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Adsorption of Barbiturates on an Electrode Surface

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In order to elucidate the interaction of structurally nonspecific drugs with a charged surface, the adsorption of six barbiturates (barbital, phenobarbital, amobarbital, allobarbital, cyclobarbital and hexobarbital) on a gold electrode surface has been studied by specular reflectivity measurement in 0.1 M NaClO₄. These barbiturates are adsorbed in the potential range around the point of zero charge. From the potential and concentration dependences of their adsorption, it can be deduced that the surface behavior of all these barbiturates is essentially the same. Electrosorption of barbiturates may provide a very simple model of the combination of barbiturates with the synaptic membranes.

Keywords—barbiturate; adsorption; gold electrode; electrode-solution interface; specular reflectivity

Examination of the interfacial behavior of biomolecules at a charged electrode-electrolyte solution interface may provide significant information regarding the interaction of these molecules at a biomembrane surface-biological fluid interface.¹⁾ In our previous paper,²⁾ the adsorption of acetylcholine and related drugs on a gold electrode was examined and the adsorption behavior was discussed from the standpoint of a model of the interaction of these drugs at cholinergic receptor sites. It has been noted that the binding strengths of the drugs at their receptor sites can be explained in relation to their adsorptivity.

Based on the mode of pharmacological action, drugs can be divided into two classes: structurally specific and structurally nonspecific. Structurally specific drugs are those whose pharmacological action results essentially from their chemical structure, which should be appropriately related to the three-dimensional structure of receptors in the organism. On the other hand, structurally nonspecific drugs are those in which the pharmacological action is not directly subordinated to chemical structure, except to the extent that structure affects physicochemical properties.³⁾ Acetylcholine and related drugs belong to the former class. If it is not important for structurally nonspecific drugs to conform to the three-dimensional structure of receptors, no difference in the adsorptivity of drugs having various degrees of pharmacological action is expected for the drugs, in contrast to the adsorption of acetylcholine and related drugs. Barbiturates, which are well-known sedative-hypnotic drugs, are known to be structurally nonspecific drugs.

The objective of the present work was to investigate the adsorption of several barbiturates on a gold electrode surface by specular reflectivity measurement, and to elucidate the surface behavior of barbiturates as examples of structurally nonspecific drugs.

A number of studies on the electrochemical behavior of barbiturates have been reported.⁴⁾ For example, Kunimatsu and Parsons^{4f)} investigated the system of mercury in contact with an aqueous solution of barbiturates by means of ellipsometry and described the optical properties of adsorbed layers of several barbiturates. However, no work has been done on the adsorption from the bioelectrochemical standpoint.

Experimental

The experimental techniques used have already been described.²⁾ The working electrode was a polycrystalline gold plate of 99.99% purity, 0.1 mm in thickness and 25 mm by 22 mm in size. An Ag/AgCl electrode and a gold plate were used as the reference and counter electrodes, respectively. Allobarbitol, amobarbital, barbital, cyclobarbitol, hexobarbital and phenobarbital were obtained from Tokyo Kasei Co., Ltd. A sodium perchlorate solution (0.1 M) was used as the base electrolyte.

Results and Discussion

Barbiturates are classified according to the duration of their hypnotic action as long-, intermediate-, short-, and ultrashort-acting barbiturates.⁵⁾ The barbiturates used in this study are listed in Table I.

Cyclic voltammograms and reflectivity-potential (R/R_0-E) curves of barbital measured simultaneously on gold in 0.1 M NaClO₄ are shown in Fig. 1. The base electrolyte gave a flat double-layer region on the voltammogram over the whole potential range investigated ($-1.0-0.4$ V vs. Ag/AgCl). The presence of barbital caused no appreciable change on the voltammogram, except for small humps at about $-0.1-0.2$ V. Since the current at the humps is not diffusion-controlled and increases with barbital concentration up to *ca.* 10^{-4} M, the humps seem to reflect adsorption-desorption of barbital. Therefore the voltammogram indicates that no redox reaction of barbital occurs over the whole potential region. The R/R_0-E curve of the base electrolyte gave an approximately straight line intersecting at -0.15 V, which corresponds to the point of zero charge (pzc) for gold in neutral solutions. The addition of barbital results in a marked decrease in reflectivity on the R/R_0-E curves at potentials more positive than -0.4 V, indicating that the adsorption of barbital on the

TABLE I. Classification and Structure of the Barbiturates Studied

Duration of action	Name	Substituents	
		C-5	N-3
Long	Barbital	Ethyl, ethyl	H
	Phenobarbital	Ethyl, phenyl	H
Intermediate	Amobarbital	Ethyl, isopentyl	H
	Allobarbitol	Allyl, allyl	H
Short	Cyclobarbitol	Ethyl, cyclohexenyl	H
Ultrashort	Hexobarbital	Methyl, cyclohexenyl	Methyl

Fig. 1. Current-Potential (Upper) and Reflectivity-Potential (Lower) Curves of Gold in 0.1 M NaClO₄ Containing Various Concentrations of Barbital

Barbital concentration: a and c, 0; d, 1.3×10^{-6} ; e, 1.0×10^{-5} ; f, 2.2×10^{-5} ; b and g, 1.0×10^{-4} M. Potential sweep rate: 100 mV s^{-1} . Wavelength: 500 nm.

electrode surface takes place at potentials more positive than -0.4 V . The decrease is enhanced with increasing barbital concentration up to $\text{ca. } 6 \times 10^{-4} \text{ M}$. Hysteresis was evident at the barbital concentration of $\text{ca. } 1.0 \times 10^{-5} \text{ M}$ on the R/R_0 - E curves and became less pronounced at high concentrations.

Similar results were also obtained for other barbiturates, indicating that they are also adsorbed on a gold electrode.

The reflectivity change ($\Delta R/R_0$) at adsorption equilibrium was measured by the potential step technique: the potential was first set at -1.0 V , where adsorption of barbiturates does not occur, and was then stepped to a more positive potential. The R/R_0 at this potential was recorded as a function of time until no further decrease in R/R_0 took place, *i.e.*, adsorption was equilibrated.⁶⁾ The same procedure was also applied to the base electrolyte in the absence of barbiturates as a reference. By subtracting the magnitude of reflectivity decrease at equilibrium in the presence of a barbiturate from that in its absence, the net change, denoted as $|\Delta R/R_0|$, due to the adsorption of the barbiturate was obtained.

In Fig. 2, the values of $|\Delta R/R_0|$ thus obtained are plotted against the potential for the barbiturates examined. Provided that the optical constants of the adsorbed layer and substrate and the thickness of the adsorbed layer remain unchanged during adsorption, $\Delta R/R_0$ at coverage θ is proportional to θ when the adsorption amount is less than that required for monolayer coverage.⁷⁾ Therefore, the $|\Delta R/R_0|$ - E curves may be regarded as representing the potential dependence of adsorption. All the curves in Fig. 2 are of quasi-bell-type having a maximum at -0.1 V , implying adsorption of these neutral organic compounds at around the pzc, tending toward desorption as the electrode potential deviates from the pzc, as a result of competitive adsorption with H_2O and/or supporting electrolytes on the electrode surface. It should be noted that the potential dependences of adsorption of these barbiturates are quite similar to each other.

As can be seen in Fig. 2, the $|\Delta R/R_0|$ values at each potential increase with barbiturate concentration. Assuming the limiting value of $|\Delta R/R_0|$ at the pzc correspond to the $|\Delta R/R_0|$ at $\theta = 1$, adsorption isotherms were obtained (Fig. 3). The isotherms were analyzed based on the Langmuir-like equation employed previously.²⁾

$$\theta/(1-\theta)^p = cK \quad (1)$$

Fig. 2. Potential Dependence of the Reflectivity Change Obtained with 0.1M NaClO₄ Solutions Containing Barbiturates

Concentration: barbital (○) 1.3×10^{-6} ; (△) 2.2×10^{-5} ; (●) 1.0×10^{-4} , phenobarbital (○) 2.0×10^{-6} ; (△) 1.5×10^{-5} ; (●) 1.3×10^{-4} , amobarbital (○) 1.5×10^{-6} ; (△) 1.5×10^{-5} ; (●) 1.6×10^{-4} , allobarbitol (○) 1.1×10^{-6} ; (△) 1.2×10^{-5} ; (●) 1.2×10^{-4} , cyclobarbitol (○) 1.7×10^{-6} ; (△) 1.7×10^{-5} ; (●) 1.5×10^{-4} , hexobarbital (○) 1.5×10^{-6} ; (△) 1.4×10^{-5} ; (●) 1.3×10^{-4} M.

Fig. 3. Isotherms of (A) Barbital, (B) Phenobarbital, (C) Amobarbital, (D) Allobarbitol, (E) Cyclobarbitol and (F) Hexobarbital Adsorption on Gold at a Fixed Potential

Applied potential: ○, -0.1 V; △, -0.3 V vs. Ag/AgCl.

In Eq. 1, p is the number of water molecules replaced by one molecule of the adsorbed species, and c , the bulk concentration. The constant K is the adsorption coefficient given by the following equation.⁸⁾

$$K = \exp\left(-\frac{\Delta G_{\text{ad}}^{\circ}}{RT} + \frac{\alpha F \bar{E}}{RT}\right) \quad (2)$$

where $\Delta G_{\text{ad}}^{\circ}$ is the standard free energy change of adsorption at the pzc; F , the Faraday constant; α , a constant and $\bar{E}$, the potential difference between the pzc and the potential at which the observation is made. The values of p and $\Delta G_{\text{ad}}^{\circ}$ for the barbiturates used were calculated and are listed in Table II.

The $\Delta G_{\text{ad}}^{\circ}$ values of the barbiturates are essentially equal to each other, implying minor

TABLE II. Adsorption Parameters of Barbiturates on Gold^{a)}

Barbiturates	p	$\Delta G_{\text{ad}}^{\circ}$ (kJ mol ⁻¹)
Barbital	4.0 ± 0.2	-41.4 ± 0.8
Phenobarbital	4.3 ± 0.1	-51.9 ± 2.1
Amobarbital	3.6 ± 0.2	-42.7 ± 0.8
Allobarbital	3.9 ± 0.1	-43.1 ± 0.8
Cyclobarbital	3.6 ± 0.1	-42.7 ± 2.1
Hexobarbital	3.8 ± 0.1	-45.6 ± 1.3

a) Standard state, 1 M in solution and a value of θ for with $\theta/(1-\theta)^p = 1$ on the surface.

Fig. 4. Most Probable Orientations of Barbiturates Adsorbed on a Gold Electrode

All the orientations are presented as viewed from an oblique position. For the sake of clarity, all hydrogen atoms are omitted.

effects of substituents on the trioxypyrimidine ring on the adsorptivity.

Assuming that an adsorbed water molecule occupies an area of 0.09 nm^2 , the area occupied by one adsorbed molecule on the electrode surface was estimated from the p value: an area of 0.36 nm^2 was occupied by one barbital molecule; 0.39 nm^2 by phenobarbital; 0.35 nm^2 by allobarbital; 0.32 nm^2 by amobarbital; 0.32 nm^2 by cyclobarbital; and 0.34 nm^2 by hexobarbital. Based on the stereoscopic molecular structures of the barbiturates⁹⁾ and the areas estimated in the present study, it can be proposed that the barbiturates are adsorbed with their trioxypyrimidine rings almost flat with respect to the surface together with the alkyl groups at the C-5 position (Fig. 4).

From studies of the structure-activity relationship of barbiturates in some biochemical systems; such as inhibition of rat brain oxygen consumption and reduced nicotinamide adenine dinucleotide oxidation, steric and electronic effects have been found to play a minor role, but a very good correlation has been found with the relative hydrophobic properties of the drugs.¹⁰⁾ Although a living organism is very complex, it has been found that the hypnotic activity of barbiturates in rats, mice and rabbits depends almost entirely on their relative lipophilic character as defined by their octanol-water partition coefficients.¹¹⁾

Barbiturates are generally used as sedatives and hypnotics in a wide variety of conditions: barbital (JP X) and phenobarbital (JP X), long-acting barbiturates, are hypnotic-sedatives with a duration of action of about 8–16 h, and amobarbital (JP X) and allobarbital (JP IX), intermediate-acting barbiturates, have a duration of action of about 4–8 h. Cyclobarbital (JP IX), a short-acting barbiturate, is a sedating hypnotic with a duration of action of about 3 h, and hexobarbital (JP XIII), an ultrashort-acting barbiturate, has a duration of action of less than 1 h. These six barbiturates were examined in the present study, and little difference was found in surface behavior among them. This is in marked contrast to the findings on cholinergic and anticholinergic drugs in the previous paper.²⁾ These results suggest that the interaction of structurally nonspecific drugs with a biosurface/fluid interface is essentially the same within a series of related drugs such as barbiturates, whereas that of structurally specific drugs varies depending on the structural and electrical properties.

The ability of barbiturates to pass through biological membranes is a function of their lipid solubility. This means that the rate of entry into the central nervous system, which is most sensitive to the actions of barbiturates, is strongly influenced by the lipid solubility. Thus,

structural changes that increase the lipid solubility decrease the duration of action and latency to onset of activity.^{5,12)} Once barbiturates have entered the central nervous system, they produce their effects by modifying some steps in chemical synaptic transmission. The depression of synaptic responses by barbiturates at most sensitive synapses probably results from a presynaptic decrease of transmitter release, but postsynaptic inhibition has also been demonstrated at membranes upon which γ -aminobutyric acid (GABA) has an inhibitory action.¹²⁾ In the mechanism of these inhibitory effects, binding of barbiturates with the presynaptic and the postsynaptic membranes must play an important role. Electrosorption of barbiturates may provide a very simple model of this binding.

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