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Fluorophilicity of alkyl and polyfluoroalkyl nicotinic acid ester prodrugs

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ABSTRACT

The fluorophilicity of a series of hydrocarbon and fluorocarbon-functionalized nicotinic acid esters (nicotinates) is measured from their partitioning behavior (log K_p) in the biphasic solvent system of perfluoro(methylcyclohexane) (PFMC) and toluene. The chain length of the hydrocarbon or fluorocarbon alkyl group of the ester ranges from one to twelve carbon atoms. Knowledge of the fluorophilicity of these solutes is relevant to the design of these prodrugs for fluorocarbon-based drug delivery. The experimental log K_p values range from −1.72 to −3.40 for the hydrocarbon nicotinates and −1.64 to 0.13 for the fluorinated nicotinates, where only the prodrug with the longest fluorinated chain (2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyl nicotinic acid ester) partitions preferentially into the fluorinated phase (log K_p = 0.13). Predictions of the partition coefficients using solubility parameters calculated from group contribution techniques or molecular dynamics simulation are in reasonable agreement for the perhydrocarbon nicotinates and short chained perfluorinated nicotinates (≈0.3–39% deviation). Significant deviations from experimental partition coefficients (greater than 100%) are observed for the longest chain perfluoroalkyl nicotinates.

1. Introduction

Fluorocarbons and perfluorinated moieties have demonstrated potential for a variety of novel industrial [1,2] and pharmaceutical applications, including liquid ventilation therapy, diagnostic ultrasound imaging and as blood contrast agents [3–8]. The potential to extend fluorinated solvent applications to drug delivery is limited by the poor solubility of typical hydrocarbon-based polar and non-polar pharmaceuticals in these solvents [9,10]. The use of a prodrug, in which cleavable functional groups facilitate solubility of the drug in the fluorocarbon solvent, is a viable approach for the delivery of pharmaceuticals [6,11]. The prodrug or functionalized drug molecule is clinically inactive and conversion to the parent drug compound, typically through enzymatic cleavage, is necessary to induce the desired pharmacological effects [6]. The fluorocarbon solvent system must provide sufficient solubility of the prodrug, while promoting its subsequent extraction from solution and delivery to the tissues. In addition, the prodrug/fluorocarbon solvent systems are selected to minimize the biological toxicity and maximize the prodrug efficacy. Previously, our group studied the viability of nicotinic acid ester (nicotinate) prodrugs functionalized with hydrocarbon and fluorinated side groups to facilitate delivery in a fluorocarbon medium (perfluorooctyl bromide; PFOB) for administration through the pulmonary route [11]. In passive diffusion to the target lung cells, the nicotinate prodrugs are expected to encounter immiscible fluorocarbon, organic and aqueous solvent layers, making biphasic partition studies particularly relevant to the study of prodrug uptake through a cellular matrix. Knowledge of partition coefficients provides a thermodynamic interpretation of drug delivery and cytotoxicity. Limited studies address the partitioning behavior of homologous series of fluorinated solutes and provide direct comparisons to their hydrocarbon analogues. The ability to predict partitioning behavior has the potential to improve drug design for delivery by fluorinated solvents.

This work examines the partitioning behavior in perfluoro(-methylcyclohexane); PFMC))–toluene of a series of hydrocarbon and fluorocarbon-functionalized nicotinic acid esters (Scheme 1). The PFMC–toluene partition coefficients are widely adopted benchmark of fluorophilicity in partitioning studies [12,13]. The nicotinates are classified according to the alkyl chain of the ester as perhydrocarbon (C1F0–C12F0); perfluorinated, each linked by one methylene chain to the carboxyl group (C2F3–C8F15); and partially fluorinated, with either a terminal hydrogen atom (C3F4 and C5F8) or two methylene group (C8F13) linkages in the fluorinated chain of the ester. Nicotinic acid, the parent drug compound of the nicotinic acid esters (nicotinates), has clinical benefit in the treatment of cancer. It is a precursor of cofactors, nicotinamide adenine dinucleotide (NAD) and NADP, that could alleviate injury to lungs caused by poisons and natural toxic compounds [6,14]. The PFMC–toluene partition coefficient (log K_p) is an established measure of fluorophilicity [12,13,15–17] and is

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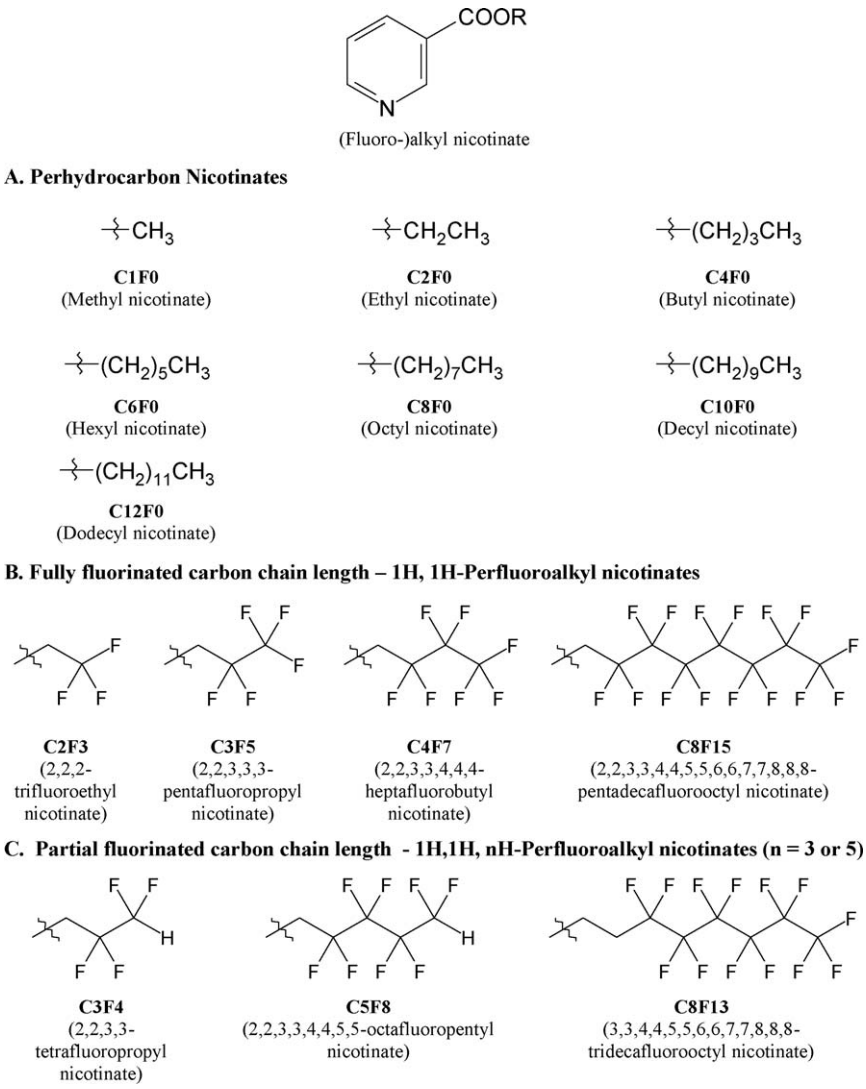

Scheme 1. (A) Perhydrocarbon nicotinates. (B) Fully fluorinated carbon chain length – 1H, 1H-Perfluoroalkyl nicotinates. (C). Partial fluorinated carbon chain length – 1H, 1H, nH-Perfluoroalkyl nicotinates (n = 3 or 5).

calculated from the concentration ratio of prodrug in fluorocarbon phase (PFMC) to hydrocarbon phase (toluene). Similar to the octanol/water partition coefficient for the measurement of lipophilicity and the interpretation of drug pharmacokinetics [18,19], fluorocarbon/hydrocarbon partition coefficients have the potential to be a predictive tool to describe the ability to deliver drugs from a fluorinated solvent to target cells. This study compares the experimental partition values of prodrugs in PFMC–toluene with liquid–liquid partitioning predicted from regular solution theory (RST). Two methods of solubility parameter estimations are compared: Fedors Group Contribution [20,21] and molecular dynamic simulations using (Materials Studio (Accelrys Inc. (California), Version 4.0). Predictive methods provide a screening tool to assess the effect of functional group chain length and structure on partitioning behavior, allowing the design of prodrug candidates for fluorocarbon drug delivery.

2. Experimental

2.1. Materials

Perfluoro(methylcyclohexane) (PFMC ($CF_3C_6F_{11}$) ≥95%) was purchased from Sigma–Aldrich and toluene (($CH_3C_6H_5$) of ≈100% purity) was purchased from Mallinckrodt Baker Inc. (Paris, Kentucky). Synthesis of the nicotinate acid ester prodrugs (nicotinates) was described previously [6,22] and involves the addition of anhydrous dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) to a mixture of nicotinic acid and the corresponding alcohol in anhydrous dichloromethane. The nicotinic acid esters or nicotinate prodrugs were synthesized with greater than 98% purity as determined by GC/MS analysis.

2.2. Apparatus and procedure

The partition coefficients for the nicotinate prodrugs in perfluoro(methylcyclohexane)–toluene system were determined from the depletion of the prodrug in the fluorocarbon phase into a known volume of toluene (as measured by FID gas chromatography (Varian CP-3800 FID)). The nicotinic acid esters were initially dissolved in 3 ml or 5.5 ml volumes of fluorinated solvent (PFMC), resulting in a known prodrug concentration in the range of 1–4 mM. Volume ratios of 1:1 and 5:1 in PFMC–toluene systems were used to achieve measurable equilibrium concentration differences in the fluorocarbon phase after contacting with the hydrocarbon phase. The stir flask method [19] was employed, where only the denser fluorocarbon phase was gently stirred to facilitate equilibration, with a goal of avoiding emulsion formation. All experiments were performed at 25 °C. More than one hour was allowed for