant increase in the amount of ouabain required to elicit ectopic rhythm in cats when administered before the infusion of the glycoside. Of these four compounds, the last three also show local anesthetic activity in the corneal reflex test in rabbits. Reversal of the amide group in procaine amide significantly reduces the activity in prolonging the refractory period of cardiac tissue and does not seem to improve the antiarrhythmic activity of the parent compounds.

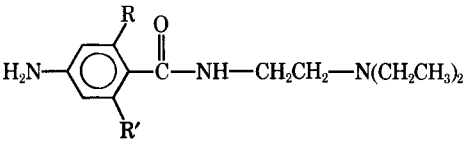
Keyphrases □ Antiarrhythmic agents, potential—synthesis □ Procaine amide activity—amide reversal, *ortho*-methylation, effects □ Structure-activity relationships—procaine amide derivatives □ IR spectrophotometry—identity

It is frequently noted that several pairs of compounds with analogous pharmacological activities can be obtained by reversing the position of the functional group. For example, a large increase in analgesic activity is reportedly caused by this type of reversal in the ester functional group of meperidine (1). As part of a continuing investigation on the structure–activity relationships of procaine amide (2), it was, therefore, considered of interest to determine whether this type of isosterism is possible in procaine amide. Accordingly, 3-diethylamino-4′-aminopropionanilide (I*a*) was synthesized. For comparative purposes, 2-diethylamino-4′-aminoacetanilide (I*b*), 3-diethylamino-4′-amino-2′,6′-dimethylpropionanilide (I*c*), and 2-diethylamino-4′-amino-2′,6′-dimethylacetanilide (I*d*) were also prepared. Compounds I*c* and I*d* can be regarded as analogs of lidocaine, which is useful clinically in the prevention and treatment of cardiac arrhythmias.



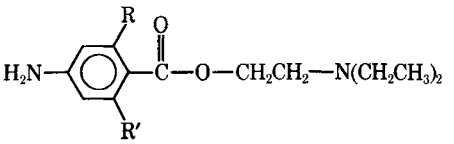
I*a*, $n = 2$; R and R′ = H
I*b*, $n = 1$; R and R′ = H
I*c*, $n = 2$; R and R′ = CH_3
I*d*, $n = 1$; R and R′ = CH_3

The fact that 4-amino-*N*-(2-diethylaminoethyl)-2-chlorobenzamide was 4 times as active as procaine amide in blocking atrial fibrillation in dogs (3) prompted the preparation of 4-amino-*N*-(2-diethylaminoethyl)-2-methylbenzamide (II*a*) and 4-amino-*N*-(2-diethylaminoethyl)-2,6-dimethylbenzamide (II*b*) in an attempt to study the effect on activity of substitution of one or two methyl groups on the benzene ring *ortho* to the amide linkage in procaine amide.



II*a*, R = CH_3; R′ = H
II*b*, R and R′ = CH_3

Two additional compounds, 2-diethylaminoethyl 4-amino-2-methylbenzoate (III*a*) and 2-diethylaminoethyl 4-amino-2,6-dimethylbenzoate (III*b*), were included in



III*a*, R = CH_3; R′ = H
III*b*, R and R′ = CH_3