Tributyltin-Mediated Exchange Diffusion of Halides in Lipid Bilayers

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ABSTRACT This paper describes the effect of tributyltin (TBT) on the inorganic anion permeability of lipid bilayers. When this compound is added in micromolar concentrations to one or both sides of a phosphatidyl ethanolamine (PE) membrane formed in 0.1 M NaCl or KCl (pH 7), there is no change in the electrical conductance. Under these circumstances, the Cl self-exchange flux measured with \(^{36}\)Cl \((M_{CI})\) increases from a value of \(\sim 10^{-12}\) mol·cm\(^{-2}\)·s\(^{-1}\), to \(\sim 10^{-8}\) mol·cm\(^{-2}\)·s\(^{-1}\). It was further found that the relation between chloride flux and [TBT] and [Cl\(^{-}\)] can be described as: \(M_{CI} = B[TBT][Cl]\). When chloride was replaced by an equimolar concentration of different univalent anions in the trans compartment, the heteroexchange flux of chloride followed the sequence: \(I > Br > Cl > F > NO_3\). Under all experimental conditions tested, the chloride flux was always more than \(10^5\) times the maximum flux predicted from the value of the membrane conductance, and at least 100 times higher than the expected fluxes of ion pairs (TBT-Cl) diffusing across the unstirred layers. Thus, the mechanism by which tributyltin increases anion permeability in bilayers seems to be that of an obligatory exchange diffusion, with the reaction between tributyltin and the halides occurring at the membrane surface. Measurements of interfacial potentials indicate that tributyltin chloride lowers the positive intrinsic dipole potential of PE membranes by \(\sim 70\) mV (at a TBT concentration of \(30\) \(\mu\)M) without substantial alteration of other parameters of the bilayer. The estimated adsorption coefficient of TBT-Cl was found to be \(3 \times 10^{-4}\) cm.

INTRODUCTION

The highly toxic trialkyltin compounds (\(R_SnX\)) have been shown to be potent inhibitors of mitochondrial oxidative phosphorylation because they produce a rapid chloride-hydroxide exchange across the mitochondrial membrane (Selwyn et al., 1970 b). That this effect is not due to an interaction with the specific anion transporting system of mitochondria or other mitochondrial protein(s) can be inferred from studies conducted in red blood cells and lipid vesicles (Selwyn et al., 1970 a). From these studies it was concluded that the trialkyltin compounds act as carriers for Cl and OH, with the tin complex located in the membrane interior and performing the exchange via a heterogenous reaction. Recently, Motais et al. (1977) found that tripropyltin could mediate Cl-Cl as well as chloride-hydroxide exchanges in red blood cells. Wieth and Tosteson (1977) have further shown that this enhanced permeability to chloride is the conse-
quence of a trialkyltin-induced Cl exchange diffusion which does not alter the red cell membrane permeability to the net flux of chloride. Because of the molecular heterogeneity of the red cell membrane, and because simultaneous electrical and flux measurements are impossible in small mammalian red cells, we decided to study the effects of tributyltin (TBT) on Cl flux and electrical properties of planar lipid bilayers of known molecular composition. We measured the Cl self-exchange flux as well as the total membrane conductance both as a function of the TBT concentration and in the presence of different Cl concentrations. The selectivity of the carrier for the metal halides was established via measurements of the Cl flux when this anion was replaced by an equimolar concentration of the other halides in the trans compartment (heteroexchange). The results indicate that the exchange mechanism induced by tributyltin is an obligatory anion exchange in which TBT acts as the carrier, with the unloaded carrier being unable to cross the membrane.

MATERIALS AND METHODS

Membrane Formation and Electrical Measurements

Membranes were formed from bacterial phosphatidyl ethanolamine (PE), either by the brush technique first described by Mueller et al. (1962) or by apposition of two separate monolayers spread at the air-solution interface, a technique first described by Montal and Mueller (1972). The aqueous solutions contained the Na or K salts of the various halides at the concentrations indicated, buffered to pH 7 with phosphate (5 mM), and the experiments were conducted at room temperature (20°C). The area of the bilayers was determined either by direct measurements with a calibrated eyepiece ("painted membranes," area 1-3 \( \times 10^{-2} \) cm²) or by continuous determination of the membrane capacitance ("Montal and Mueller," area 4-6 \( \times 10^{-4} \) cm²). The value of the capacitance was used in conjunction with the value of the specific capacitance of this type of membranes (0.65 \( \mu \)F·cm⁻²), to obtain the area (Alvarez and Latorre, 1978). Perfusion of the chambers was carried out using a pair of matched, mechanically coupled 5-ml syringes. The contents of both chambers were stirred continuously with magnetic stirrers. The membrane conductance was determined by measuring the steady-state current flowing across the membrane in response to an applied potential difference, using silver-silver chloride electrodes connected to the chambers via agar bridges. For the experiments with tetraphenylborate (TPhB), current measurements were made with a voltage pulse technique. The current was recorded between 0.05 and 10 ms after the voltage pulse was applied. Inasmuch as the current decayed exponentially with time (after its initial response to the pulse), the initial value of the current was determined from membrane current extrapolated to zero time on a semilogarithmic plot (Anderson and Fuchs, 1975). The initial conductance was then calculated from the magnitude of the zero time current and the applied potential.

Flux measurements

The unidirectional flux of Cl was measured with \(^{36}\)Cl. After membrane formation, one of the chambers was perfused with 5 ml of the initial solution and subsequently used to determine background. After this, an aliquot of the radioactive solution was added to one chamber (cis) either before or after addition of TBT. A small portion of the solution in the cis chamber was withdrawn to determine the specific activity of this compartment.
Samples from the \( \text{trans} \) compartment were then obtained at different time intervals by perfusion of this compartment. At the end of each flux period, the \( \text{trans} \) chamber was perfused successively with four 5-ml aliquots of nonradioactive solutions, the volume of the chambers being 1.5 or 3.0 ml; when TBT was present in both chambers, the nonradioactive solutions contained TBT at the appropriate concentration. The time elapsed during these washouts, 10-15 s, was negligible compared to the flux periods (minimum 5 min). At the end of this washout procedure, no radioactivity could be detected in the \( \text{trans} \) chamber. The collected 5-ml samples were then counted in a liquid scintillation counter (Packard TriCarb, Packard Instrument Co., Downers Grove, Ill.) after addition of 10 ml of liquid scintillation cocktail.

Under the experimental conditions described, the total amount of \(^{36}\text{Cl}\) transported across the membrane was found to be directly proportional to the duration of the flux period, and the backflow of tracer was negligible, because the specific activity of the \( \text{trans} \) compartment was always < 1% of that of the \( \text{cis} \) chamber. The \( \text{Cl} \) flux was calculated by the expression:

\[
M_{\text{Cl}} = \frac{^{36}\text{Cl}^\tau(\text{Cl})}{tA(^{36}\text{Cl})^\circ};
\]

where \( M_{\text{Cl}} \) (in moles per square centimeter per second) is the \( \text{Cl} \) flux; \( ^{36}\text{Cl}^\tau \) (in counts per minute) is the total radioactivity collected from the \( \text{trans} \) compartment at the end of the flux periods; \( (\text{Cl})^\circ \) (in moles per milliliter) is the \( \text{Cl} \) concentration in the \( \text{cis} \) compartment; \( (^{36}\text{Cl})^\circ \) (in counts per minute per milliliter) is the concentration of \(^{36}\text{Cl}\) in the \( \text{cis} \) solution; \( t \) (in seconds) is the length of the flux period and \( A \) (in square centimeters) is the area of the membrane.

To measure the effect of replacing \( \text{Cl} \) with another anion in the \( \text{trans} \) compartment, chloride self-exchange was first measured for two to three flux periods as described above and then the \( \text{trans} \) chamber was perfused with a solution containing the desired substitute anion. These fluxes were always measured in the presence of 5 mM \( \text{Na}_2\text{SO}_4 \) to prevent the formation of polyhalides. It was found that \( \text{Na}_2\text{SO}_4 \) had no effect on \( \text{Cl} \) self-exchange.

**Materials**

Bacterial phosphatidyl ethanolamine was purchased from Supelco, Inc. (Belmont, Pa.); tetraphenylborate (Na salt) was obtained from Eastman Organic Chemical Div., Eastman Kodak Co. (Rochester, N.Y.), tetraphenylarsonium chloride, from Aldrich Chemical Co., Inc. (Milwaukee, Wis.), and tributyltin chloride from BDH Chemicals Ltd. (Poole, England). The \(^{36}\text{Cl}\) was obtained from ICN Pharmaceuticals, Inc. (Irvine, Calif.) in the HCl form and subsequently neutralized to pH 7 by addition of concentrated KOH or NaOH. The liquid scintillation cocktail used was Aquasol purchased from New England Nuclear (Boston, Mass.). Tetraphenylborate and tributyltin were dissolved in ethanol and added to preformed bilayers. The amount of ethanol in the chambers was kept <1%. For the experiments in the presence of tetraphenylarsonium, the membranes were formed in the presence of this compound.

**RESULTS**

**Effects of TBT on the Cl Fluxes across Bilayers**

Fig. 1 shows that addition of tributyltin to one of the solutions (\( \text{cis} \)) bathing a PE bilayer increases the \( \text{Cl} \) flux. This increase in the flux was not accompanied by a change in the membrane conductance which remained at a value of ~ 3-5 \( \times \)
$10^{-9}$ S·cm$^{-2}$ as shown in Table I, which further shows that for PE bilayers, as is the case for membranes formed with synthetic diphytanoylphosphatidylcholine in decane (Toyoshima and Thompson, 1975), the Cl flux in the absence of TBT is 1,000 times higher than the value obtained from measurements of the total membrane conductance by assuming that all of the current is carried by Cl ions. In the presence of TBT, because the total membrane conductance is not changed appreciably, whereas the Cl flux increases by several orders of magnitude, the discrepancy between the measured flux and that calculated from electrical measurements is even higher (cf. Table I). This suggests that Cl crosses the membrane in an electrically neutral form, probably complexed with tributyltin. This interpretation is further substantiated by the fact that clamping the membrane voltage at ±60 mV had no effect on the Cl flux (cf. Fig. 2).

**Effects of $[\text{Cl}]$ on the TBT-Induced Cl Flux**

The effects of increasing the chloride concentration on the chloride fluxes induced by tributyltin were studied in the presence of the compound on one and both sides of the membrane. The results of these experiments are shown in Fig. 5, where it can be seen that the fluxes are proportional to the Cl

![Figure 1](image-url)
concentration. The slope of the lines (apparent permeability coefficients) were found to be \((0.96 \pm 0.2) \times 10^{-4} \text{cm.s}^{-1}\) in the case of unilateral addition of TBT and \((2.4 \pm 0.3) \times 10^{-4} \text{cm.s}^{-1}\) when TBT was present on both sides of the membranes. This result suggests that the TBT concentration difference in the aqueous phases, when the compound is added unilaterally, dissipates in the unstirred layers (or in a region close to the membrane surface) because of the

\[
\text{Table I}
\]

| Tributyltin | \(M_{cl}\) | \(G_m\) | \(G_{cl}\) | \(G_{cl}G_m\) |
|------------|-----------|--------|-----------|-------------|
| \(\mu M\)  | pmol.cm\(^{-2}\).s\(^{-1}\) | nS.cm\(^{-1}\) | \(1 \times 10^{4}\) | \(5 \times 10^{4}\) |
| 0          | 5.7 \pm 1.8 | 29 \pm 5 | \(2.1 \times 10^{4}\) | \(1 \times 10^{4}\) |
| (n = 18)   |           |         |           |             |
| 18         | 6,900 \pm 1,800 | 46 \pm 28 | \(2.5 \times 10^{7}\) | \(5 \times 10^{4}\) |
| (n = 22)   |           |         |           |             |

Membranes used to determine Cl flux in the absence of TBT were made with a modification of the method described by White (1978), as described by Tosteson and Tosteson (1978): 10 \(\mu l\) PE dissolved in chloroform (12 mg/ml) were spread at the air-water interphases, and the membranes were formed (by raising both levels) on a \(1.06 \times 10^{-2}\) cm\(^2\) hole on a teflon partition which had been prepainted with a solution of 2% squalene in pentane. Values of the fluxes and \(G_m\) (steady-state membrane conductance) determined as indicated in Methods, are given as means \pm standard deviation (n = number of flux periods). Flux periods were 30 min in the absence of TBT, and varied from 10 to 30 min in its presence. \(G_{cl} = M_{cl}F^3/RT\). 0.1 M KCl, pH 7.

![Figure 2](image)

**Figure 2.** Effect of potential on TBT-induced Cl flux. Experimental points from one membrane made with the Mueller et al. (1962) technique. 0.1 M KCl, pH 7. Addition of TBT to **cis** compartment.

formation of the complex (TBT-Cl) at the membrane surface. Inasmuch as the membrane is located at the midpoint of the thickness of these layers, the concentration at this surface is half that of the bulk aqueous phase to which TBT was added.

Double logarithmic plots of \(M_{cl}\) as a function of [TBT] (in the range 2–18 \(\mu M\)) and of \(M_{cl}\) as a function of [Cl] (in the presence of TBT on one and both sides of the membrane) are linear with a slope of one, indicating that one
molecule of Cl complexes with one molecule of TBT and that the flux can be expressed as: \( M_{Cl} = B[TBT][Cl] \), (where \( B \) is a constant of proportionality).

**Effects of Other Anions on the TBT-Induced Cl Flux**

The selectivity of TBT for other anions was determined in heteroexchange experiments, where Cl was replaced on the trans side with equimolar salts of different anions. Fig. 4 shows that when Cl was replaced by NO₃, the flux was reduced considerably, whereas addition of NO₃ to the cis side did not change the Cl flux. It seems, then, that NO₃ apparently can neither displace Cl from TBT nor alter the permeability of the membrane to TBT-Cl. Therefore, it is reasonable to conclude that the observed reduction in \( M_{Cl} \) is due to the absence of an exchange partner for Cl on the trans side and the low permeability of the membrane to free TBT. This conclusion is further supported by the following results obtained in red cells: measurements of the self-exchange flux of chloride in the presence of 2 mM KCl + 165 mM KNO₃ showed a very slight reduction of the rate constant compared to the one obtained in the presence of 165 mM KCl (Wieth and Tosteson, 1979).

Table II shows the results of experiments in which chloride was replaced by other halides in the trans compartment. These results indicate that I and Br are better, and F worse, than Cl as exchange partners in the TBT-mediated
transport. This sequence is the same as that obtained for Cl heteroexchange experiments in red blood cells (Weith and Tosteson, 1979). The inhibition of the Cl flux by F, unlike that by NO₃, seems to be due to the formation of water soluble polyionic complexes of F with TBT (Cotton and Wilkinson, 1966), which seem to have a very low partition coefficient in the membrane phase. Because, when either NO₃ or F replaced Cl in the trans compartment, $M_{CI}$ was found to be about 100 times higher than the Cl flux in the absence of TBT, this flux could be due to an exchange with OH, as has been shown to occur in mitochondria, red blood cells, and lipid membranes (Selwyn et al., 1970a; Motais et al., 1977; Wieth and Tosteson, 1979).

**Effects of TBT on Intrinsic Membrane Parameters**

Experiments were designed to explore the effects, if any, that TBT (or TBT-Cl) has on intrinsic membrane parameters such as surface charge and the intrinsic dipole and chemical potentials. This was done by measuring the change in the membrane conductance for large hydrophobic ions upon addition of TBT to the aqueous solutions. The justification for this approach has been extensively discussed (Szabo, 1977; McLaughlin, 1977). Fig. 5 shows the relative conductance ($G^r$ defined below) for tetraphenylboron (TPhB⁻) and tetraphenylarsonium (TPhAs⁺) as a function of the TBT concentration. The figure shows that increasing the TBT concentration has opposite effects on the conductance of lipophilic anions and cations (nonactin-K⁺ used as a cationic probe (6 M LiCl + 0.1 M KCl) gave essentially the same results as TPhAs⁺ (not shown). Clearly this effect cannot be explained solely on the basis of a change in the standard chemical potential for the probes in the membrane phase, because such a
change would modify the permeability to cations and anions in the same direction, independent of charge. The fact that TBT (or TBT-Cl) increases the membrane conductance induced by TPhAs+ and nonactin-K+ and promotes the opposite effect in membranes exposed to TPhB- is strong evidence that TBT (or TBT-Cl) affects the internal potential of the membrane. Furthermore, because these effects were found to be independent of the ionic strength of the salt solution (cf. Fig. 5), TBT (or TBT-Cl) must be acting at the level of the intrinsic dipole potential of the membrane.

A way of quantitating this change in dipole potential induced by the addition of TBT to the aqueous phases is by describing the conductance induced by the lipid soluble ions in the presence of TBT relative to that in its absence (Szabo, 1977). In a Nernst-Planck formalism:

\[ G^r = \frac{G^TBT}{G^0} = (u^r \cdot k^r) \exp(-zF \cdot \Delta \Phi / RT); \]

where \( G^0 \) is the zero current-zero potential conductance of the probe in question and \( G^TBT \) is that in the presence of TBT; \( z \) is the valence of the lipophilic ion; \( F \) the Faraday constant; \( R \) the gas constant; \( T \) the absolute temperature; \( u^r \) the relative mobility; \( k^r \) the relative partition coefficient; and \( \Delta \Phi \) the change in the internal dipole potential.

An estimate of the electrical and chemical contributions to the change in conductance can be obtained by assuming that the relative mobility and partition of the probes are affected equally by TBT. In this case:

\[ \Delta \Phi = (RT/F) \ln(G^0_r / G^0_r) \frac{1}{2}; \quad (u^r \cdot k^r) = (G^TPhAs^+ \cdot G^TPhAs^+)^{1/2}, \]

where \( G^r \) is the relative conductance for TPhB- and \( G^r \) is the relative conductance for TPhAs+.

Fig. 6 shows the values obtained for the change in dipole potential and the chemical potential as a function of the TBT concentration. It is seen that

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**Table II**

HETEROEXCHANGE FLUXES OF CHLORIDE

| Anion | M_{cl}/M_{el} | M_{cl} | Bilayers | Red cells |
|-------|---------------|--------|----------|-----------|
| Cl    | Cl            | 2.0 ± 0.4* |
| Cl    | Br            | 2.6 ± 0.3‡ |
| Cl    | F             | 0.3 ± 0.04 |
| Cl    | I             | 4.8 ± 0.4 |

Fluxes were measured as indicated in Methods. Values of the fluxes given ± SD, \( n \) (number of flux periods) = 10 for all conditions; three different membranes in which all anions were tested. [TBT] = 18 \( \mu \)M, 0.1 M NaCl + 5 mM Na_2SO_4, pH 7. Membranes formed with the Montal and Mueller (1972) method.

* TBT-induced Cl fluxes measured in the presence of Na+ were found to be significantly lower than those measured in the presence of K+. (cf. Fig. 1 and Table I).

‡ Significantly different than the Cl flux at 0.2% level.
although TBT lowers the dipole potential by 70 mV, it produces only a small (1.6 times) increase in the term $u^r k^r$ (sometimes called the intrinsic conductance).

**DISCUSSION**

The data presented in this paper are consistent with the idea that the trialkyl tin compounds promote an electrically silent flux of inorganic anions, inasmuch as

![Figure 5. Effect of TBT on the conductance of hydrophobic ions. The conductance $G^r$ (normalized to that in the absence of TBT) is plotted as a function of the TBT concentration (micromolar) in both compartments on a semilogarithmic scale. (•) TPhAs$^+$; membranes were formed with the Montal and Mueller (1972) technique in unbuffered 0.1 M NaCl (pH 6) + 7 $\times$ $10^{-4}$ M TPhAs. The zero current-zero voltage membrane conductance ($G^o$) was $6 \times 10^{-8}$ S cm$^{-2}$ under these conditions. Points are mean values (three different membranes). (●) Addition of NaNO$_3$ to both sides to a concentration of 2 M after the last addition of TBT to test for the effect of increased ionic strength. (▲) TPhB$^-$; membranes were formed with the Montal and Mueller method in 0.1 M NaCl buffered to pH 7 and TPhB$^-$ subsequently added to both sides to a concentration of $3.3 \times 10^{-8}$ M. The zero current-zero voltage membrane conductance ($G^o$) was $1.2 \times 10^{-8}$ S cm$^{-2}$. Under all experimental conditions studied there was no change in the conductance of the bilayers (implying that no new charge carriers had been added to the system under these conditions), and the flux of halides increased more than 1,000 times (cf. Table I). Thus, the anions must cross the membrane complexed with tributyltin. From the magnitude of the fluxes it is possible to determine if
the ion pairing occurs in the unstirred layers or at the membrane surface; the maximum value of the flux of the complex through the unstirred layers can be estimated using Fick's law. For example, for a TBT concentration of 10 μM, and assuming that all of the compound is complexed, that the thickness of the unstirred layers (Δx) is ~ 10^-2 cm (Holz and Finkelstein, 1970) and that the diffusion coefficient (D_{TBT-Cl}) is ~ 5 × 10^-8 cm^2 s^-1,

\[ M_{TBT-Cl} = D_{TBT-Cl}[TBT](Δx)^{-1} = 5 \times 10^{-12} \text{mol} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}. \]

Inspection of Fig. 1 shows that this flux is 1,000 times lower than the measured Cl flux. Thus, the experiments indicate that the process by which tributyltin enhances chloride (halide) permeability is one of obligatory exchange at the membrane surface rather than one in which ion pairs, formed in the water, diffuse unimpeded across the bilayer.

The tendency of the flux to saturate as the TBT concentration in the aqueous phase is increased (cf. Fig. 1) might be due to the fluxes being limited (at the high TBT concentrations) by the diffusions of Cl in water. The estimated Cl flux due to free diffusion across the unstirred layers (using Fick's law and a Cl concentration of 0.1 M) would be in the order of 10^-7 mole·cm^-2·s^-1. The highest flux measured, at a TBT concentration of 24 μM and a [Cl] of 0.1 M, is only ~ 10 times lower than this value.

On the other hand, no saturation of the Cl flux was observed when the Cl
concentration was increased up to 1 M, in the presence of 18 μM TBT, (cf. Fig. 3), presumably because the association constant for the complex (most likely a heterogeneous reaction) is much less than 1 M⁻¹.

The results of the studies on the effect of tributyltin on the membrane conductance induced by hydrophobic ions indicate that this compound alters the intrinsic properties of the bilayer (cf. Fig. 6). This effect seems to be of an electrostatic nature, inasmuch as TBT promotes opposite effects on cations (TPhAs⁺) and anions (TPhB⁻). Moreover, because these effects were independent of ionic strength (Fig. 5), it is possible to conclude that TBT lowers the positive intrinsic dipole potential of the PE bilayer by ~70 mV when the concentration of TBT is 30 μM.

From the change in dipole potential with the TBT concentration in the aqueous phases, it is possible to calculate a minimum value for the adsorption coefficient for TBT-Cl in the membrane, assuming that all of the molecules are distributed on the surface of the membrane with their dipoles oriented perpendicular to the surface. Using the equation derived by Rideal (Davies and Rideal, 1963) for the dipole potential due to an array of n dipoles of dipole moment μ,

\[ \Delta \Phi = 12 \eta \mu / \epsilon, \]

and

\[ \beta = n/[TBT]N_A, \]

where β (centimeters) is the absorption coefficient, ΔΦ (millivolts) is the change in dipole potential, μ(mD) is the dipole moment of TBT, ε is the dielectric constant and N_A is Avogadro’s number. Assuming that the value for the dipole moment of TBT-Cl is the same as that for triethyl tin chloride (3.4D) (Le Fevre, 1953) and that the dielectric constant is 2, the value obtained for the partition coefficient: 6 \times 10^{-4} \text{ cm}, is quite close to the one obtained for the partition of TBT-Cl in red blood cell membranes (1.7 \times 10^{-3} \text{ cm}) (Wieth and Tosteson, 1979).

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