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Brønsted acid–base pairs of drugs as dual ionic liquids: NMR ionicity studies

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ABSTRACT

Twenty-eight protic ionic liquids (PILs) have been prepared from Active Pharmaceutical Ingredients (APIs). They have been characterized by TGA, DSC and NMR. An important property of Ionic Liquids (ILs) such as the 'degree of ionicity' has been estimated from quantitative determinations by ^{1}H NMR in DMSO-d_6 solutions.

1. Introduction

At present, the considerable ongoing research on ionic liquids (ILs) due to their interesting applications in a number of areas of science, is so extensive that it cannot be summarized in an introduction.[1] Our aim is much more restricted and was inspired by the work of Robin D. Rogers et al.[2] who proposed some years ago ILs based on active pharmaceutical ingredients (APIs). In general, the physicochemical properties of ILs may confer a novel effect for the bioactivity of an API due to slow-release properties in addition to novel delivery mechanisms. Since then, other groups have reported pharmaceutically active cation/anion combinations based on analgesics, antiseptics, anti-inflammatories and anti-bacterial agents, amongst others.[3] It has also been described pharmaceutically active protic ILs (PILs) as active compatible acids and bases with dual activity. Liquid salts will avoid the presence of polymorphs and solve this critical pharmaceutical problem that hampers drug's efficacy. PILs with lower ionicity may cross biological membranes easier than ionic species.[4]

Among the potential benefits expected from the administration of drugs in combination as ILs instead of two independent salts are the improvements in their pharmacokinetics and pharmacodynamics properties. As an example, the ions from an IL will dissolve in bodily fluids in exactly the same way whereas two separate solid forms may dissolve at different rates.[5] Molecular dynamics studies of imidazolium-based room temperature ionic liquids suggested that ILs, instead of dissolving as independent ions, could be induced to form organized nanostructures in aqueous media.[6] This fact has also been reported using NMR techniques.[7] Regarding membrane transport, several PILs were synthesized and FTIR-ATR and Walden plot studies were used to assess the proton transfer and determine the 'degree of ionicity' of the compounds.[4b]

There are several uses of the term 'ionicity' in chemistry. The most common one introduced by Pauling as 'bond ionicity'[8] in his classical *The Nature of the Chemical Bond*,[9] is nowadays calculated from Natural Bond Order (NBO) analysis.[10] Regarding ionic liquids, there are two uses of ionicity depending on the ILs: aprotic (what in organic chemistry are called 'quaternary salts') or protic, PILs.

In the case of ILs, the ionicity is related to the degree of association between the anion and the cation and it is usually determined using the Walden plot or Walden rule. There are many ILs where the Walden plot is used reporting conductivity at a given viscosity.[11,12]

For PILs[13] the degree of ionicity is related to the three possible states of a hydrogen-bonded complex (Fig. 1).

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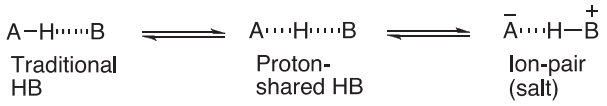


Fig. 1. Hydrogen-bonded complex.

The traditional and proton-shared HBs are, in general, indistinguishable differing only in the position of the proton. On the other hand, the formation of a salt has important consequences of the physicochemical properties of the ILs. Some authors have written that incomplete proton transfer results in poor ionic liquids (poor ILs);[14] others that the use of very basic guanidines results in high ionicity.[15] Therefore, PILs with lower ionicity are more desirable for drug delivery as they may cross the membrane barrier more easily than the more ionized species.[4b]

It is well known the difficulty of ionic drugs to cross biological membranes. Since we are interested in APIs combinations and how their solution in a well-known vehicle in pharmacological studies such as DMSO can affect their ionic state, we describe herein the synthesis, characterization and ionicity experiments using NMR spectroscopy of 28 APIs combinations. In the context of APIs, several reasons can be taken into account for choosing two specific active compounds (e.g., lidocaine docusate).[2] It could go from selecting counterions to synergistically enhance the desired effects or to neutralize unwanted properties of active species.

Our 28 PILs result from the combination of four bases, three local anesthetics (Lidocaine, Prilocaine, Bupivacaine) and one antidiabetic drug (Metformin) with a series of acids: salicylic acid (the active metabolite of aspirin and an anti-acne agent), three NSAIDs (nonsteroidal anti-inflammatory agents: flurbiprofen, diclofenac and flufenamic acid), two artificial sweeteners (saccharine and acesulfame K) and a laxative (docusate) (Fig. 2).

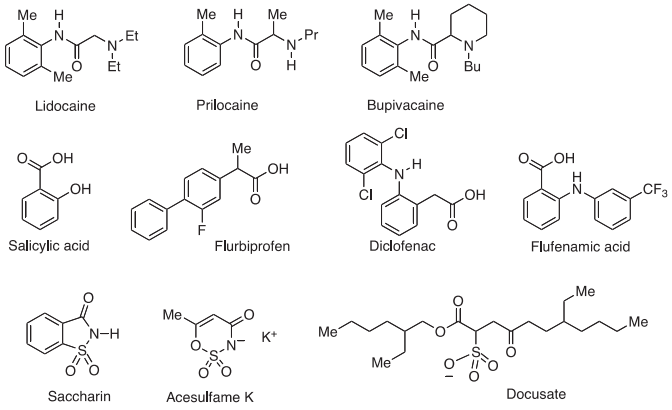


Fig. 2. Brønsted bases and acids.

Local anesthetics have a wide variety of applications. They are an inexpensive and effective addition to an integrated pain management protocol. In the case of metformin, apart from its application as antidiabetic drug it has also been used for females with acne and polycystic ovarian syndrome (PCOS).[16] Since salicylic acid is also used for the treatment of acne and other skin diseases, a combination of these two APIs could boost the pharmaceutical properties of the existing drugs separately.[17] On the other hand, the introduction of sweeteners as second functionalities in a formulation broadens the possibilities of certain drugs to be administered orally.

2. Results and discussion

We describe in Fig. 2 the different Brønsted bases and acids under study and in Table 1 the different combinations. Most of these 'salts' are reported here for the first time but some of them are already known, for instance, lidocaine salicylate that has been previously reported by Rogers and co-workers.[2]

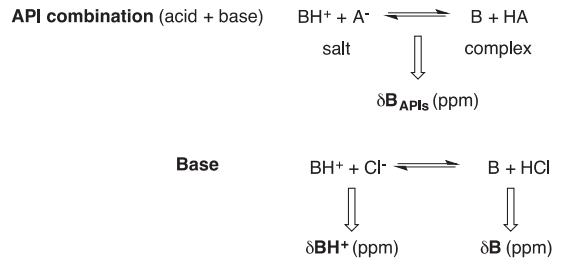
Table 1
Combination of APIs

No.	Reagents	Salt
1	Lidocaine+salicylic acid	Lidocaine salicylate
2	Lidocaine+Flurbiprofen	Lidocaine flurbiprofenate
3	Lidocaine+Diclofenac	Lidocaine diclofenac salt
4	Lidocaine+saccharin	Lidocaine saccharinate
5	Lidocaine+acesulfame K	Lidocaine acesulfame
6	Lidocaine+docusate	Lidocaine docusate
7	Lidocaine+flufenamic acid	Lidocaine flufenamic salt
8	Prilocaine+salicylic acid	Prilocaine salicylate
9	Prilocaine+Flurbiprofen	Prilocaine flurbiprofenate
10	Prilocaine+Diclofenac	Prilocaine diclofenac salt
11	Prilocaine+saccharin	Prilocaine saccharinate
12	Prilocaine+acesulfame K	Prilocaine acesulfame
13	Prilocaine+docusate	Prilocaine docusate
14	Prilocaine+flufenamic acid	Prilocaine flufenamic salt
15	Bupivacaine+salicylic acid	Bupivacaine salicylate
16	Bupivacaine+Flurbiprofen	Bupivacaine flurbiprofenate
17	Bupivacaine+Diclofenac	Bupivacaine diclofenac salt
18	Bupivacaine+saccharin	Bupivacaine saccharinate
19	Bupivacaine+acesulfame K	Bupivacaine acesulfame
20	Bupivacaine+docusate	Bupivacaine docusate
21	Bupivacaine+flufenamic acid	Bupivacaine flufenamic salt
22	Metformin+salicylic acid	Metforminin salicylate
23	Metformin+Flurbiprofen	Metforminin flurbiprofenate
24	Metformin+Diclofenac	Metforminin diclofenac salt
25	Metformin+saccharin	Metforminin saccharinate
26	Metformin+acesulfame K	Metforminin acesulfame
27	Metformin+docusate	Metforminin docusate
28	Metformin+flufenamic acid	Metforminin flufenamic

These 28 combinations were studied using NMR to determine their ionicity in DMSO-d_6. These combinations could still be salts (as written) or the so-called 'proton transfer compound' where a proton transfer from the base to the acid had turned them into complexes. This transformation may affect the pharmacokinetics of a drug, in particular the bioavailability, and therefore it should be taken into account when preparing new combinations. The properties exhibited by these combinations will depend on the degree of proton transfer from the acid to the base plus their hydrogen bonding network.

The three expected outcomes are i) mostly ionized combinations, ii) a mixture of salt-proton transfer compound, and iii) mostly unionized acid and base complex.[4]

The process followed for each combination of APIs is summarized in Scheme 1. The percentage of unionized base (B) in the synthesized APIs was calculated by interpolation of both models and determined from Equation 1. Proton NMRs in DMSO-d_6 from free base (B), base hydrochloride (BH^+) and base in the API mixture were studied and used for calculations.



Equation 1: $B\ (\%) = (\delta B_{APIs} - \delta BH^+)\cdot 100/(\delta B - \delta BH^+)$

Scheme 1. APIs and free base chemical equilibria.