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Increasing permeability of phospholipid bilayer membranes to alanine with synthetic α-aminophosphonate carriers

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Abstract—A series of aminophosphonates was synthesized, and their ability to carry alanine, a model hydrophilic molecule, across phospholipid bilayer membranes was evaluated. Aminophosphonates facilitate the membrane transport at moderate rates, which make them a suitable platform for the design of carriers for continuous drug release devices.

One of the most important challenges in designing liposome based drug release systems is the precise control of transport kinetics across bilayer boundaries.[1,2] Encapsulated drugs should remain within liposomes during storage, and release should only begin after the administration. In an ideal system, a triggering event will initiate continuous release with well-controlled rate. Synthetic carriers of polar organic molecules through lipid bilayers can potentially provide an elegant way to achieve this goal. Insertion of carriers into bilayers of drug-containing liposomes immediately prior to administration would trigger the release. Transport kinetics can be regulated by varying the concentration of carriers in the bilayer.

Previously, a relatively small number of studies focused on synthetic carriers for the transport of organic molecules across bilayer lipid membranes compared to well explored areas of artificial ion channels[3,4] and transport in supported liquid membranes.[5–8] In the recent years, however, the field has been gaining considerable interest. Several papers described synthetic carriers for carbohydrates,[9,10] nucleosides,[11] small peptides,[12] and other molecules.[13,14] Among the most recent beautiful examples is the transport of oligonucleotides guided by umbrella carriers in the innovative 'needle and thread concept'.[15] Sunamoto et al. reported on the transport of phenylalanine using a photoresponsive carrier.[16]

Traditionally, high selectivity and fast transport rates were viewed as desirable albeit challenging. These characteristics may not be necessary in the design of carriers suitable for continuous drug release. This application requires slow release of a single component over a long period of time, measured between hours and weeks, and neither selectivity nor fast transport is critical. In fact, slow carriers are likely to have an advantage of inherently low cytotoxicity, an important safety consideration in the case a carrier molecule separates from a liposome and inserts into a cellular membrane. Small size of carriers is likely to be beneficial for rapid incorporation into the liposomal bilayer.

Considering the above, we decided to synthesize and evaluate a series of α-aminophosphonates as carriers of hydrophilic organic molecules across phospholipid membranes. We used alanine, an amino acid, as a model hydrophilic bifunctional molecule for transport studies. In our view, aminophosphonates are excellent carrier platforms. They possess two binding sites, a hydrogen bond donor and a hydrogen bond acceptor suitable for two-point binding of hydrophilic molecules creating in the case of amino acids a complex with hydrophobic exterior.[17,18] They are readily prepared in a one-pot synthesis by the Kabachnik–Fields reaction from a primary amine, a phosphite, and a carbonyl compound.[19,20] Their hydrophilic–hydrophobic balance can be easily

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