Diffusion behavior of liquid state aliphatic phenothiazine compounds

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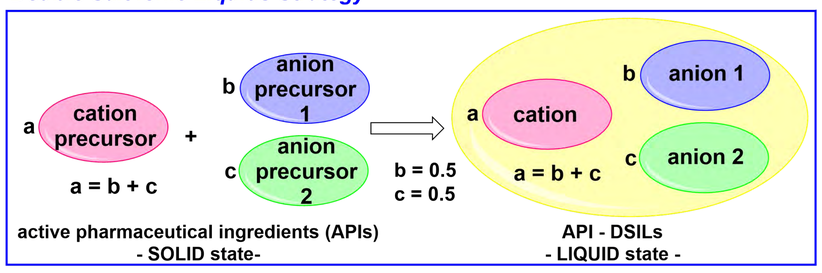
Abstract

Ionic compounds are high melting compounds comprised of cations and anions held together through electrostatic interactions. When these ionic compounds contain either an organic cation or anion they tend to melt below 100 ºC and they are referred to as ionic liquids (ILs). Double salt ionic liquids (DSIL) are complex ILs with either one anion and several cations, several anions and one cation or several anions and several cations. Both the ILs and DSILs have important applications in drug design as they will keep the pharmacological properties of the constituent ions while having improved properties (such as bioavailability and aqueous solubility) when compared to the corresponding neutral precursors. Thus, by modifying the ionic composition and molar ratio, one can easily formulate new ILs and DSILs with specific purposes. One powerful technique for characterizing these liquid state compounds is diffusion-ordered spectroscopy (DOSY). When applied to ILs and DSILs, DOSY measures the self-diffusion coefficients for the constituent anion(s) and cation(s). The work presented here focuses on using DOSY to determine the diffusion behavior of several DSILs obtained by combining aliphatic phenothiazine cations (promazine, chlorpromazine or triflupromazine) with two anions, namely the ibuprofenate (a known non-steroidal anti-inflammatory drug) and docusate (a penetration enhancer) anions.

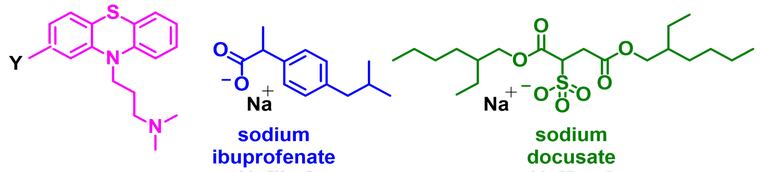
Introduction

- The efficacy of drugs is related to their intrinsic properties. Most therapeutic pharmaceuticals available on the market are distributed in a solid form, which can be either amorphous or crystalline. As a result, properties such as low bioavailability and water solubility affect the efficacy of APIs in solid form. [1]
- Conversion of the solid state pharmaceuticals into a liquid form (i.e., *ionic liquids*, IL, OR double salt ionic liquids, DSIL; ionic salts with melting points M.P. < 100 ℃ [2] or, in the case of pharmaceuticals, with a M.P. < body temperature) overcome these issues.
- Double salt ionic liquids (DSILs) are complex ILs that contain in their structure more than two types of ions (e.g., several anions and several cations) in various molar ratios Their properties (e.g., solubility) depend on the chemical interactions between the ions; changing the molar ratio between the component ions can lead to new coulombic interactions between the component ions and to new properties. Therefore, one can easily take advantage of this behavior and develop new task specific DSILs.

Double Salt Ionic Liquids Strategy



Cation and Anion Precursors



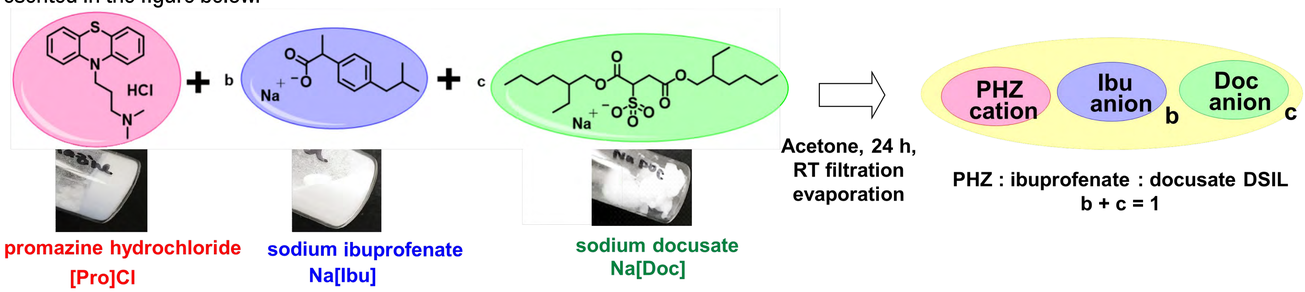
y = H-promazine, [Pro]Cl
y = Cl-promazine, [CPro]Cl
y = CF_3-fluopromzine, [FPro]Cl

Objective

- Determine the diffusion behavior of phenothiazine DSILs obtained by combining aliphatic phenothiazine cations with ibuprofenate and docusate anions in a 1:0.5:0.5 molar ratio.

Synthesis of DSILs

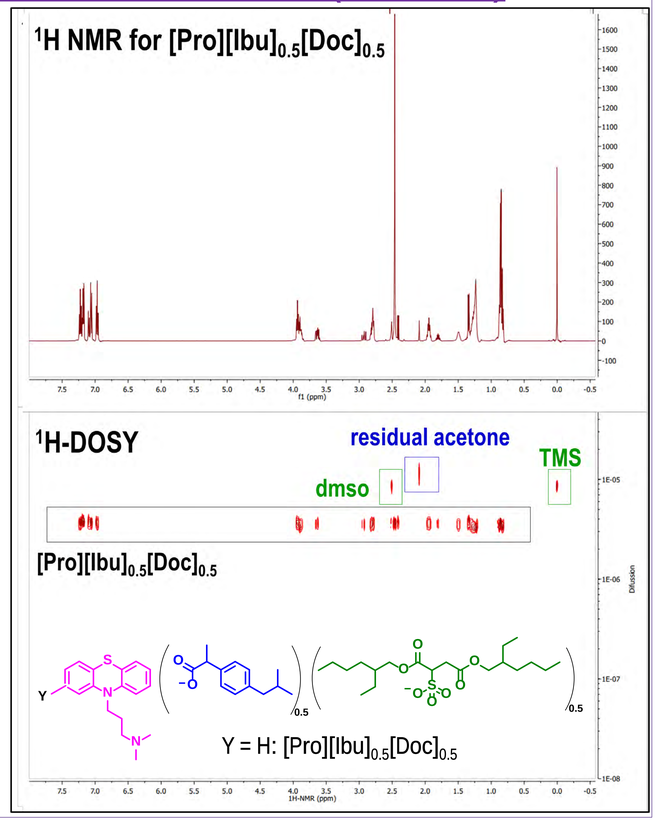
- Three new dual functional DSILs were synthesized by pairing the phenothiazine (PHZ) cations (promazine, [Pro]; chlorpromazine, [CPro]; triflupromazine, [FPro]), with ibuprofenate ([Ibu]) and docusate ([Doc]) anions.
- The new compounds were synthesized using the *metathesis reaction* between phenothiazine hydrochloride, sodium ibuprofenate, and sodium docusate according to the procedure presented in the figure below.



^{1}H-NMR Characterization: ^{1}H-DOSY NMR (dmso-d6)

- Used to investigate if the cation and two anions remain associated in 0.06 M dmso-d6 solution.
- Provides information on the transport properties of the compounds
- Helps with the structural characterization of the compounds.
- The presence of only one specie in each DOSY spectrum is consistent with the existence of the phenothiazine cation and the two anions ([Ibu] and [Doc]) in an associated form.

	Ibuprofenate : Docusate anion ratio, [Ibu] : [Doc]
	0.5 : 0.5
Promazine cation, [Pro]	
Chlorpromazine cation, [ClPro]	
Triflupromazine cation [FPro]	



Future Work

- Used to investigate if the cation and two anions remain associated in 0.06 M dmso-d6 solution.
- Determine thermal stability using Thermogravimetric Analysis
- Determine melting point using Differential Scanning Calorimetry
- Solubility studies and membrane transport studies will be conducted to determine a potential new method of administration.

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References

[1] (a) Yde, C. W., Clausen, M. P., Bennetzen, M. V., et al. Anticancer Drugs 20, 723–735 (2009) (b) Eriksson A, Yachnin J, Lewensohn R, Biochem Biophys Res Commun 283, 726–731 (2001) (c) Liang W, Yang C Z. Chin. Sci Bull. 43, 1179–1183 (1998). [2] Zhang Y., Johnson K. C. Int. J. of Pharm. 154, 179-183 (1997). [3] Jaszczyszyn, A., Gasiorowski, K., Swiatek, P., Malinka, W., Cieoelik-Boczula, K., Petrus, J., Czarnik-Matusewicz, B. *Pharm. Rep.* 64, 16-23 (2012). [4] Simonetti, G., Simonetti, N., Villa, A. J. Chemother. 16, 38 (2004). [5] Reid, M. L., Brown, M. B., Moss, G. P., Jones, S. A. J. Pharm. Pharmacol 60, 1139 (2008).