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**Mechanochemical Synthesis and Physicochemical
Characterisation of Multicomponent Phases
Comprising Lidocaine and Dicarboxylic Acids**

A dissertation submitted for the degree of

Doctor of Philosophy

at the School of Pharmacy & Pharmaceutical Sciences,

Trinity College Dublin,

the University of Dublin, Ireland

by

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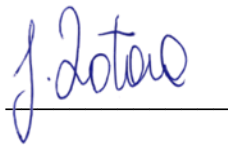
Under the supervision of Prof. Lidia Tajber

2023

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Summary

Tuning of physicochemical properties of multicomponent phases incorporating active pharmaceutical ingredients (APIs) with counterions or coformers is a challenge that opens up unlimited possibilities for expanding applications and controlling biological activity of drugs. Mechanochemistry has been recognised as an optimal route for the synthesis of multicomponent phases as it eliminates the need for large volumes of solvents and purification steps, thus making it a sustainable alternative to conventional solution synthesis. In this work a range of multicomponent systems incorporating lidocaine (LID) and a series of unbranched aliphatic dicarboxylic acids as the counterions were synthesised by neat grinding and the effect of an alkyl chain length on the phase formation was investigated. The acids employed were structurally related aliphatic dicarboxylic acids with n carbon chain length, where $n = 5-8$: glutaric adipic, pimelic and suberic dicarboxylic acids. The systems obtained included a high-melting crystalline salt, a cocrystal, eutectics and ionic liquids. The evaluation of thermal and dynamic behaviours as well as crystallographic analysis of the systems was performed in an attempt to devise a prediction tool for structure-property relationship. Alternating trends in morphology, melting points, glass transition temperatures and crystallographic properties of the new phases were observed across the dicarboxylic acid series.

The effect of changing LID and azelaic acid ($n=9$) ratios on the physicochemical properties of their corresponding multicomponent systems was also investigated using a thermodynamics-based approach. Microscopy, X-ray diffraction analysis, infrared spectroscopy, nuclear magnetic resonance, and thermogravimetric analysis provided complementary characterisation. Mechanochemical synthesis of LID:azelaic acid systems at a range of stoichiometries yielded at least two distinct liquid phases and two distinct crystalline phases, one of which involved a unique 2:3 LID:counterion composition not observed previously. Furthermore, the formation of oligomeric ionic liquids involving dicarboxylic acids has also been achieved for the first time. This investigation highlights the need for a careful and comprehensive characterisation of multicomponent systems, especially for pharmaceutical applications.

The investigation of LID:long-chain dicarboxylic acid systems has shown that increasing length and flexibility of the long carbon backbone affect molecular recognition and crystallisation of new multicomponent phases. As a result of mechanochemical synthesis of LID with long-chain dicarboxylic acids, where $n = 10-13$, partial component ionisation

was observed. The construction of thermodynamic phase diagrams provided evidence that H-bonding and partial proton transfer has led to solid eutectic formation in all the systems. However, no new crystalline multicomponent phases were obtained.

The driving force for the multicomponent phase research is enhancement and optimisation of pharmaceutical outcome of the drugs. The influence of the observed structural variation of the LID:dicarboxylic acid systems synthesised on their stability, solubility, dissolution, lipophilicity, permeability and aggregation behaviour was evaluated. The even-odd alternating trends in physicochemical properties were also evident in the pharmaceutical attributes assessed. Incorporating LID within LID:dicarboxylic acid systems has significantly enhanced its solubility and dissolution parameters in the range of the systems investigated.

The study of the systems comprising the entire range of dicarboxylic acids enhanced current understanding of the mechanisms of multicomponent phase formation and contributed to the advancement of a systematic approach for multicomponent phase discovery and development for pharmaceutical applications. In addition, the structure-property relationships were explored.

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Publications and Presentations

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Zotova, J.; Wojnarowska, Z.; Twamley, B.; Tajber, L. Formation of Stoichiometric and Non-Stoichiometric Ionic Liquid and Cocrystal Multicomponent Phases of Lidocaine with Azelaic Acid by Changing Counterion Ratios. *J. Mol. Liq.* **2021**, *344*, 117737.

Zotova, J.; Twamley, B.; Tajber, L. Impact of the Dicarboxylic Acid Chain Length on Intermolecular Interactions with Lidocaine. *Mol. Pharmaceutics*. **2022**, *19* (8), 2980–2991.

Zotova, J.; Umerska, A.; Tajber, L. Behaviour of Lidocaine-Dicarboxylic Acid Ionic Liquids in Aqueous Solutions. *Pharmaceutics* (manuscript in preparation)

Publications not associated with the thesis

Wojnarowska, Z.; Smolka, W.; Zotova, J.; Knapik-Kowalczyk, J.; Sherif, A.; Tajber, L.; Paluch, M. The Effect of Electrostatic Interactions on the Formation of Pharmaceutical Eutectics. *Phys. Chem. Chem. Phys.* **2018**, *20* (43), 27361–27367.

Wojnarowska, Z.; Zotova, J.; Knapik-Kowalczyk, J.; Tajber, L.; Paluch, M. Effect of Electrostatic Interactions on the Relaxation Dynamics of Pharmaceutical Eutectics. *Eur. J. Pharm. Sci.* **2019**, *134*, 93–101.

Umerska, A.; Bialek, K.; Zotova, J.; Skotnicki, M.; Tajber, L. Anticrystal Engineering of Ketoprofen and Ester Local Anesthetics: Ionic Liquids or Deep Eutectic Mixtures? *Pharmaceutics* **2020**, *12* (4), 368.

Tajber, L.; Mesallati, H.; Zotova, J.; Wojnarowska, Z.; Umerska, A. “New” Solutions to the Problem of Poorly Soluble Drugs - the Role of “Green”, Anti-Crystal Engineering. In The 1st International Electronic Conference on Pharmaceutics; *MDPI*: Basel, **2020**.

Umerska, A.; Zotova, J.; Tajber, L. Formation of Low Melting Point Binary Systems Comprising Ketoprofen and an Amide Local Anaesthetic. *Int. J. Pharm.* **2021**, *607*, 120969.

Presentations

Podium presentation (online): Lidocaine Ionic Liquids: Correlation of anion structure with aqueous solution behaviour. Open Research Biopharmaceutical Internships Support (ORBIS) project; 9th March 2020, Zentiva, Prague, Czech Republic.

Poster presentation: The effect of dicarboxylic acid chain length on the aqueous solubility of lidocaine ionic liquids. 41st All Ireland Schools of Pharmacy Conference; 17th-18th April 2019, Trinity College Dublin, Ireland.

Podium presentation: Thermal analysis and characterisation of the new phase formation of lidocaine/dicarboxylic acid binary systems. RSC Molten Salts Discussion Group Early Career Researcher Meeting; 13th September 2018, Queen's University, Belfast, UK.

Podium presentation: Eutectic, deep eutectic and other multicomponent phases of lidocaine with dicarboxylic acids. The 1st International Conference on Contemporary Pharmacy Challenges: Amorphous Pharmaceuticals and Biopharmaceuticals; 9th-11th September 2018, Wisla, Poland.

Poster presentation: Eutectic, deep eutectic and other multicomponent phases of lidocaine with dicarboxylic acids. 40th All Ireland Schools of Pharmacy Conference; 26th-27th March 2018, Ulster University, UK.

Poster presentation: Eutectic, deep eutectic and other multicomponent phases of lidocaine with dicarboxylic acids. 11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology; 19th-22nd March 2018, Granada, Spain.

List of Abbreviations and Symbols

2θ	2 theta (diffraction angle)
ΔH_{fus}	enthalpy of fusion
η	viscosity
Λ	molar conductivity
ρ	density
σ_{dc}	dc-conductivity
ν	vibration frequency
χ	mole fraction
ABL	aqueous boundary level
API	active pharmaceutical ingredient
ATR-FTIR	attenuated total reflectance- Fourier transform infrared spectroscopy
BDS	broadband dielectric spectroscopy
C5	glutaric acid
C6	adipic acid
C7	pimelic acid
C8	suberic acid
C9	azelaic acid
C10	sebacic acid
C11	1,9-nonanedicarboxylic acid
C12	dodecanedioic acid
C13	1,11-undecanedicarboxylic acid
CCDC	Cambridge Crystallographic Data Centre
CP MAS NMR	cross-polarisation magic-angle spinning nuclear magnetic resonance
CSD	Cambridge Structural Database
DA	dicarboxylic acid
DEM	deep eutectic mixture
DFT	density functional theory
dm/dt	change in mass per unit time
d_{norm}	normalised contact distance
DSC	differential scanning calorimetry
DVS	dynamic vapor sorption
EMLA	eutectic mixture of local anaesthetics

ESP	electrostatic potential
FTIR	Fourier-transform infrared spectroscopy
GIPF	general interaction properties function
GRAS	generally regarded as safe
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HPLC	high-performance liquid chromatography
ICH	International Conference on Harmonisation
IDR	intrinsic dissolution rate
IL	ionic liquid
IPM	isopropyl myristate
IUPAC	International Union of Pure and Applied Chemistry
KPI	Kitaigorodskii packing indices
LAG	Liquid-assisted grinding
LID	lidocaine
LID:DA	lidocaine:dicarboxylic acid system
LogD	distribution coefficient
LogP	partition coefficient
NMR	nuclear magnetic resonance
NSAID	non-steroidal anti-inflammatory drugs
PAMPA	parallel artificial membrane permeability assay
PBS	phosphate-buffered saline
Pe	effective permeability
PIL	protic ionic liquid
pKa	negative base-10 logarithm of the acid dissociation constant
POM	polarised optical microscopy
PXRD	powder X-ray diffraction
R	gas constant
RH	relative humidity
RMSD	Room-Mean-Square-Deviation
RT	room temperature
SvL	Schroeder van Laar
SXRD	single-crystal X-ray diffraction
T _{fus}	temperature of fusion
T _g	glass transition temperature

TGA	thermogravimetric analysis
T_m	melting point temperature
US FDA	United States Food and Drug Administration
VFT	Vogel-Fulcher-Tamman

Chapter 1: General Introduction

1.1 Mechanosynthesis of multicomponent phases

1.1.1 Multicomponent Phases

It has been estimated that around 60% of new drug candidates suffer from low aqueous solubility.¹ This issue has fuelled an interest in optimisation of old medicines in lieu of discovering new chemical entities. Alteration of a solid state form of a drug has demonstrated to be a suitable strategy to enhance the performance of active pharmaceutical ingredients (APIs) without affecting their chemical integrity and biopharmaceutical profile.² The alteration of a solid state can be achieved through preparation of different polymorphs of a single-component system, amorphisation, solvate or hydrate formation or multicomponent phase synthesis.³ Different multicomponent forms are distinguished by their crystallisation behaviour, melting points and ionisation state. **Figure 1.1** presents a selection of multicomponent phases and defines the scope of this work. All the systems presented will be discussed in more detail, with an emphasis on liquid forms (*vide infra*). Multicomponent phase synthesis relies on the formation of non-covalent intermolecular interactions between the molecules or ions. The nature of these interactions, i.e. whether they are ionic, or driven by dipole-dipole interactions, determines the classification of these systems. Both, solid and liquid multicomponent phases might be found anywhere along the ionisation continuum,⁴ posing a challenge to their classification as the components in such systems can be partially ionised or may contain mixtures of ionised and unionised species. For example, Lengauer et al. found that crystals of tenofovir alafenamide derivatives exist as a mixture of salt and cocrystal complexes as determined by cross-polarization magic angle spinning nuclear magnetic resonance spectroscopy (CP MAS NMR).⁵ Some other examples of complex systems include lidocaine:salicylic acid oligomeric ionic liquid, where a labile proton was labelled as “confused” due to being permanently delocalised in a homoconjugated salicylic acid anion.⁶

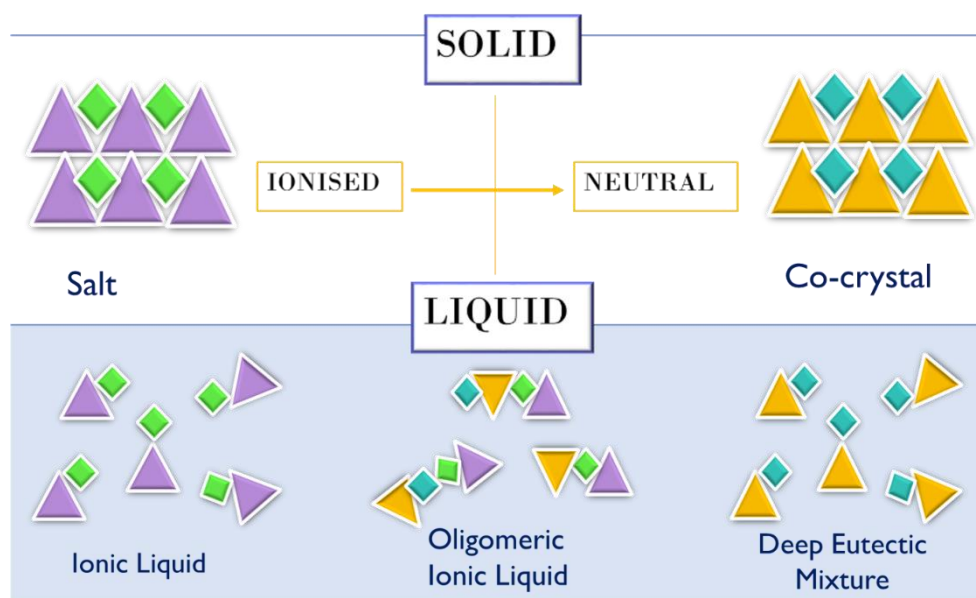


Figure 1.1. Examples of liquid and solid pharmaceutical multicomponent systems.

Systems intended to be used for pharmaceutical applications generally contain an API and a second component, i.e. a coformer or a counterion, which should be Generally Recognised as Safe (GRAS).⁷ It is also possible to combine an API with another API to form a drug-drug system offering dual functionality. Such systems have gained a lot of interest, especially for the potential use in combination therapy.⁸ Umerska et al. have explored different combinations of a non-steroidal anti-inflammatory drug (NSAID) ketoprofen with a range of local anesthetics as a potential non-opioid strategy for acute and chronic pain management.⁸ Wang et al. have synthesised dual API ionic liquids combining diphenhydramine with ibuprofen and naproxen, as the commercially available combinations of these drugs have exhibited superior sleep aid and analgesic efficacy.⁹ EMLA, which is a Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine), is a commercially successful drug-drug multicomponent system.¹⁰

Multicomponent phases may exist at equimolar compositions, as well as other stoichiometric configurations.^{11–14} Varying stoichiometric configurations has proven to be an effective method to modulate physicochemical properties of multicomponent phases. Wang et al. have studied rates of drug transport through a model membrane of lidocaine:ibuprofen complexes at various stoichiometric ratios. They have found that varying drug composition can modify the degree of proton transfer, thus, affecting permeability. In the presence of excess ibuprofen, lidocaine was found to be more strongly ionised leading to slower membrane transport rates of both APIs.¹⁵

1.1.2 Mechanochemistry

The International Union of Pure and Applied Chemistry (IUPAC) Compendium of Chemical Technology has defined mechanochemical reactions as chemical reactions that are induced by the direct absorption of mechanical energy generated by shearing, stretching and grinding.¹⁶ Mechanochemistry in pharmaceutical applications has experienced an astonishing growth in the past decade resulting in numerous publications and reviews.^{17,18,19,20,21} The technique has been identified as a fast, sustainable and high-yield alternative to a traditional solution synthesis of multicomponent phases.¹⁸ The avoidance of solvent use is of particular significance in the context of green chemistry. Furthermore, waste prevention, atom economy, safety of synthetic techniques, among another 12 Principles of Green Chemistry, have been attributed to mechanochemistry.²²

Mechanochemical synthesis can be broadly categorised into solvent-free and solvent-assisted processes. It is important to note that solvent-free processes do not involve deliberate addition of solvents. However, atmospheric moisture, water forming a part of the crystalline structure of the parent materials and generation of solvent byproducts (e.g. acetic acid) may be present in the reaction.²³

Contact formation represents the simplest case of a mechanochemical reaction, where physical mixing of the components under controlled conditions results in a spontaneous formation of a multicomponent phase (**Figure 1.2**).²⁴ Spontaneous process indicates that a product is a thermodynamically stable phase. Although the products can form upon simple mixing with a spatula, pre-milling of the starting materials has shown to markedly increase the cocrystallisation rate in pharmaceutical cocrystals.²⁵

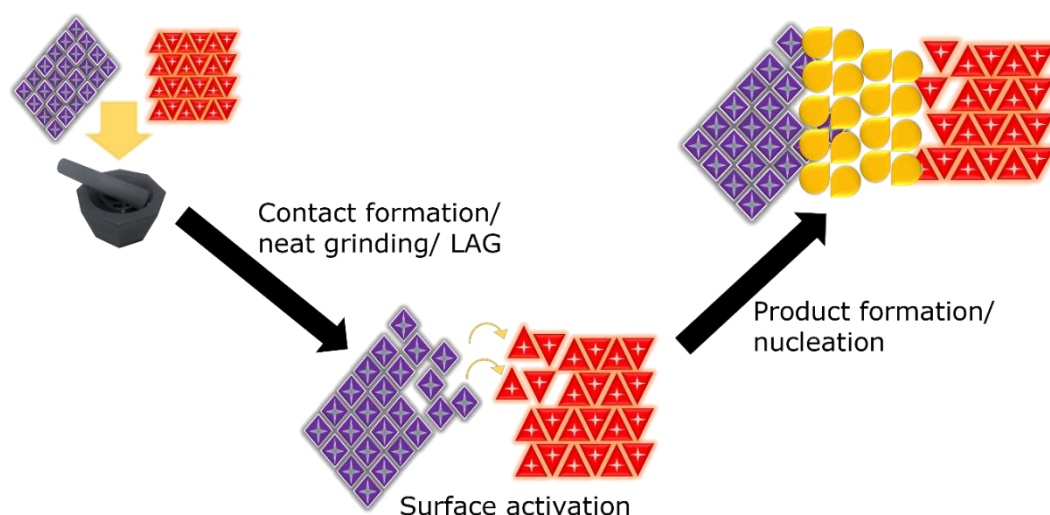


Figure 1.2 Schematic representation of a mechanochemical reaction mechanism.

Neat grinding is another mechanochemical technique which combines two or more counterions or coformers by grinding or milling. It can be performed manually by placing the reactants in a mortar and grinding them with a pestle. However, manual grinding is labour intensive and experiences issues with reproducibility as the process depends on the physical strength of an operator. To circumvent these limitations, automated milling processes, such as using a planetary ball mill, may be employed. Automated milling is considerably less labour intensive and allows significantly higher control of experimental conditions to attain better reproducibility. Furthermore, the reaction is performed in a closed vessel limiting exposure of an operator to the reagents and exposure of the reactants to environmental factors. Both, manual and automated neat grinding is prone to an incomplete reactivity and conversion of the reactants. In this case the resulting mixture contains the product and remaining unreacted starting materials. In a lot of cases annealing can be used alongside, when thermal stability of the starting components and the product allows. The use of nonstoichiometric quantities of the starting components in the mixture may allow the discovery of non-stoichiometric products. The study by Johansson et al. of 1:1 N-methylpyrrolidine–acetic acid mixture has revealed an ionic liquid formation, albeit with a very low degree of ionicity. The investigation of other stoichiometries of the N-methylpyrrolidine–acetic acid mixture has uncovered the formation of much more ionic oligomeric ionic liquids at 2:1 and 3:1 ratios.²⁶ This emphasises the need for a range of molar compositions to be investigated during mechanochemical screening.

Liquid assisted grinding (LAG) or solvent-drop grinding involves addition of a very little amount of solvent to impart additional degrees of freedom (orientational and conformational) to the reacting molecules and to serve as a catalyst.¹⁶ An empirical parameter η has been proposed to define the ratio of the volume of liquid phase V to the amount of solid present m (**equation 1**). Hence, grinding of mixtures with low η ($< 1 \mu\text{L mg}^{-1}$) represents a typical LAG reaction, while a large η ($> 10 \mu\text{L mg}^{-1}$) is characteristic to solution crystallisation.²⁷

$$\eta = \frac{V \text{ (liquid, } \mu\text{L)}}{m \text{ (sample, mg)}}$$

(Eq. 1)

A series of reviews have highlighted the great efficiency of LAG on promoting the formation of multicomponent phases.^{21,28} It has been shown that addition of an appropriate solvent significantly increases the rate of product formation.²³ Martins et al. have demonstrated that LAG can be used to synthesise ionic liquids incorporating an active pharmaceutical ingredient (API-ILs) in a faster, more reproducible, selective and higher yielding manner when compared to a conventional solution synthesis.¹⁸ Moreover, the amount of the solvent added has shown to affect polymorph selectivity in caffeine-anthranilic acid multicomponent crystal, where different amounts of solvent resulted in different polymorphic forms of the system.²⁹ Many studies were performed to systematise solvent selection, however, current studies still rely on empirical methods.²³

1.1.3 Anti-crystal engineering

Crystal engineering relies on principles that are derived from an understanding of the intermolecular interactions that prevail in molecular solids to design crystal structures of organic species with desired physical and chemical properties.³⁰ Specific intermolecular interactions play a role in molecular recognition that connects molecules like building blocks. These include weak van der Waals forces, dipole-dipole interactions, hydrogen bonding, halogen bonding and electrostatic interactions. The intermolecular forces are primarily responsible for the formation of organic crystals by minimising the energy of the molecules in the crystal.³¹

There are two basic types of molecular recognition that facilitate the formation of acid-base multicomponent phases. Self-complementary functional groups are capable of forming supramolecular homosynthons, such as carboxylic acid-carboxylic acid or amide-amide homodimers. Functional groups that engage with a different but complementary functional group form supramolecular heterosynthons, such as carboxylic acid-amide heterodimer.³² The molecular recognition and self-assembly of synthons comprising carboxylic acid and amide groups in the context of crystal engineering have been studied extensively to aid understanding and prediction of multicomponent phase formation.^{33,34,35} Consequently, Saha and Desiraju have demonstrated that understanding of acid-amide synthon formation allows to anticipate mechanical properties of the cocrystals and to select the desired material properties, i.e. property engineering.³⁶ In the context of pharmaceutical applications, tuning of component complexation through supramolecular synthon formation was used as a strategy to modulate solubility and membrane permeability of theophylline and isomeric aminobenzoic acid systems.¹²

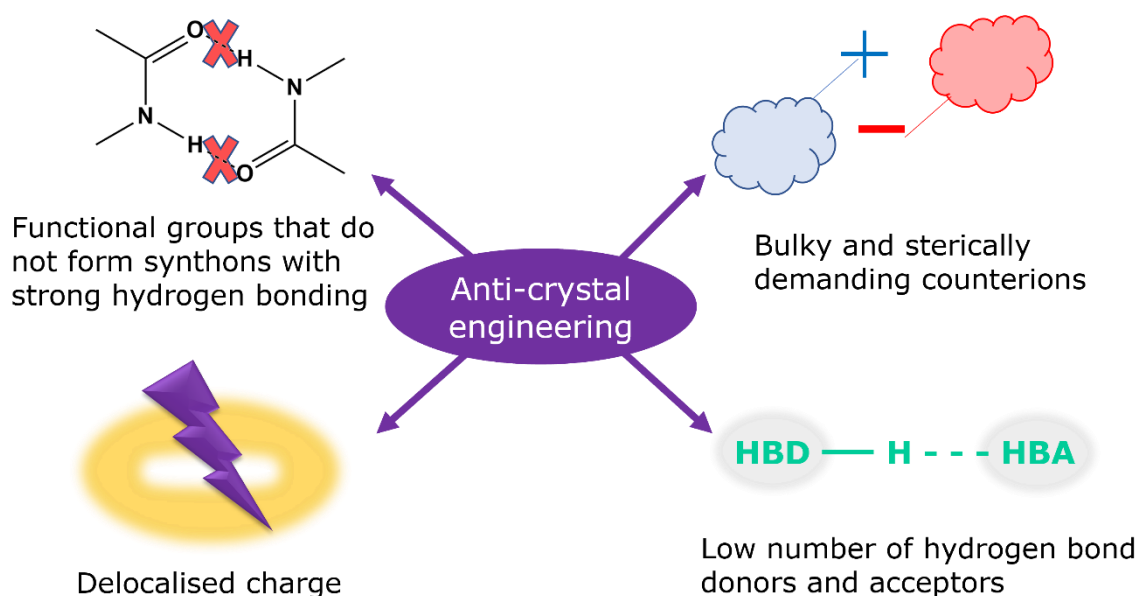


Figure 1.3. Schematic representation of the main considerations of the anti-crystal engineering approach.

The fundamental knowledge of molecular interactions and their role in supramolecular crystal architecture has led to the evolution of the reverse process of “anti-crystal engineering” (**Figure 1.3**). The term has been coined by Dean et al. for the synthesis of a series of pharmaceutical Active Ionic Liquids (AILs).³⁷ Anti-crystal engineering approach is used to identify and intentionally avoid crystallisation of counterion pairs for the synthesis of non-crystalline salts, i.e. ionic liquids (ILs). At present, the main factors that are considered to be inhibiting crystallisation of pharmaceutical salts include the choice of counterions with functional groups that do not form robust synthons with strong hydrogen bonding.³⁷ It is also preferred for the counterions to be bulky and sterically demanding, with delocalised charge and a minimal number of hydrogen bond donors and acceptors.³⁸ These structural factors lead to weak coordination and minimise anion-cation interactions. More studies are underway to identify forces that are driving liquefaction of pharmaceutical salts.^{39,40,41,42}

1.1.4 Salts

The IUPAC Compendium of Chemical Terminology defines a salt as a chemical compound comprising an assembly of cations and anions.⁴³ Many marketed drug substances are organic acids or bases that are capable of forming salts.⁴⁴ Approximately 50% of the United States Food and Drug Administration (US FDA) approvals consist of APIs in the salt

form.⁴⁵ Salt formation, or salification, has been recognised as an effective strategy to manipulate and optimise a drug's absorption, pharmacodynamics and pharmacokinetics.^{46,47} This is achieved by changing of a counterion without altering the molecular integrity of an API. The counterion charges must be balanced requiring a salt to have a definite stoichiometry. Counterion selection is a crucial step in the drug development process and most common counterions used in the preparation of pharmaceutical salts include chloride, sodium, sulphate, calcium, citrate, phosphate, among many others.⁴⁸ A crystal engineering approach together with the help of Cambridge Structural Database (CSD) which fulfils an invaluable function of providing an access to a comprehensive database of molecular crystal structures form the basis of counterion selection and salt design.⁴⁹

It is generally accepted that the most important molecular parameter for salt screening is the difference between the acid and base dissociation constants (pK_a). Crystalline solids are generally described as ionic when the difference between the base and acid pK_a values ($\Delta pK_a = pK_a[\text{base}] - pK_a[\text{acid}]$) is $\Delta pK_a > 3$.⁵⁰ Conventional solid salts can either be crystalline or amorphous. Salts in crystalline solid form possess long-range molecular ordering, a strong crystal lattice and a high melting point. Examples include widely available salts, such as lidocaine hydrochloride and ibuprofen sodium. In contrast, molecules in amorphous salts are randomly oriented and do not exhibit long-range ordering. Polymeric salts of ciprofloxacin reported by Mesallati et al. are examples of amorphous salts.⁵¹ They do not display a sharp endothermic melting transition. Instead, amorphous solids are characterised by the presence of a glass transition (T_g) that indicates a temperature at which the molecular mobility in the solid changes significantly.⁵²

Crystalline salts tend to suffer from the issue of polymorphism as a vast majority of drugs can crystallise into several polymorphic forms. Polymorphism in crystalline solid materials is manifested in different lattice structures or different molecular conformations of the same chemical substance.⁵³ Each polymorph of a crystalline drug is characterised by a unique set of physicochemical properties and different bioavailability. For example, Pudipeddi and Serajuddin have shown that polymorphs exhibit different aqueous solubilities, which in turn, affect drug bioavailability.⁵⁴ Aramini et al. have demonstrated an unexpected salt/cocrystal polymorphism of a ketoprofen-lysine system. The newly discovered salt polymorph exhibited a significantly higher absorption and different pharmacokinetics compared to a commercially available ketoprofen-lysine cocrystal.⁵⁵ To overcome the issue of polymorphism salts may be formulated as amorphous materials in the form of co-amorphous systems⁵⁶ or amorphous polymeric salts⁵¹. However, in many cases

amorphous forms of drugs are not the most thermodynamically stable and spontaneous crystallisation is not uncommon.⁵⁷ Suitable storage conditions for amorphous materials need to be considered carefully. It has been demonstrated that drugs stored at temperatures significantly below their T_g maintain their amorphous state. Increasing the temperature above the T_g enhances molecular mobility within the systems which facilitates crystallisation thus compromising stability.⁵⁸ Rumondor et al. have investigated the effect of polymer type on crystallisation rates of amorphous solid dispersions of felodipine. They have shown that the choice of stabilising polymer has a great influence on the sensitivity of the amorphous dispersions towards changes in relative humidity.⁵⁹

1.1.5 Ionic Liquids

Ionic liquids are defined as salts with a melting point or a glass transition temperature lower than 100 °C.⁶⁰ They often incorporate bulky asymmetric counterions that lead to weak coordination consequently destabilising the crystal lattice, hence, causing melting point depression.⁶¹ They are being termed “designer” solvents for the ability to be tuned to match specific requirements for the particular system. ILs incorporating APIs (API-ILs) or ILs that replace organic solvents for solubilisation of APIs are generally referred to as third generation ILs.⁶² The three generations of ILs manifest the advances of understanding of their characteristics (**Figure 1.4**). The first generation recognised their unique physical properties such as low melting point, low vapour pressure, high thermal stability and high conductivity. These ILs included ethylammonium nitrate⁵⁸ and dialkylimidazolium chloroaluminate melts⁶³. However, the earliest ILs that were developed were air and moisture sensitive. The second generation of ILs utilised these physical properties and tuned them to target the desirable chemical properties which could allow ILs to be used for a wide range of applications, such as 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF(6)] being used as a replacement for organic solvents in biocatalysis.⁶⁴ And finally, the third generation ILs were developed as task-specific agents with specific targeted biological activity.⁶⁵ The synthesis of ranitidine docusate, one of the earliest API-ILs reported, demonstrated the ability of a liquid salt to avoid polymorphism, increase solubility and attain double functionality by combining with a pharmaceutically active counterion.⁶⁵

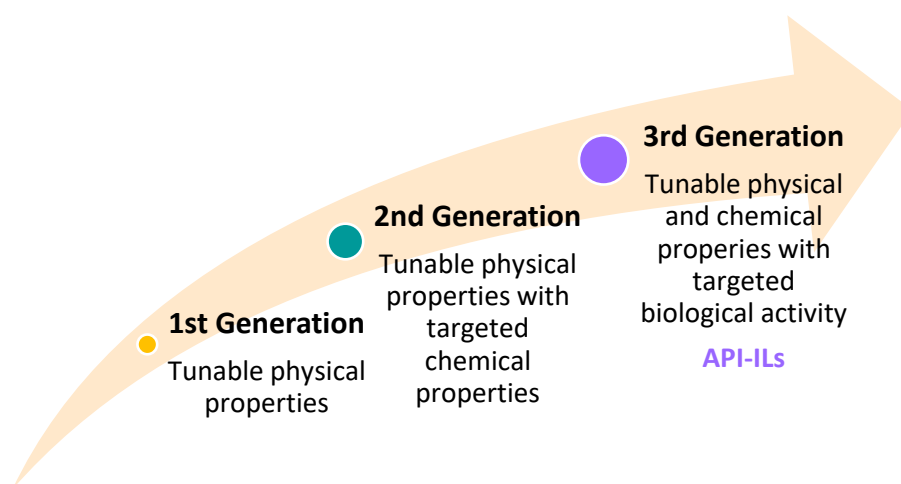
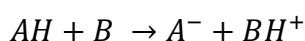


Figure 1.4. The three generations of ionic liquids.

ILs are subclassed into aprotic and protic ionic liquids based on the nature of their ionicity. Protic ionic liquids (PILs) are salts or ion-pairs of Brønsted acids and bases held together by partially-transferred labile protons and are often prepared by simple acid-base neutralisation reactions (**Scheme 1.1**). On the other hand, ionisation in aprotic ILs does not involve proton transfer and the preparation of such systems requires more complex synthetic routes and additional purification steps.

Scheme 1.1. Acid-Base neutralisation reaction, where AH is the Brønsted acid, B is the Brønsted base, and A^+ and BH are their conjugate base and acid, respectively.



It was initially thought that ILs are composed only of dissociated ions. However, studies have shown that many protic ILs are found in equilibrium with their conjugate acids and bases.⁶⁶ Properties exhibited by PILs depend on the degree of proton transfer between the acid and the base, in addition to the hydrogen bonding in which the proton is engaged.⁶⁷ Similar to conventional solid salts, in mixtures composed of weak acids and bases the ΔpK_a value determines whether a neutralisation reaction may occur. Analogous to solid salts, ILs are generally expected to be ionised at $\Delta pK_a > 3$.⁵⁰ The magnitude of ΔpK_a is directly proportional to the driving force for proton transfer, i.e. the larger the ΔpK_a , the higher the degree of ionisation. It is important to note, that this value was derived for dilute aqueous solutions and is only a qualitative predictor for solids.⁶⁶ In some cases $\Delta pK_a > 3$ is not

sufficient for a proton transfer to take place due to weak hydrogen bond ability of a protonated base cation. For example, Stoimenovski et al. found that tertiary amines require a greater ΔpK_a value to produce a substantial proton transfer as compared to primary amines. They attributed the findings to a greater availability of hydrogen bond sites and additional intermolecular interactions in primary amines.⁵⁰ Nevertheless, ΔpK_a is a useful tool to rank acid-base pairs in terms of their likelihood to undergo proton transfer in ILs.

Alternatively, Davidowski et al. have proposed a method for predicting ionisation in ILs based on proton affinity values.⁶⁸ They have observed a linear relationship between a ^1H NMR chemical shift of an exchangeable proton with a gas phase proton affinity of acids calculated using density functional theory (DFT). They have argued this method is a better predictor of ionicity than aqueous ΔpK_a values. However, both methods may only provide qualitative predictions but not quantitative measurements of proton transfer.⁶⁹

1.1.6 Cocrystals

Pharmaceutical cocrystals are defined as solid crystalline materials composed of two or more neutral components (i.e. coformers) in a stoichiometric ratio where at least one component is an API.⁷⁰ The components are held together by non-covalent intermolecular interactions, such as Van der Waals forces, hydrogen bonding, $\pi \cdots \pi$ stacking, etc. Cocrystal formation results in a new unique crystal structure which is entirely independent from the parent components. This approach imparts modified physicochemical properties of APIs without altering their molecular structures. Currently, considerable research efforts are concentrated on development of cocrystal structure and property prediction tools as, in the majority of cases, they cannot be reliably predicted from the structures and properties of the starting materials.^{71–73}

APIs that do not possess a suitable functionality required for salification can be considered as candidates for cocrystal formation. It is generally accepted, that the distinction between a salt and a cocrystal is based on whether the system components are neutral or charged. As previously discussed, ΔpK_a is a useful indicator for ionisation within multicomponent systems. $\Delta pK_a \leq 0$ is a reliable criterion for the lack of proton transfer from a Brønsted acid to a Brønsted base.⁴ In the case when $0 \leq \Delta pK_a \leq 3$, the system might be identified either as a salt, a cocrystal or might contain delocalised protons or mixed ionisation states that fall in between the ionisation spectrum that cannot be assigned to either category.

The cocrystal strategy involves an application of crystal engineering concepts for the discovery and development of drug:coformer combinations that have the potential of forming stable self-assembling complexes with desired physicochemical and pharmacological properties. Common hydrogen-bonded synthons targeted for cocrystal formation include carboxylic acid:carboxylic acid dimers, carboxylic acid:amide dimers and carboxylic acid:pyridine dimers.⁷⁴ In addition to forming dimers, supramolecular synthetic complexity may increase to include ternary and other higher-order cocrystals.⁷⁴ Moreover, cocrystals may also be formed via halogen bonding.⁷⁵ The design of high-throughput crystallisation and screening technologies has attracted significant research interest to minimise the time and effort during cocrystal discovery and development processes.^{76,77}

Cocrystallisation has proven to be a useful method of improving solubility of poorly soluble APIs.⁷⁸ Although, the majority of cocrystal research is focused on oral formulations, increasingly more studies are investigating cocrystals intended for alternative routes of administration.⁷⁹ For example, Alhalaweh et al. have reported the formation of theophylline cocrystals with a series of coformers for potential use in pulmonary delivery.⁸⁰ Topical formulations of cocrystals comprising ferulic acid with a series of coformers relevant to skin care were described by Aitipamula and Das for potential application in sunscreen cosmetics and anti-aging products.⁸¹

1.1.7 Eutectics and Deep Eutectic Mixtures (DEMs)

A eutectic is a heterogeneous solid phase that is formed by co-solidification of two miscible liquid phases yielding a crystalline microstructure that has a lower melting point relative to that of either pure constituent.⁸² It is heterogeneous, meaning that the microstructure exhibits periodicity of starting components arranged in separate domains held together by weak interphase boundaries. Weak interphase bonding, as well as imperfect molecular arrangement create a strain leading to high thermodynamic functions, and hence, melting point depression.⁸³ Eutectic formation requires assessment of mutual miscibility of the constituents in the liquid phase and immiscibility in the solid phase. The eutectic composition is determined empirically by constructing a temperature-composition phase diagram as shown in **Figure 1.5**. Melting points of the starting materials as a function of compositions are represented as liquidus curves. The point of intersection of the two liquidus curves is referred to as a eutectic point. Compositions to either side of the eutectic point contain mixtures of the solid eutectic and excess starting materials. A deep eutectic mixture (DEM) is defined as a mixture of pure constituents for which the eutectic point temperature

is below that of an ideal liquid mixture. The magnitude of the melting point depression is taken as the difference between the ideal and the observed eutectic point.⁸⁴ The theoretical phase diagram and eutectic point for an ideal liquid mixture can be calculated using the Schroeder van Laar equation (**Equation 2**):

$$T = \left(\frac{1}{T_{fus}} - \frac{R \ln \chi}{\Delta H_{fus}} \right) \quad (\text{Eq.2})$$

where R is the gas constant, χ is the mole fraction of the studied component at a given temperature T ; ΔH_{fus} (J mol^{-1}) and T_{fus} denote the enthalpy of fusion and melting temperature of the pure component, respectively.

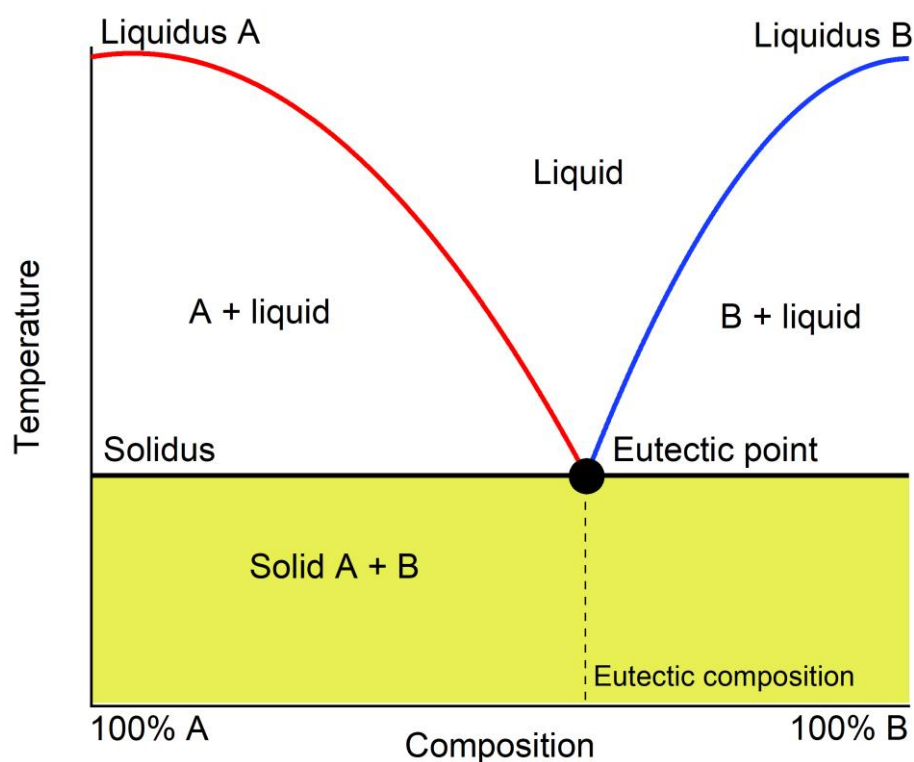


Figure 1.5. Thermodynamic phase diagram depicting eutectic phase formation.

Eutectic formation approach has been used to enhance aqueous solubility of drugs by lowering the temperature of fusion of the solidified material.⁸⁵ An example of a successfully

marketed formulation is EMLA which is a eutectic mixture of lidocaine and prilocaine intended for topical application of local anaesthesia.¹⁰ A vast array of eutectic and deep eutectic mixtures for potential pharmaceutical applications have been reported in recent years.⁸⁵ Eutectic mixtures are not limited to drug-coformer or drug-counterion compositions. Drug-drug eutectics have been reported for multidrug therapy. Alshaikh et al. studied eutectic mixtures comprising caffeine with aceclofenac, flurbiprofen and meloxicam prepared by neat grinding. The eutectic mixtures investigated exhibited enhancement in dissolution rates and anti-inflammatory response.⁸⁶ Furthermore, salts comprising Brønsted acid and Brønsted base can form eutectics with excess of either of the starting components. For example, Bialek et al. has demonstrated that propranolol:dicarboxylic acid salts at 1:1 stoichiometry form eutectics when mixed with either excess propranolol or dicarboxylic acids, giving rise to additional thermodynamic phase diagrams.^{87,88}

1.2 Solid-state characterisation of multicomponent phases

Correlation of structure and properties of starting components to characteristics of the resulting multicomponent phases in a systematic way is a current challenge that is being addressed by many research groups.⁸⁹ Advances in analytical studies of multicomponent phases using thermal techniques, X-ray diffraction, spectroscopy, theoretical modelling, and other theoretical approaches has provided invaluable contribution to our understanding of their formation and properties. However, a large proportion of multicomponent systems is still being discovered empirically. Once a new modification of a physical form of an API is suspected its full characterisation needs to be performed in order to evaluate the altered physicochemical properties and to enable correct classification. Generally, qualitative characterisation of the proton transfer, solid-state structure, purity of the product and relevant pharmaceutical characteristics are addressed.⁶⁶

1.2.1 Thermal behaviour

Thermal analysis comprises a set of techniques in which a physical or chemical change of the material is measured as a function of temperature. Differential scanning calorimetry (DSC) is one of the most common thermal techniques and it is used to measure the amount of energy absorbed or released by a sample when it is heated, cooled or kept at isothermal conditions.⁹⁰ Thermodynamic information that can be obtained by this technique includes temperature and enthalpy of fusion, crystallisation and polymorphic transitions as well as glass transition temperature of amorphous samples. When the material is subjected

to a heating cycle, DSC measures the energy (i.e. heat flow) necessary to establish a nearly-zero temperature difference between the sample and a reference standard. DSC is used to construct thermodynamic phase diagrams (see **Figure 1.5**) which present the temperatures of the thermal events as a function of molar ratio of binary mixtures of the starting components. Thermodynamic phase diagrams allow identification and characterisation of events, such as melting point depression, phase crystallisation and new phase formation. For example, the appearance of an endothermic transition at a temperature lower than the temperatures of fusion of the starting components might indicate the formation of a eutectic or a cocrystal. Conversely, a new endothermic peak at higher temperatures might indicate the formation of a new salt. A complete disappearance of any thermal transitions might indicate a formation of an amorphous solid or an ionic liquid. DSC thermograms of the higher-order heating cycles can also be used to construct a thermodynamic phase diagram. Following the completion of a heating cycle, a sample might be subjected to a cooling step to allow recrystallisation of a salt, cocrystal or the starting materials. Cooling to a temperature below glass transition at a rate that is faster than the maximum crystallisation rate inhibits nucleation and facilitates glass formation.⁹¹ Subsequent heating cycles may then exhibit crystallisation and melting peaks or glass transition events, depending on the intrinsic tendency of the material to form a supercooled state.

Thermogravimetric analysis (TGA) is another common thermal analytical technique which measures the change of sample mass as a function of temperature or time under controlled conditions. It is often employed to assess sample desolvation processes and material degradation upon heating. TGA and DSC can be used together as an integrated system allowing the endothermic transitions to be directly correlated to weight losses as a function of temperature or time.⁹²

1.2.2 Crystalline properties

Detailed investigations of crystalline properties of multicomponent phases rely on X-ray crystallographic studies and on theoretical simulations. Single crystal X-ray diffraction (SXRD) is one of the most definitive tools for structural analysis at an atomic level and provides a wealth of accompanying chemical data, including unit cell composition, atomic positions, bond lengths/angles, crystal packing and hydrogen bonding. Additional crystallographic information and characterisation of intermolecular interactions in multicomponent crystals based on the elucidated crystal structure can be obtained from Hirshfeld surface analysis.^{93,94} It calculates a unique 3D Hirshfeld surface and 2D fingerprint

plots permitting a more comprehensive interpretation of the nature and type of intermolecular interactions in the crystal. Structural information gathered from SXRD analysis allows a variety of solid state properties, such as stability, morphology and hygroscopicity to be modelled or predicted and related structures to be engineered by applying the principles of crystal engineering.⁹²

However, it might be difficult or outright impossible to obtain single crystals that satisfy size and quality requirements to be analysed by SXRD. In this case, powder X-ray diffraction (PXRD) can be used as a reliable technique for rapid new phase identification. Although, PXRD provides considerably less structural information than SXRD. PXRD instruments can be coupled with temperature or humidity control accessories to study solid state phase transitions, desolvation, melting and recrystallisation.⁹⁵ Moreover, considerable progress has been observed in crystal structure elucidation from data obtained by PXRD.^{96–98}

Difficulties in structural phase characterisation arise when a material is liquid. X-ray diffraction studies cannot be performed with liquid ILs or DEMs. However, it has been shown that there is a correlation between structures of materials in their solid and liquid states.^{99,100} In cases, where a solid form of an IL or a DEM can be obtained, elucidation of crystal structures may allow a direct insight into the spatial relationship between the molecules, thus, contributing to further understanding of structural features of liquid multicomponent phases. In addition, solventless neat NMR can be a useful tool for structural characterisation of these systems.¹⁰¹ This method allows to probe structural features of liquid samples without disturbing their bulk structures via addition of solvents. Instead, samples are standardised against a reference contained in a coaxial tube insert.¹⁰²

1.2.3 Ionisation state

The importance of determining the extent of proton transfer cannot be overstated as it has an implication on the classification of the multicomponent phase (i.e. whether it is a true IL, a DEM, etc.) There are numerous complementary analytical techniques used to identify and quantify the degree of ionisation in multicomponent phases. These techniques include spectroscopic methods, such as Fourier-Transform Infra-Red analysis (FTIR)¹⁰³, Nuclear Magnetic Resonance (NMR)¹⁰⁴ and Broadband Dielectric Spectroscopy (BDS)¹⁰⁵. However, it is important to remember that in many cases the distinction between a fully

ionised ion pair, a partially transferred proton in an acid-base complex or a hydrogen-bonded complex can be ambiguous.

FTIR is a vibrational spectroscopic method which provides information on structure and molecular conformation by probing vibrations of atoms. The technique allows qualitative assessment of proton transfer. Stoimenovski et al. have shown that synthesised ILs based on tuaminoheptane, 2-pyrrolidinoethanol and salicylic acid produce FTIR spectra that are notably different to those of the starting materials.⁶⁷ One of the most prominent peaks, corresponding to a -C=O carbonyl stretching vibration of the acid, was not present in the spectra of ILs. In addition, the evolution of a carboxylate ion peak was noted. These observations indicate a complete proton transfer from the acid to the base, i.e. a protic IL formation. FTIR has also been used as a technique to distinguish ILs from DEMs on the basis of the appearance of carbonyl and carboxylate stretching vibrations in the IR spectra. Bica et al. have observed the formation of a neutral DEM comprising lidocaine and oleic acid. FTIR spectrum of the complex has revealed the -C=O stretching peak of the oleic acid is in the range of $\sim 1710\text{ cm}^{-1}$ rather than $\sim 1560\text{ cm}^{-1}$, as would be expected for the deprotonated carboxylate ion.¹⁰⁶

NMR is another useful technique that can provide valuable information about the position of an exchangeable proton in an acid-base complex. It can be used to monitor proton transfer as a function of composition, temperature or time. In the same study of lidocaine and oleic acid complex¹⁰⁶ ^1H and ^{15}N NMR studies were used to monitor the dynamics of hydrogen bonding. It has been observed, that an increasing molar fraction of the acid leads to a gradual downfield shift of the $\alpha\text{-CH-N}$ protons of lidocaine tertiary amine. In addition, ^1H - ^{15}N heteronuclear multiple-bond correlation (HMBC) NMR spectroscopy revealed the increasing ^{15}N chemical shift as a function of acid content, with a maximum shift difference in the deep eutectic composition region. These observations indicate the involvement of the lidocaine amine in hydrogen bonding which appears to be the strongest in the deep eutectic composition region. In a different study, Moreira et al. proposed a method for estimating the degree of ionicity based on quantitative determinations by ^1H NMR. They have calculated the magnitude of the proton chemical shifts to determine the percentage of proton-transferred complex in the API combinations.¹⁰⁷

A Walden plot has also been shown to be a valid tool for quantifying the degree of ionicity in ILs.¹⁰⁸ A Walden plot can be constructed using the Walden rule (**Equation 3**).

$$\Lambda\eta = k \quad (\text{Eq. 3})$$

Where Λ is the molar conductivity of ionically conducting liquid, η is its viscosity, and k is a temperature-dependent constant. An estimate of the k constant can be obtained from the ideal line constructed from the data for a 0.01M aqueous solution of KCl, which is used as a standard as it is considered to be an example of a fully dissociated salt. The Walden plot allows classification of ILs based on their position in relation to the ideal line (**Figure 1.6**).

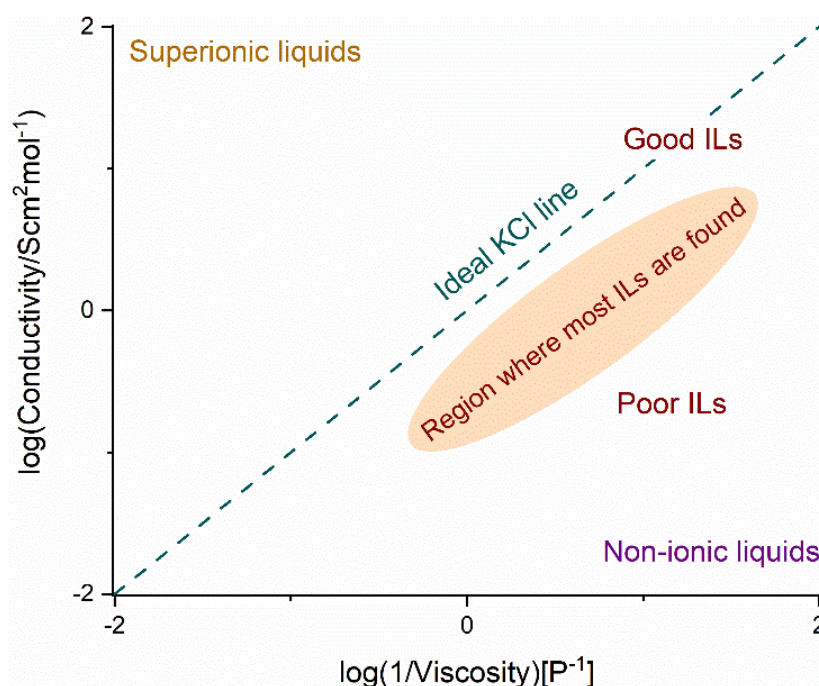


Figure 1.6. A diagram depicting a typical Walden plot.¹⁰⁹

1.3 Effect on relevant pharmaceutical attributes

Multicomponent phase formation has a great effect on various pharmaceutical attributes. One of the main purposes of seeking new multicomponent phases of APIs is enhancement of API solubility and dissolution profile. Salification, melting point depression, weakening of intermolecular interactions and disruption of crystal lattice contribute to the desired modification of solubility.^{38,110} Chantreau et al. have synthesised NSAID-based ILs which exhibited up to 100 times higher solubility as compared to their respective NSAID precursors.¹¹¹ Multicomponent phase formation has also been employed as a strategy to increase or modulate dissolution rates of drugs. For example, Balk et al. have reported enhancement of dissolution rates for pharmaceutical ILs. They have recorded a 900-fold

increase in dissolution rate for ibuprofen IL, a 250-fold increase for ketoprofen IL, a 1000-fold increase for naproxen IL, and 20-fold increase for sulfamethoxazole IL as compared to their free acid forms.¹¹²

Permeability is yet another important pharmaceutical attribute that directly affects bioavailability and is impacted by physicochemical properties of drug forms. A design strategy aiming at increasing lipophilicity via lipophilic counterion selection may improve permeability of drugs through lipid membranes at the expense of reduced solubility and dissolution rate. Wu et al. have studied the effect of a counterion structure on the relevant pharmaceutical attributes for potential transdermal delivery of ibuprofen. From the selection of the counterions studied, they have concluded that counterions with long alkyl chains decrease aqueous solubility of ibuprofen and increase permeability through a skin model.¹¹³ Tuning and controlling membrane transport via multicomponent phase formation can also provide a path to slow, continuous-release transdermal approaches. For example, a combination of lidocaine with docusate yields a hydrophobic IL with a reduced aqueous solubility, and thus, should exhibit extended residence time on skin.¹¹⁴

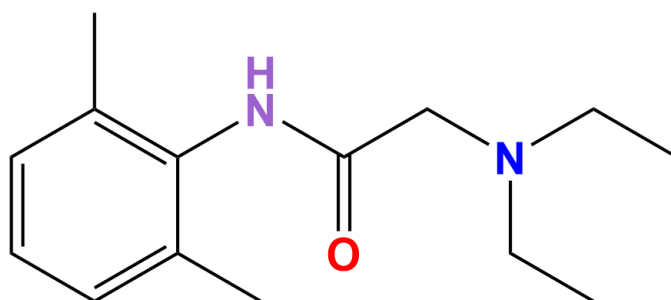
However, it is important to consider stability issues associated with multicomponent phase formation. It has been recognised that multicomponent phases, especially low-melting forms, such as ILs or DEMs suffer from compromised stability. During early development stage the stability of new forms of drugs can be assessed in a number of ways. TGA is a fast and simple method of assessing thermal stability in the form of degradation temperature of drugs. Long-term storage stability and accelerated stress testing of the samples can be performed according to the guidelines published by the International Conference on Harmonisation (ICH).¹¹⁵ This approach involves storage of the samples at controlled conditions of temperature and humidity over a specified period of time. At defined time points, physicochemical characterisation of the samples is performed to assess if any changes have occurred upon storage. For example, PXRD and DSC measurements may be performed to assess recrystallisation, degradation or phase transformation processes.^{116,117} Dynamic vapour sorption analysis is another technique that can provide valuable information about the stability of compounds in the form of their moisture sorption propensity. The uptake of water vapor by a solid at a given relative humidity and temperature is referred to as hygroscopicity and it is one of the most important pharmaceutical attributes to consider during development of new multicomponent forms of drugs.¹¹⁸ Hygroscopicity can induce alteration of physicochemical properties of multicomponent phases, including crystallinity, chemical and physical stability, solubility, dissolution, etc.¹¹⁹ Moreover, water uptake can

lead to a transformation of an anhydrous form to a hydrate, triggering new multicomponent phase formation. Liquid and amorphous forms of drugs have particularly high propensity for water sorption as vapour can permeate into the bulk of the substance more easily in contrast to crystalline materials for which vapour mainly adsorbs to the surface.¹²⁰

1.4 Lidocaine

Lidocaine (LID), defined as 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide according to IUPAC, is a local anaesthetic and class I antiarrhythmic drug commonly formulated as a topical or parenteral preparation. It is a weak base with a $C_{14}H_{22}N_2O$ molecular formula and its molecular structure is shown in **Scheme 1.2**. LID molecule contains a tertiary amine moiety which can participate in hydrogen bonding or ionic interactions by accepting a proton. A carbonyl functionality that is a part of an amide group can also act as a hydrogen bond acceptor. The -NH moiety of the amide group can participate in hydrogen bonding as either a hydrogen bond donor or acceptor. LID has a pK_a of 8.0 enabling it to form ionic interactions with complementary acids.¹²¹ Most of the known salts of LID are formed through protonation of the tertiary amine moiety.^{122,123} Furthermore, LID can undergo internal rearrangement resulting in amide – imidic acid tautomerism.¹²⁴

Scheme 1.2. Structural formula of LID.



British Pharmacopoeia contains a number of monographs for lidocaine formulated preparations. These include lidocaine ointment and gels for topical administration and a range of preparations for parenteral administration.¹²⁵ All of the described formulated preparations are based on lidocaine hydrochloride monohydrate due to LID base being practically insoluble in water.¹²⁶ However, a fully ionised LID HCl salt exhibits poor membrane permeability as anaesthetic diffusion through lipid membranes depends on the

extent of API protonation.¹²⁷ Poor aqueous solubility of LID and poor permeability of LID HCl highlight a demand for new strategies of improvement of aqueous solubility of the API without compromising membrane permeability. LID possesses favourable structure and functionality required for the formation of electrostatic and supramolecular interactions and is commonly used as a model drug in the research of new multicomponent phases. Numerous reports have shown that LID can interact with a range of complementary counterions or coformers to form conventional salts, cocrystals, DEMs, ILs.^{128,129,130}

1.5 Aims

Solvent-free mechanochemical synthesis of multicomponent phases incorporating an API and a complementary counterion or a coformer has proven to be a suitable strategy to modulate and fine-tune a range of physicochemical and pharmaceutical properties without altering the physical form of a drug. The design and discovery of new systems employ the principles of crystal engineering and molecular compatibility. However, the majority of new multicomponent phases are still being discovered empirically. The aim of this work was to study multicomponent phase formation of LID as a model drug with a series of closely related dicarboxylic acids to contribute to the pool of current knowledge and understanding of the structure-property relationship of multicomponent phase formation.

Chapter 2 focuses on mechanochemical synthesis of novel multicomponent phases of LID with a series of closely related dicarboxylic acids: glutaric, adipic, pimelic and suberic. A special emphasis was placed on the in-depth investigation of the effect of varying dicarboxylic acid chain length on the physicochemical properties of the product systems. Experimental analytical techniques were used in conjunction with theoretical calculations to examine morphology, thermal behaviour, degree of ionisation, crystal structure and packing of a newly synthesised salt and ILs as a function of length of the acid carbon backbone.

Mechanochemical synthesis performed as part of the work presented in Chapter 2 has yielded a unique LID:azelaic acid system. Mixing of LID and azelaic acid at various molar fractions has yielded multiple distinct solid and liquid multicomponent phases. Consequently, Chapter 3 focuses on structural and physicochemical investigation of the mixtures and the resulting cocrystal, IL, oligomeric IL and oligomeric crystalline IL phases.

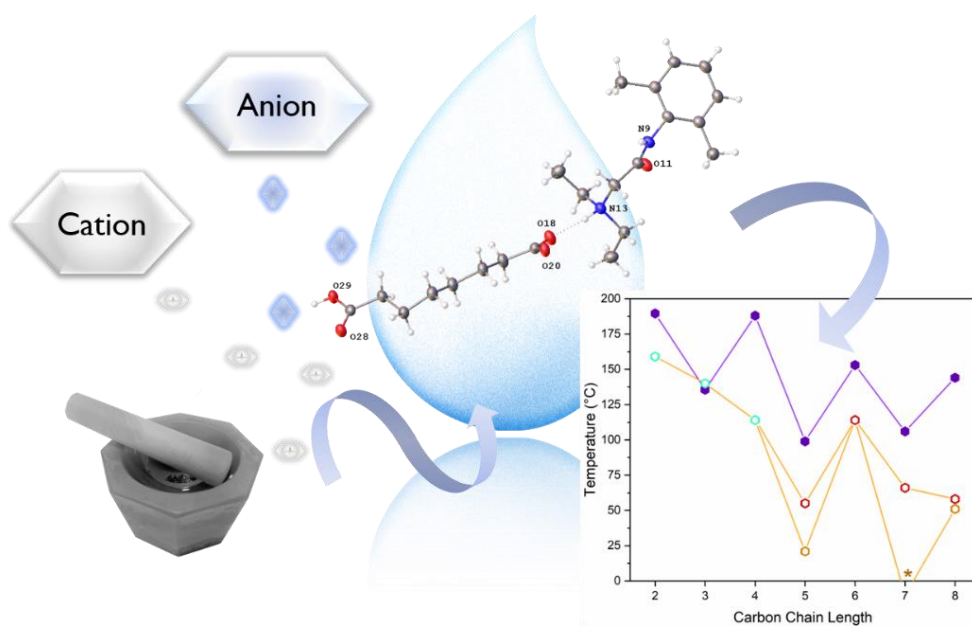
The objective of Chapter 4 involves taking the gained knowledge further to explore physicochemical properties of the LID systems with a series of long-chain dicarboxylic acids: decanedioic (sebacic), undecanedioic, dodecanedioic and tridecanedioic acids. Due to

the steric constraints and flexibility of the bulky dicarboxylic acids it was anticipated that at a certain carbon chain length LID protonation would cease to be possible. Structural and physicochemical properties of the resulting mixtures were performed. Unrelated to the original aim, a crystal structure of a previously unreported 1,11-undecanedioic acid polymorph was solved and is presented.

The objective of Chapter 5 was to investigate aqueous behaviour of a selection of the novel systems synthesised and discussed in previous chapters. The work performed as part of Chapter 5 discusses solubility, dissolution, lipophilicity, stability and permeability attributes of the systems.

Finally, Chapter 6 presents a summary and general discussion of the findings obtained in the current work. An outline of the possible future research directions is presented.

Chapter 2: Green Synthesis of Lidocaine Ionic Liquids and Salts: Mechanisms of Formation and Interactions in the Crystalline and Supercooled States



2.1 Introduction

One of the areas of pharmaceutical research that has seen a significant increase in interest lies in the optimisation of physical forms of active pharmaceutical ingredients (APIs).^{2,131} By tuning the solid form of an API it is possible to improve a drug's solubility, permeability and thus, bioavailability. As a result, a significant amount of research has led to the development of various multicomponent API systems, including crystalline salts, co-crystals, eutectics, deep eutectic mixtures, ionic liquids and solid dispersions.¹³²

Purely ionic and purely neutral multicomponent systems are the two opposite extremes of a physical modification spectrum. Solid ionic salts constitute approximately 50% of currently marketed drug substances.⁴⁴ On the opposite end of the spectrum, neutral multicomponent systems, such as cocrystals, are in the spotlight of current research and a rapidly growing pharmaceutical form of choice.

One of the possible physical modifications that can achieve the balance between the desired physicochemical properties and maintenance (or even enhancement) of pharmacological function of APIs is a low melting salt or ionic liquid (ILs). ILs are salts with melting points or glass transition temperatures below 100 °C.¹³³ In molten states the ions are not randomly distributed but form aggregates, clusters or regular 3D networks via intermolecular interactions. The advantage of employing ILs in pharmaceutical formulations is the ability to obtain highly tunable systems and simultaneously avoid polymorphic interconversions which are often encountered in solid forms.^{65,134,135} Protic ionic liquids (PILs) are fused salts held together by partially-transferred labile protons and are often prepared by simple acid-base neutralisation reactions.

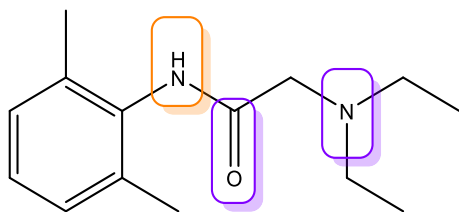
PILs can be prepared by a number of different methods, including conventional solution synthesis or by a simple mechanochemical technique. In most cases it involves milling, neat grinding or solvent-assisted grinding of chemical substances at ambient temperatures or with heating.²¹ Neat mechanochemical synthesis initiates a series of mechanisms which include molecular diffusion, eutectic formation and crystallisation through an amorphous phase.¹³⁶ This technique eliminates the need for large volumes of solvents and lengthy conventional solution syntheses and it has been demonstrated that the products prepared via mechanochemistry are obtained in higher yields, without solvent residues and in a shorter time span.¹⁸ Over the years, ILs have become renowned as sustainable and green materials.^{60,137}

Reactivity in crystals depends on a balance between steric packing factors and electronic properties and the fundamental problem is how the two processes are interrelated. Sufficient difference in pK_a values (i.e. $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$) allows ionisation to take place, however bulky molecular structures of the counterions do not allow the molecules to come into close contact hence inhibiting crystallisation. Identification of suitable counterions for API-PIL formation is a challenge currently faced and involves recognising certain structural characteristics, such as a diffuse delocalised charge, low symmetry and a low tendency of the counterion to crystallise.⁹⁹ Nevertheless, many attempts to correlate the structural considerations of the starting materials and the melting points of the synthesised salts have not provided an accurate prediction tool for IL formation.^{61,40} Currently, an anti-crystal engineering approach is regarded as the most effective prediction method for IL formation.^{8,37}

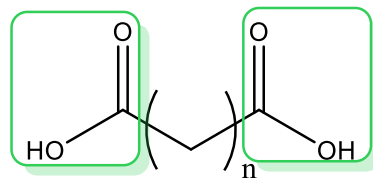
Over the last decade many different API-PIL and other multicomponent drug forms have been studied. Lidocaine (LID) has been one of the most widely studied APIs as a component in PILs. It is an aminoamide drug used as a local anaesthetic and cardiac depressant. It has also been shown to possess antibacterial¹³⁸ and antifungal¹³⁹ properties. However, when formulated as a salt its charge does not allow it to effectively penetrate biological membranes¹²⁷ and thus, significantly reduces its membrane permeability. By selecting a suitable counterion LID can be formulated as a protic ionic liquid system.

In this work, a green approach into the synthesis of multicomponent phases of lidocaine – dicarboxylic acid (LID:DA) systems was applied and the mechanism of the various phase formations studied to determine the effect of an alkyl chain length on the phase formation. Molecular structures of LID and DAs are shown in **Scheme 2.1**. The dicarboxylic acids chosen were medium chain dicarboxylic acids with carbon chain length ranging $n=5-8$ and their relevant physicochemical properties are presented in **Table 2.1**. In addition to meeting the physicochemical requirements, antifungal and antibacterial properties exhibited by some of the dicarboxylic acids render them suitable as potential companions for LID in topical formulations as dual API-ILs.¹⁴⁰

Scheme 2.1. Chemical structures of the molecules investigated in this study: lidocaine base (LID); dicarboxylic acids (DA), where n is the number of carbon atoms in the backbone. Orange: H-bond donor and acceptor; purple: H-bond acceptor; green: carboxylic acid groups.



Lidocaine (LID)



Dicarboxylic Acid (DA)

Table 2.1. Summary of physicochemical properties of the dicarboxylic acids (C5-C8) investigated.¹⁴¹ Crystallographic data obtained from Cambridge Structural Database (CSD). Polymorphic groups are described using Space Group notation, where P is a primitive and C is a single-face centred lattice type. Both space groups are monoclinic.

Dicarboxylic acid	T _m (° C)	pK _{a1}	pK _{a2}	Polymorphic forms
<i>Glutaric acid (C5)</i>	95-98	4.34	5.41	C 2/C
<i>Adipic acid (C6)</i>	152	4.41	5.41	P 2 ₁ /C
<i>Pimelic acid (C7)</i>	103-105	4.50	5.43	C 2/C, P 2 ₁ /C
<i>Suberic acid (C8)</i>	141-144	4.53	5.50	P 2 ₁ /C

2.2 Experimental section

2.2.1 Materials

LID (as a base), glutaric acid (C5), adipic acid (C6), pimelic acid (C7) and suberic acid (C8) were purchased from Sigma-Aldrich (Ireland). Potassium bromide (KBr) for infrared analysis was obtained from Honeywell Fluka (Ireland) and was dried in a vacuum oven at room temperature prior to use. Ultrapure water was purified with Millipore Elix[®] 3 Water Purification System (Ireland). HPLC grade acetonitrile was purchased from VWR (Ireland). The purity of the compounds was at least 98%. All compounds were used as obtained.

2.2.2 Methods

2.2.2.1 Sample preparation

LID was processed with each of the acids (C5-C8) at a range of molar fractions between 0.1:0.9 to 0.9:0.1 (LID:DA). The constituents were accurately weighed with a Mettler Toledo MT5 microbalance (Mettler Toledo, Switzerland) and ground in an agate mortar and pestle until homogenous mixtures were obtained. A total of 200 mg of each sample was produced. A sample of each mixture was immediately analysed by DSC, TGA, FTIR and PXRD and the remaining mixtures were transferred to 2 mL Eppendorf tubes and kept at room temperature for further analysis.

2.2.2.2 Polarised optical microscopy (POM)

Prior to analysis LID and DAs were recrystallised from ethanol. A small crystal of each, LID and DA, were placed on a glass slide and were pushed together with the help of a needle. The glass slide was examined using an Olympus BX53 polarising optical microscope (Ireland) equipped with a U-POT cross polarizer and a U-ANT analyser. Images were taken with an integrated Q IMAGING Fast 1394 camera (Olympus, Japan). The experiment was performed at room temperature.

2.2.2.3 Differential scanning calorimetry (DSC)

DSC measurements were carried out using a PerkinElmer Pyris Diamond DSC unit (USA). The unit was refrigerated using a ULSP B.V. 130 cooling system (Netherlands). Approximately 3-6 mg samples were weighed into aluminium pans and sealed. The samples were heated over the following temperature ranges: 5 °C – 105 °C for LID:C5, 25 °C – 160 °C for LID:C6, 0 °C – 110 °C for LID:C7 and 25 °C – 150 °C for LID:C8. The heating rate of 10 K min⁻¹ was employed with nitrogen at a flow rate of 40 mL min⁻¹ used as the purge gas. Following the heating step the samples were cooled to – 60 °C at 300 K min⁻¹ cooling

rate and then subjected to a second heating cycle. Thermograms were analysed using Perkin Elmer Pyris software. The temperature values for endothermic and exothermic transitions are onset values, while the midpoint of transitions were taken as glass transition temperatures (T_g). The measurements were performed at least in duplicate.

Fast-scan DSC (Hyperscan) with helium as the purge gas was performed using the same instrumental set up. Sealed aluminium pans containing approximately 0.5-0.6 mg of LID:C7 samples were heated at 300 K min^{-1} heating rate in the $-20 \text{ }^{\circ}\text{C} - 105 \text{ }^{\circ}\text{C}$ temperature range. The measurements were performed in duplicate.

2.2.2.4 Powder X-ray diffraction (PXRD)

PXRD was carried out at room temperature using Rigaku Miniflex II X-ray diffractometer (Japan) equipped with Cu $K\alpha$ radiation ($1.54 \text{ \AA}$) X-ray source. The samples were scanned over a 2θ degrees range of $2-40^{\circ}$ with a scan rate of $0.05^{\circ}/\text{s}$. The tube voltage and tube current used were 30 kV and 15 mA, respectively. LID:C6 and LID:C8 samples were heated for 5 min at $70 \text{ }^{\circ}\text{C}$ prior to analysis.

2.2.2.5 True density

Density measurements were carried out on AccuPyc II 1340 (Micromeritics, USA) using Helium as purge gas. Prior to analysis, the samples were dried under vacuum for 12 h. Approximately $0.2 - 0.8 \text{ g}$ of sample was placed in a 1 cm^3 aluminium cell where each sample was measured five times. Experiments were performed in duplicate.

2.2.2.6 Broadband dielectric spectroscopy (BDS)

BDS measurements were performed and data was analysed by Dr Zaneta Wojnarowska, University of Silesia. Conductivity of samples was measured using a Novocontrol Alpha Analyzer over a broad temperature and frequency range. The temperature was precisely controlled with a Quattro temperature controller using a nitrogen gas cryostat (accuracy of 0.1 K). During the measurements, the samples tested were placed between the steel electrodes of a capacitor (15 mm diameter), with a fixed distance between the electrodes (0.988 mm) provided by a quartz ring. The applied electric field was 0.1 V .

2.2.2.7 Viscoelastic characterisation

Viscoelastic characterisation was performed and data analysed by Dr Zaneta Wojnarowska, University of Silesia. Complex viscosity of supercooled samples was measured by an ARES G2 Rheometer. The instrument was equipped with aluminium parallel plates geometry (diameter = 8 mm). The gap distance between the plates was set from 0.9 to 1.100 mm . The oscillation, temperature-dependent measurements were performed within the

linear viscoelastic region. The samples were measured on heating from T_g up to 363 K. For the oscillation frequency rheological experiments, the investigated samples were tested in the frequency range from 0.1 to 100 rad/s (10 points per decade).

2.2.2.8 Fourier-transform infrared spectroscopy (FTIR)

Infrared spectra were recorded on Spectrum One spectrometer (Perkin Elmer, USA). LID:C5, LID:C7 and LID:C8 samples were heated for 5 min at 70 °C and LID:C6 samples were heated for 5 min at 120 °C prior to analysis. The samples were prepared as KBr disks using direct compression. Sample loading was approximately 1% (w/w). A spectral range of 650-4000 cm^{-1} and accumulation of 6 scans were used. Spectra were analysed using Spectrum v. 5.0.1 software.

2.2.2.9 Single crystal preparation by solution crystallisation

Lidocainium hemiglutarate: LID and C5 were ground at 1:1 molar stoichiometry and heated in an oven at 60 °C for 5 min. The sample crystallised upon storage at 4 °C after 6 months.

Lidocainium hemiadipate: LID_{0.5}:C6_{0.5} was dissolved in a small quantity of acetonitrile and was left at ambient conditions until complete solvent evaporation. Small colourless crystals were obtained.

Lidocainium hemipimelate: LID_{0.5}:C7_{0.5} was dissolved in a small quantity of ultrapure water at 25 °C. The solution was dried under vacuum at 70 °C for 48 hours. A drop of the concentrated solution was placed on a glass slide and small colourless crystals formed within a few hours.

Lidocainium hemisuberate: LID and C8 were ground at 1:1 molar stoichiometry and heated in an oven at 60 °C for 5 min. The sample crystallised on cooling.

2.2.2.10 Single crystal X-ray diffraction (SXR)

SXR measurements were performed and structures were solved by Dr Brendan Twamley, TCD School of Chemistry. Data for samples LID:C6, LID:C8 were collected on a Bruker APEX DUO using Cu $K\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$) and data for LID:C5, LID:C7 were collected on a Bruker D8 Quest ECO using Mo $K\alpha$ ($\lambda = 0.71073$). Each sample was mounted on a MiTeGen cryoloop and data collected at 100(2) K using an Oxford Cobra and Cryostream cryosystems respectively. Data were collected by using omega and phi scans and were corrected for Lorentz and polarization effects by using APEX.¹⁴² Absorption corrections were applied using SADABS.¹⁴³ Using Olex2, the structure was solved with the XT¹⁴⁴ structure solution program, using the intrinsic phasing solution method and refined against $|F^2|$ with SHELXL using least squares minimization.¹⁴⁵ Hydrogen atoms were

generally placed in geometrically calculated positions and refined using a riding model. Details of data refinements are mentioned in **Table AI.1**. Molecular graphics were generated using OLEX2.¹⁴⁶

In all structures LID:C5-LID:C8, N-H and O-H hydrogen atoms were located on the difference map and refined using restraints (DFIX).

The experimental powder XRD patterns were profile fitted to the single crystal data using the Le Bail technique with non-linear least squares refinement using the Gauss-Newton method with peak shape functions Pearson VII, Pseudo-Voigt and TCH pseudo-Voigt. Fit and difference patterns with associated R values are given in Appendix I.

2.2.2.11 Crystallographic analysis

Mercury (version 2020.1)¹⁴⁷ was used for structure visualisation, crystal packing analysis and molecule overlay calculations. Reference structures used for calculations were obtained from Cambridge Structural Database (CSD): HITSAG, ADIPAC14, PIMELA08, SUBRAC06¹⁴⁸ and LIDCAN11¹⁴⁹. Structural similarity was calculated using Least-Squares-Fitting and is expressed in terms of Root-Mean-Square-Deviation (RMSD) value. Void spaces within crystal lattices were calculated using contact surface with probe radius of 0.2 Å and approximate grid spacing of 0.2 Å. Hirshfeld surfaces and the associated 2D fingerprint plots were generated using CrystalExplorer17 software¹⁵⁰ using Standard (High) surface resolution.

2.3 Results and discussion

2.3.1 Design strategy

Previously, short chain oxalic, malonic and succinic diacids have been probed as components for the LID:DA systems and it has been shown that molecular salts are formed through proton transfer from the dicarboxylic acids to the amine moiety on LID.¹²³ In the current study we took this concept further and aimed to synthesise new phases of LID with medium chain dicarboxylic acids. As a result of the increasing steric effect of the bulkier acids as well as employing a different synthetic method it was hypothesised that LID and DA can form interactions that are different to the ones reported in the Braga et al. work, where the LID-short DA systems were discussed. The effect of a synthesis method of choice on the formation of ionic or molecular species has been explored and emphasized previously.¹⁵¹ Depending on the presence or absence of solvent, type of solvent and the choice of the reaction temperature, systems with different physical properties, molar ratios and species (e.g. ionic or molecular) could be obtained.

Alkyl dicarboxylic acids exhibit variation in their physicochemical properties based on the carbon chain length. Properties such as melting point, thermal expansion, solubility enthalpy, sublimation and crystal packing density alternate with the even or odd number of carbon atoms present in their backbone.^{152,153,154} Lindemann proposed that crystalline structures which experience larger thermal expansion, exhibit lower melting points.¹⁵⁵ It has been shown that the diacids follow the Lindemann's correlation and this alteration has been explained in terms of their packing and conformational distortion (**Figure 2.1.A**). A static model from the 130K crystal structure data set for the C5-C8 diacids (i.e. glutaric (C5), adipic (C6), pimelic (C7) and suberic (C8) diacids) has shown that odd acids are more distorted from their equilibrium geometry to avoid unfavourable O...O repulsions, and that leads to lowering in melting point (**Figure 2.1.B and 2.1.C**).¹⁵² This distortion and higher repulsion should make it easier to disrupt the crystal and form a new phase. In addition, in the range of even and odd diacids it is evident that longer chain lengths exhibit lower melting points.

The effects of these properties on the cocrystal formation have been studied before as in the examples of acid-amide heterosynthon systems.^{156,157} A study on the formation of benzamide-DA derivatives has investigated the influence of the chain length on the formation of new phases when additional H-bond donors were competing in the heterosynthon formation.⁴⁰ In these examples it has been shown that even chain acids yield

cocrystals with higher melting points and odd diacids yield cocrystals with lower melting points. In addition, systems with stronger intermolecular interactions (i.e. salts) exhibited a smallest decrease in the melting temperature as compared to the parent components, while systems with weaker interactions (i.e. cocrystals) exhibited significant drops in melting points.

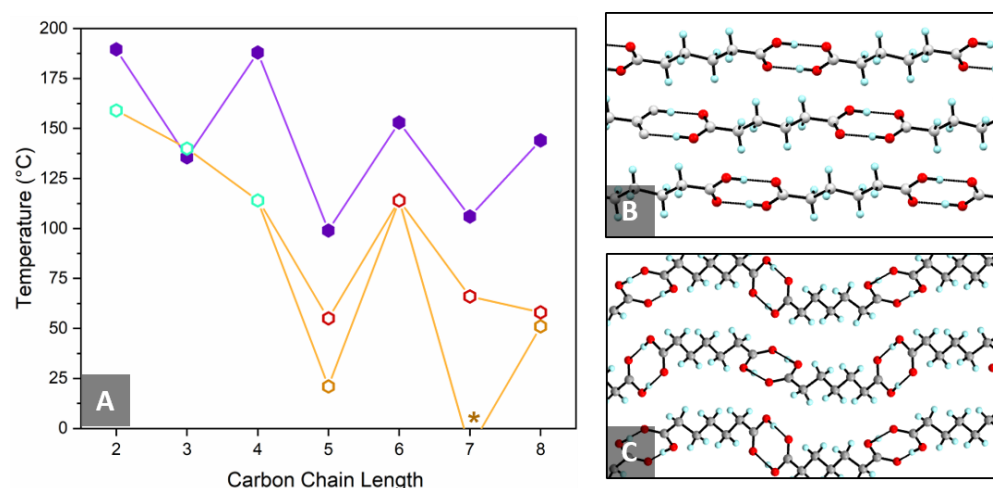


Figure 2.1. A: The melting points (purple symbols) for even and odd diacids alternate, with even diacids having higher melting points and odd diacids melting at lower temperatures. The experimental melting points (open symbols) obtained by DSC analysis for new LID:DA systems (orange symbols) show a similar alternating trend with the exception of LID:C4 (LID:succinic acid), which has a lower melting point than LID:C3 (LID:malonic acid). Data points for LID:C2 (LID:oxalic acid), LID:C3 and LID:C4 (green symbols) were obtained from literature.¹²³ The star indicates that the melting point could not be obtained as the sample is liquid above 0 °C. The red open symbols show the experimental melting points of the single crystals attained during the crystallographic studies. **B:** Crystal packing modes in even chain DAs as viewed along the *b*-axis; **C:** in odd chain diacids as viewed along the *a*-axis.

The API chosen to study the formation of multicomponent phases is lidocaine (LID) which is an amino-amide molecule with one H-bond donor and 3 H-bond acceptors. LID is a weak base (pK_a of 7.9) and most of the known LID salts undergo ionisation at the tertiary amine site.^{123,122} In addition to the amine ionisation, LID can also engage in intermolecular H-bonding with carboxylic acids yielding acid-amide heterosynthons. In the case of non-ionised H-bonded complexes LID cocrystals or deep eutectic mixtures (DEMs) may be obtained.¹⁰⁶

2.3.2 Mechanosynthesis of LID:DA systems and their morphologies

The study was initiated by solvent-free mechanochemical synthesis of the LID:DA systems. LID:C5 and LID:C7 systems with molar compositions that fall within $\text{LID}_{0.33}:\text{DA}_{0.67}$ and $\text{LID}_{0.67}:\text{DA}_{0.33}$ range yielded liquid or semiliquid samples at room temperature (**Figure 2.2.**). In contrast, LID:C6 and LID:C8 systems at all molar compositions were solid powders.

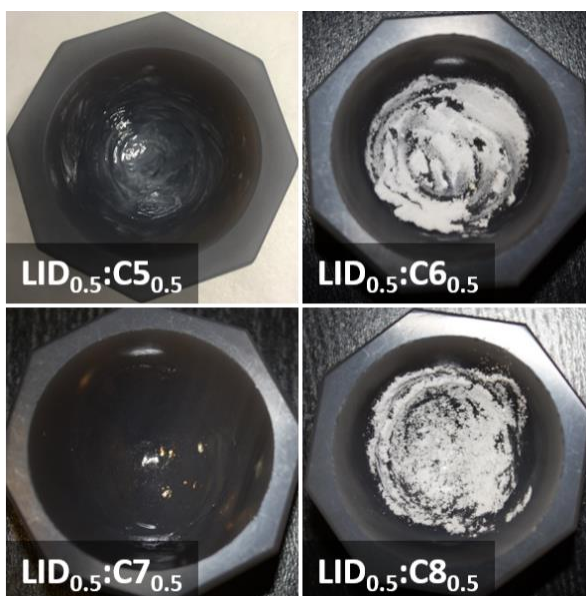


Figure 2.2. Photographs of the ground binary equimolar LID:DA mixtures immediately upon grinding in an agate mortar.

It was observed that upon physical contact LID and DAs demonstrate solid state reactivity. The crystals of the parent components were placed side by side and images obtained using Polarised Optical Microscopy (POM) illustrate that LID and DAs with C_{odd} (C5 and C7) undergo solid interdiffusion (**Figure 2.3.**). The formation of a liquid eutectic as a product of a solid-state reaction indicates that the melting point of the eutectic is lower than the reaction temperature, which in this case is room temperature. Inability to capture the melting point allows the term “deep eutectic” to be applied. LID and C8 display true solid-state reactivity with the formation of a solid eutectic at the interface. LID and C6 underwent slight reactivity, probably initiated by the shear force resulting from sample handling with no further solid interdiffusion observed after $t = 16$ h.

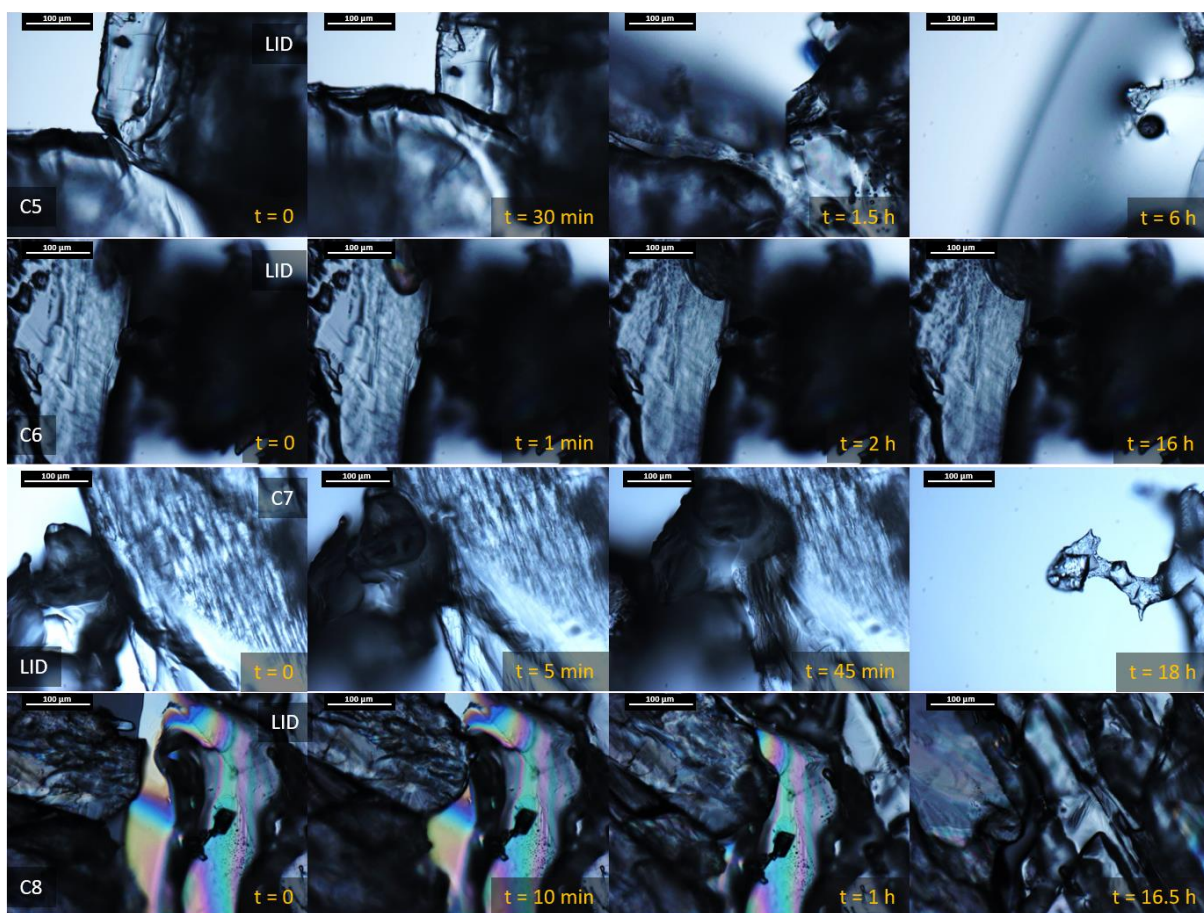


Figure 2.3. POM images of solid fusion experiments (at RT). The images were taken at various time points indicated by yellow font.

2.3.3 Mechanism of new phase formation and thermodynamic phase diagrams

Differential Scanning Calorimetry (DSC) measurements were conducted to investigate thermal behaviour of LID, DAs and their binary mixtures. Stacks of DSC traces of the mixtures at different LID:DA molar ratios are presented in **Figure 2.4**. The DSC thermogram of pure LID displays a single sharp endothermic peak at 69 °C corresponding to its melting transition. C5-C8 DAs have significantly higher melting points ranging from 95 °C to 153 °C. Multiple endothermic peaks observed in the thermograms of pure C5 and C7 DAs are attributed to the multiple polymorphic forms, the stable β and metastable α forms (**Appendix Table AI.1.**)^{158,159} In addition, the peak at 85 °C in the pure C7 corresponds to the solid-solid order-disorder transition. A similar order-disorder transition is also observed in the pure C8 at 132 °C. Beta polymorphic forms of the odd acids are more stable and those were the ones found (by powder X-ray diffraction (PXRD), **Figure 2.4.**) in precursor acids (DAs as supplied) used and also in most LID:DA samples after they were subjected to heating. Only upon heating of LID:C7 samples was a peak in the PXRD pattern

corresponding to the metastable α polymorph identified. This peak is indicated by an arrow at 23 2θ degrees in **Figure 2.4.G**.

The effect of the presence of DAs on LID was studied by observing its thermal behaviour in LID:DA binary mixtures at different molar ratios. Upon addition of an increasing molar fraction of C5 the melting point depression is observed (**Figure 2.4.A**). The red arrow indicates the shift in the melting point until it gradually disappears due to complete solubilisation of LID within the LID:C5 liquid mixture. A similar melting point depression is observed for the C5 acid with increasing LID molar fraction. Eventually, in the range of LID_{0.5}:C5_{0.5} to LID_{0.2}:C5_{0.8} the melting points of the parent materials are depressed to the extent that the system liquefies and no melting events are observed. However, upon grinding the samples obtained were not homogenous liquids but contained white solid particles suspended in the liquid matrix. DSC analysis carried out at lower temperatures revealed endothermic peaks visible in thermograms of LID_{0.33}:C5_{0.67} and LID_{0.5}:C5_{0.5} samples below room temperature, at 21°C and 22°C, respectively. These new peaks can be attributed to a new phase formation, as later confirmed by PXRD analysis.

DSC traces of LID:C6 at a range of 0.1 to 1.0 LID molar fractions display an endothermic peak at 69 °C corresponding to the melting point of LID (**Figure 2.4.B**). The lack of LID melting point depression corroborates POM images illustrating that mechanical grinding of LID and C6 does not initiate a solid state reaction. The thermograms of samples within LID_{0.7}:C6_{0.3} and LID_{0.4}:C6_{0.6} molar compositions reveal an exothermic event attributed to crystallisation with a peak temperature of 105 °C. Crystallisation is immediately followed by an endothermic peak with an onset temperature of 113 °C. The peak appears at a significantly higher temperature than the temperature of fusion of parent LID suggesting that the new phase might be a new salt that has been formed upon reaction of molten LID with C6. Salt formation was later confirmed by PXRD and single crystal X-ray diffraction (SXRD) analysis. Upon addition of excess C6 the peak corresponding to the new phase gradually diminishes and is replaced by a eutectic peak at 105 °C which could possibly arise as a result of new interactions being formed between the new phase and the excess of C6. Pure C6 has a melting point at 148 °C but the melting point is depressed upon addition of increasing molar fractions of LID until eventually, at LID_{0.3}:C6_{0.7} the peak completely disappears signifying that all of the acid is being used up in the formation of the new phase and the salt/acid eutectic.

The DSC thermograms of LID:C7 exhibit thermal behaviour similar to the one observed in the LID:C5 system. Liquefaction of LID and C7 at room temperature reveals solid state reactivity and a deep eutectic formation between the new phase and excess parent components. The depression of LID and C7 melting points is observed as the molar fraction of the corresponding counterion in the binary mixtures is increased. Eventually, the melting points of the parent materials are depressed to the extent that the system liquefies and no melting events are observed. This observation is evident in the mixtures ranging from LID_{0.6}:C7_{0.4} to LID_{0.33}:C7_{0.67} molar ratios and is shown as green DSC traces in **Figure 2.4.C**. Similar to LID:C5, upon grinding the samples obtained were not homogenous liquids but contained white solid particles suspended in the deep eutectic. However, attempts to capture the melting point of the new phase using DSC was not successful as upon heating the small crystals dispersed within a liquid matrix liquefied gradually and no endothermic peaks could be observed. DSC scans of this sample when applying a heating rate of 300 K min⁻¹ to prevent sample transformation, were also performed with an attempt to capture the melting points but these attempts were also unsuccessful.

Analogous to LID:C6, LID:C8 systems were solid in appearance. DSC thermal analysis revealed the formation of a new phase with a fusion temperature above RT at around 52 °C . Upon addition of excess C8 the formation of a new endothermic peak at 47 °C could be observed. This peak could be attributed to the fusion event of a eutectic formed between the new phase and the excess C8, as seen by POM (**Figure 2.3.**).

Plotting the temperatures of the endothermic peaks of the new phases observed in all LID:DA systems displays a matching alternating trend as in the T_m of the parent DAs (**Figure 2.1A**). This trend suggests that the melting points of the DAs used as the counterions in LID binary systems have a direct effect on the thermal behaviour of the API.

PXRD was used as the primary analytical method to identify new solid forms of LID with DAs. **Figure 2.4.E** shows the diffraction patterns of LID:C5 systems. As LID_{0.5}:C5_{0.5} and LID_{0.33}:C5_{0.67} were obtained as liquid samples, the PXRD patterns at room temperature only exhibited typical liquid “halos”. At higher LID molar fraction the PXRD pattern of LID_{0.67}:C5_{0.33} sample revealed peaks originating from the excess LID in the mixture. As a result of the system being liquid at room temperature, it is not possible to conclude whether the samples are just physical mixtures or the interactions between the parent components give rise to the formation of a new phase. However, upon keeping the LID_{0.5}:C5_{0.5} sample

at 4 °C for a prolonged time, larger crystals phase-separated from the mixture. Thus, PXRD analysis confirmed new phase formation for the LID:C5 system. The melting point of the crystallised LID_{0.5}:C5_{0.5} was determined by DSC analysis to be approximately 55 °C as shown in **Figure 2.1.A**.

LID:C6 samples analysed were solid and the changes in the diffraction patterns upon increasing LID molar fraction can be observed (**Figure 2.4.F**). The systems of LID_{0.33}:C6_{0.67} and LID_{0.67}:C6_{0.33} molar compositions display peaks arising from the PXRD patterns of the parent components. In addition to these peaks the formation of a new PXRD pattern is evident. New peaks appearing at lower 2 θ in relation to the parent components indicate the formation of a larger crystal lattice. This is observed in all LID:C6 samples with a new peak appearing at 7 2 θ degrees. At 1:1 composition only the new PXRD pattern is displayed which most likely signifies the formation of a lidocainium adipate salt. No traces of the parent materials are present at equimolar composition signifying complete conversion. New peaks in the mixtures implied that the intact crystal structures of the parent materials were completely altered via solvent-free mechanosynthesis.

LID:C7 binary mixtures obtained were liquid but contained white particles dispersed within the matrix and attempts to capture the temperature of the melting transition by thermal analysis was unsuccessful, as explained above. However, it was possible to obtain PXRD pattern of the new phase formed (**Figure 2.4.G**). The existence of a diffraction pattern inferred that the melting point of the new phase must be higher than the room temperature. When subjected to PXRD these particles exhibit a unique PXRD pattern as compared to the parent materials. The new peak at the 7.7 2 θ degrees is found at a lower position as compared to the first peaks of the diffraction patterns of the parent components indicating the formation of a larger crystal lattice. The LID_{0.33}:C7_{0.67} and LID_{0.67}:C7_{0.33} mixtures exhibit PXRD patterns which contain peaks stemming from the parent components in addition to the new peaks. The presence of the parent components within these systems suggests that the material does not participate in the formation of intermolecular interactions and crystallises out as excess. The binary mixture at 1:1 stoichiometry displays only the new peaks attributable to the new phase formed upon mechanical grinding, most likely a 1:1 lidocainium hemipimelate stoichiometry.

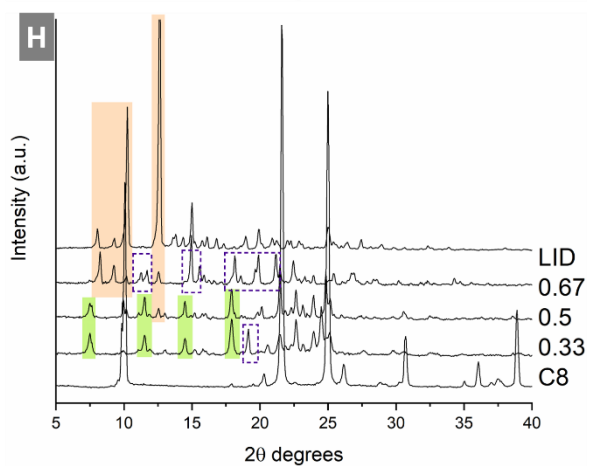
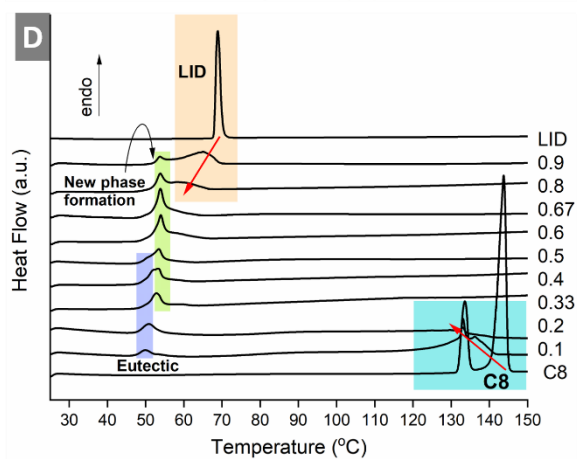
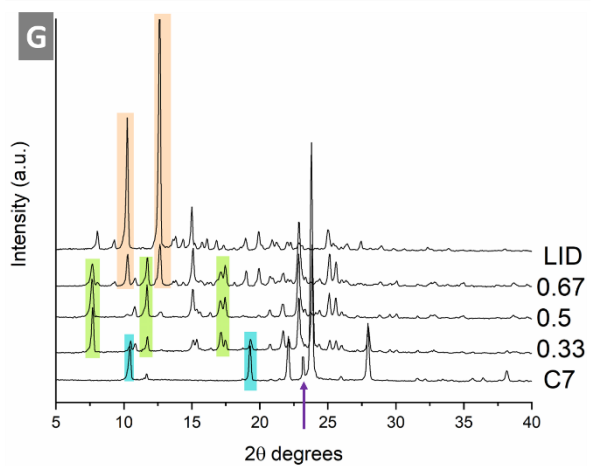
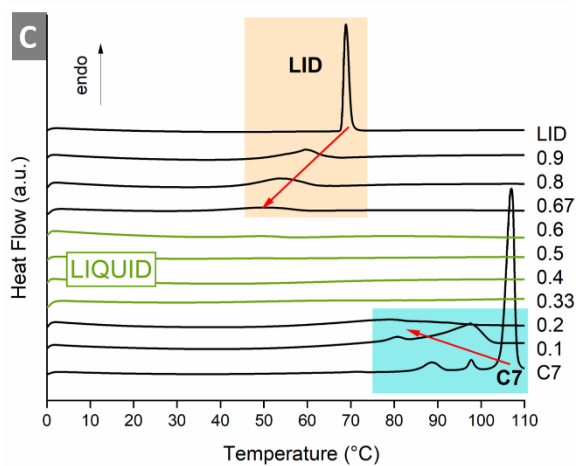
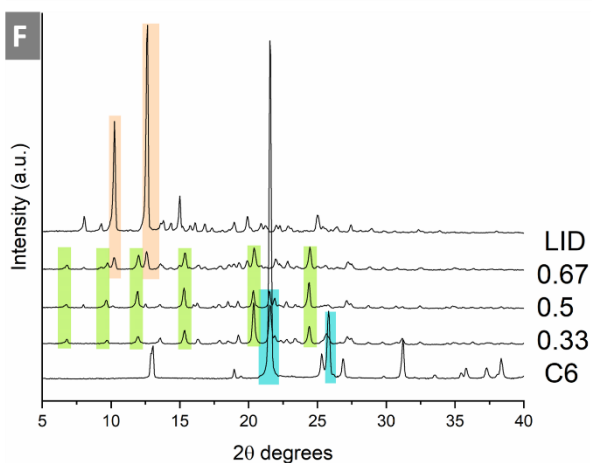
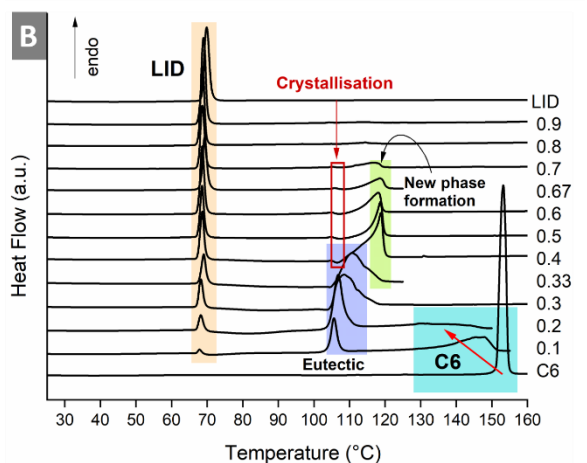
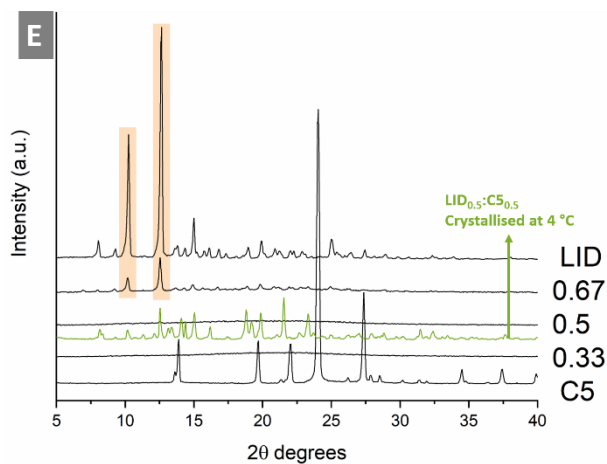
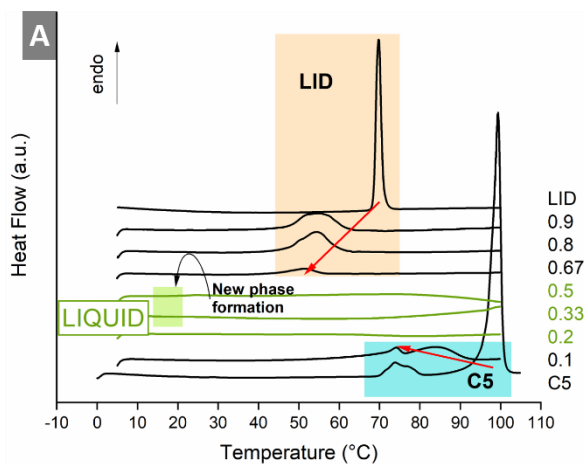


Figure 2.4. DSC thermograms of the LID:DA binary mixtures at different molar compositions, (A) – LID:C5, (B) – LID:C6, (C) – LID:C7, (D) – LID:C8. Green and black lines indicate liquid and solid samples, respectively. PXRD patterns of the LID:DA binary mixtures, (E) – LID:C5, (F) – LID:C6, (G) – LID:C7, (H) – LID:C8. Purple arrow indicates a peak stemming from the metastable α polymorph of C7 DA.

PXRD analysis of LID:C8 systems showed similar results as those observed for the LID:C7 system. PXRD patterns with 0.33:0.67 and 0.67:0.33 molar compositions exhibited newly formed peaks as well as peaks characteristic of the parent materials. At the 1:1 stoichiometry no peaks stemming from the precursors were observed indicating 1:1 lidocainium hemisuberate stoichiometry. However, the mixtures at 0.33:0.67 and 0.67:0.33 molar compositions also contain unique peaks not found in other samples (**Figure 2.4.H**, purple dashed boxes). One possible source of these peaks stems from crystallisation of non-stoichiometric phases.

Thermal analysis data was used to construct thermodynamic phase diagrams (**Figure 2.5**). The theoretical solubility lines were modelled by the Schroeder van Laar equation (**Equation 2**):

$$T = \left(\frac{1}{T_{fus}} - \frac{R \ln \chi}{\Delta H_{fus}} \right) \quad (\text{Eq.2})$$

where R is the gas constant, χ is the mole fraction of the studied component at a given temperature T ; ΔH_{fus} (J mol^{-1}) and T_{fus} denote the enthalpy of fusion and melting temperature of the pure component, respectively. From the phase diagrams obtained it is evident that only LID:C8 phase behaviour could be reasonably predicted. LID:C5 and LID:C7 systems deviate from the ideal behaviour which indicates that additional intermolecular interactions acting between the components in the mixtures contribute to the thermal events within the systems. The phase diagram obtained for the LID:C6 system shows that the theoretical model cannot be applied in this case as the melting points of the parent components are so far apart that the calculated liquidus lines never converge. In all of the cases the calculated theoretical eutectic composition was not the same as observed in DSC and PXRD studies. The investigation of intermolecular interactions using Fourier transform infrared analysis

(FTIR) has confirmed the presence of electrostatic and hydrogen bonding interactions within the systems at various molar compositions. **Table 2.2.** and **Figure 2.6.** highlight the characteristic peaks observed in the FTIR spectra. It is interesting to note that the carbonyl stretch of LID at 1665 cm^{-1} undergoes a hypsochromic shift when mixed with odd DAs and a bathochromic shift when mixed with even DAs. The observed alternation indicates alternating capability of the DAs to form H-bonds with the carbonyl group of LID.

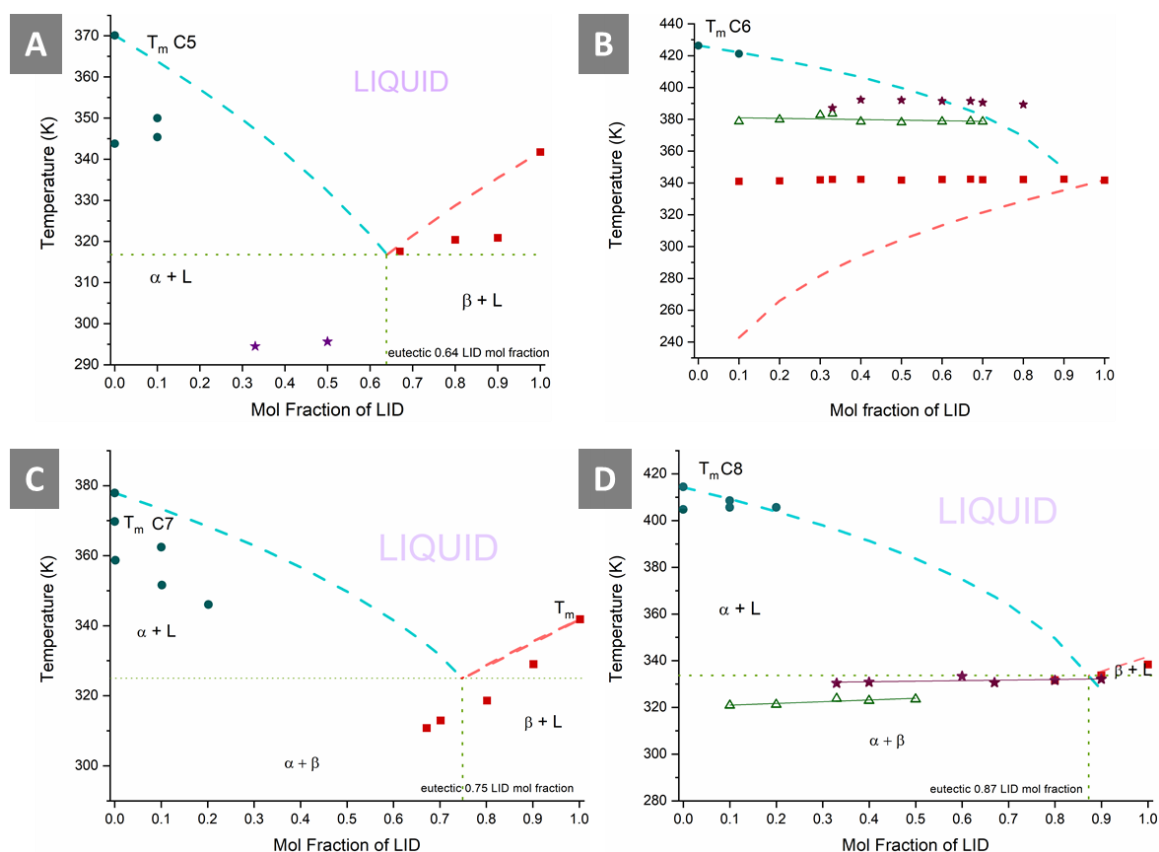


Figure 2.5. Phase diagrams constructed using the data obtained from DSC experiments. Theoretical curves were constructed using the Schroeder van Laar equation (blue dashed line – theoretical DA solubility curve; red dashed line - theoretical LID solubility curve). Legend: red squares – experimental LID T_m ; green circles - experimental DA T_m ; stars - experimental new phase T_m ; green triangles - experimental eutectic T_m ; α and β indicate diacid and LID components, respectively; L indicates liquefied components.

Table 2.2. FTIR peak assignment table for parent compounds and equimolar LID:DA mixtures.

Compound	Wavenumber (cm^{-1})			
	$\nu(\text{OH})$	$\nu(\text{NH})$	$\nu(\text{C=O})$	$\nu(\text{COO}^-)$
LID	-	3253	1665	-
C5	-	-	1701	-
C6	-	-	1694	-
C7	-	-	1696	-
C8	-	-	1697	-
LID _{0.5} :C5 _{0.5}	3432	3175	1732, 1690	1540
LID _{0.5} :C6 _{0.5}	3441	3185	1689, 1651	1549
LID _{0.5} :C7 _{0.5}	3433	3180	1724, 1689	1541
LID _{0.5} :C8 _{0.5}	3433	3234, 3189	1716 (shoulder), 1687, 1656	1546

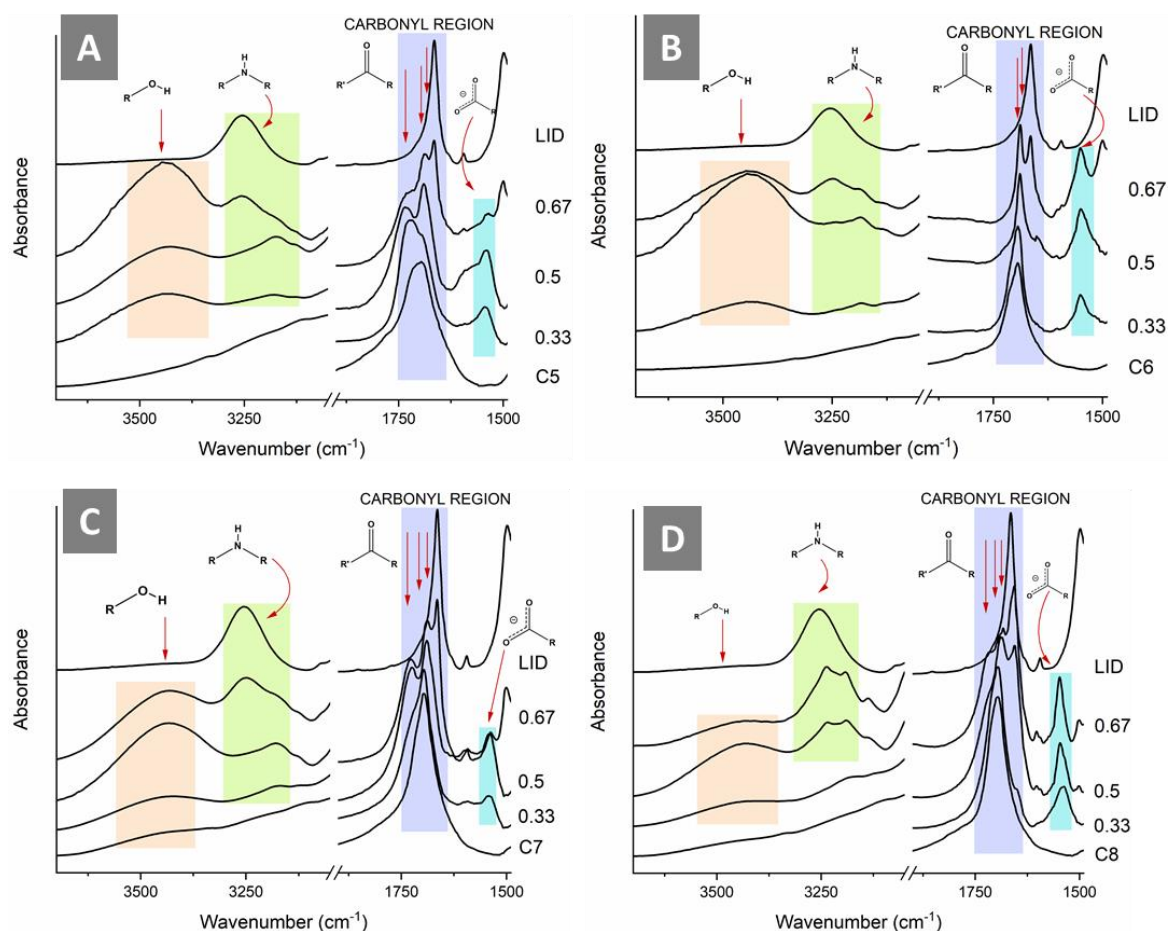


Figure 2.6. KBr-IR spectra of the LID:DA systems: (a) – LID:C5, (b) – LID:C6, (c) – LID:C7, (d) – LID:C8.

2.3.4 Thermal and dynamic behaviour of supercooled LID:DA systems

All LID:DAs composition following melting were fast cooled at a nominal rate of 300 K/min and subjected to a second heating cycle at 10 K/min. The stacks of DSC thermograms of the samples at various molar compositions are presented in **Figures AI.1-AI.4**. The presence of glass transition (T_g) events in most mixtures (with the exception of extreme molar compositions of LID:C5 and LID:C7) imply the ability of the systems to be supercooled. No glass transition events were observed for the parent materials as they crystallise immediately upon cooling. T_g behaviour of the systems was evaluated and is presented in **Figure 2.7**.

As can be seen from **Figure 2.7.A**, there is a clear maximum in T_g when the LID:C5 and LID:C7 mixtures are considered. It occurs at the equimolar composition of acid and base. Interestingly, such a trend is not observed for LID:C6 and LID:C8. In the latter case, only the continuous decrease of T_g with the mole fraction of lidocaine can be observed. The peculiar extremum in T_g behaviour found for LID_{0.5}:C5_{0.5} and LID_{0.5}:C7_{0.5} can be explained in terms of ionicity degree. Typically, the T_g becomes markedly increased when a given API is converted to the salt form e.g. hydrochloride, sulphate or phosphate.^{160,67} Additionally, it has been also confirmed that the T_g and melting point of classical aprotic ionic liquids increases when the electrostatic interactions start to dominate van der Waals forces.¹⁶¹ In this context, one can expect that in LID:C5 and LID:C7 systems there is a proton transport from acid to base, and importantly it is the most efficient in 1-1 compositions. As a consequence, LID_{0.5}:C5_{0.5} and LID_{0.5}:C7_{0.5} are expected to be composed of LID cations and acidic anions and thus reveal an ionic character.

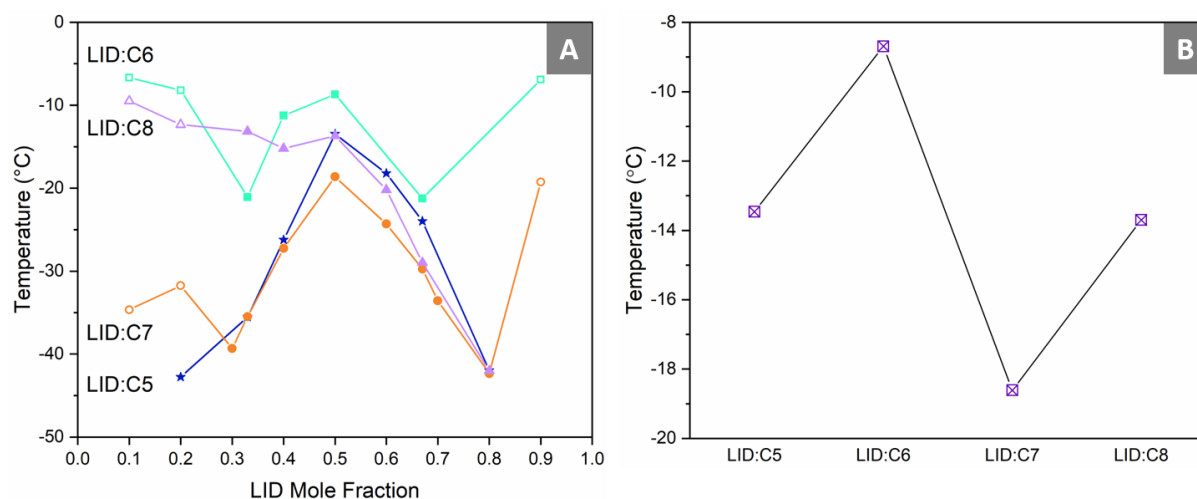


Figure 2.7. T_g values of the LID:DA systems obtained upon supercooling them in the DSC. (A) T_g values of LID:C5 (blue stars), LID:C6 (green squares), LID:C7 (orange circles) and LID:C8 (purple triangles) as a function of LID mole fraction. Open circles denote samples that have partially crystallised upon cooling or during second heating before the T_g was observed; (B) T_g values of the systems at equimolar compositions.

The most commonly explored approach for assessing ionicity in ionic liquids is the Walden plot that relates molar conductivity (Λ) of a given system to its viscosity (η), i.e. $\Lambda\eta^k = C$. If the system is composed of independent ions and their diffusion depends only on viscosity then the Walden diagram corresponds closely to the ideal line determined for 0.01 mol dm⁻³ KCl aqueous solution, with the slope equal to 1.¹⁶² Usually, the protic ionic liquids are located below this line on the lower right-hand half of the Walden plot.¹⁶³ This is due to the partial ionisation of these systems that results in a lower number of charge carriers and consequently lower conductivity than would be expected from the Walden rule. For this reason, PILs are frequently regarded as ‘poor’ ionic systems. However, as demonstrated in the literature, there are examples of superionic protic liquids and glasses that are characterised by the abnormally high mobility of charge-carrying species and fall above the ideal Walden line.^{164,165}

To examine the ionicity of LID:C5 and LID:C7 equimolar compositions, conductivity, viscosity and density of these materials need to be determined. Conductivity was measured by dielectric spectroscopy at various temperatures, from 363 K to 243 K for LID_{0.5}:C5_{0.5} and from 363 K to 246 K for LID_{0.5}:C7_{0.5}. The representative conductivity spectra

$\sigma'(f)$ of LID_{0.5}:C5_{0.5} collected in the frequency range from 10⁻¹ to 10⁶ Hz are demonstrated in **Figure 2.8.A**.

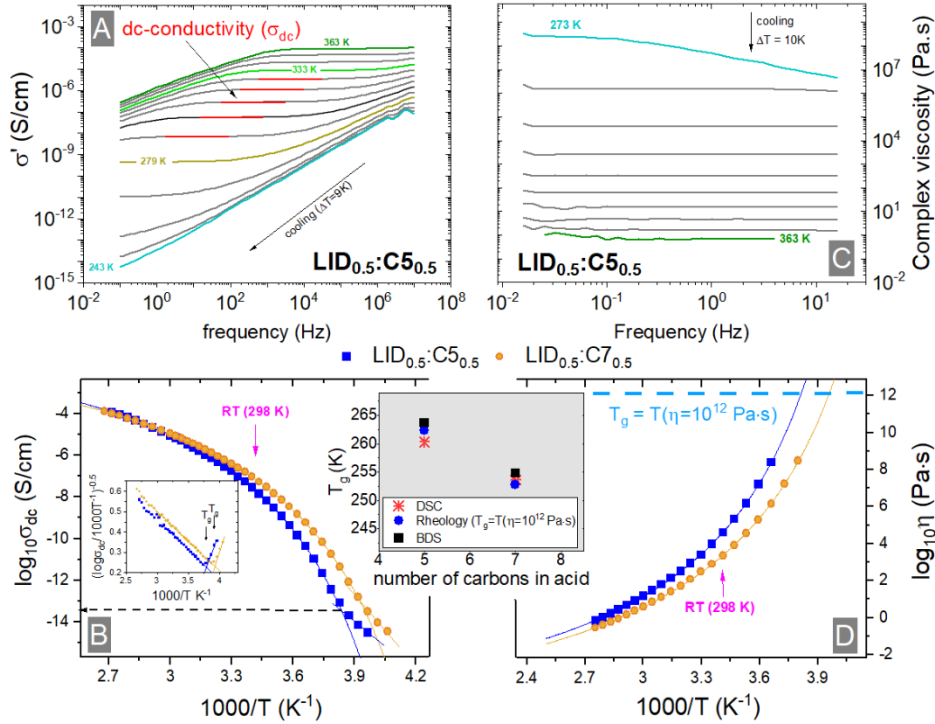


Figure 2.8. A) Dielectric spectroscopy data of LID:C5 presented in conductivity formalism. B) Temperature dependence of dc-conductivity for LID_{0.5}:C5_{0.5} (blue) and LID_{0.5}:C7_{0.5} (orange). The inset presents the Stickel analysis C) Complex viscosity spectra of LID_{0.5}:C5_{0.5}. D) Temperature dependence of complex viscosity for LID_{0.5}:C5_{0.5} and LID_{0.5}:C7_{0.5}. Solid lines are fits of the Vogel-Fulcher-Tammann equation to the experimental data. In the inset panel the T_g values for LID_{0.5}:C5_{0.5} and LID_{0.5}:C7_{0.5} determined by conductivity, viscosity and DSC are compared.

Three regions can be detected in the spectra: the polarization effect visible at low frequencies; a frequency-independent part, so-called dc-conductivity, σ_{dc} ; and the power-law behaviour at the high frequencies. Since the mobility of ions markedly slows down with cooling, the dc-conductivity also decreases with a decrease in temperature. As shown in **Figure 2.8.B**, the temperature dependence of σ_{dc} reveals a non-linear dependence and can be parameterised by the Vogel-Fulcher-Tammann (VFT) equation (**Equation 4**):

$$\log_{10}\sigma_{dc}^{-1} = \log_{10}\sigma_{\infty}^{-1} + \frac{\log_{10}e \cdot DT_0}{T-T_0}, \quad (\text{Eq. 4})$$

where σ_{∞}^{-1} is a pre-exponential factor, D is the strength parameter quantifying the deviation from the ideal Arrhenius behaviour and T_0 is known as the “ideal” glass temperature. However, the satisfactory fit to the experimental data can only be achieved in a limited temperature range. This is because below a certain temperature the experimental points follow the Arrhenius behaviour. The VFT-Arrhenius crossover can be better visualised when the Stickel operator $[\text{dlog}\tau_{\sigma}/\text{d}1000T^{-1}]^{-0.5}$ is employed¹⁶⁶ (inset **Figure 2.8.B**). It should be noted that the crossover phenomenon is a typical feature of ionic glass-formers and it has been proven to define the temperature of liquid-glass transition.¹⁰⁹ This rule is also fulfilled for the studied LID:DA compositions. As seen in the inset to **Figure 2.8.**, the T_g value determined as the crossover point of dc-conductivity data agrees well with the calorimetric T_g . However, upon closer inspection of **Figure 2.8.B** one can also note that dc-conductivity determined at T_g of the LID:DA mixtures is higher than the value of 10^{-15} S/cm typically observed at T_g of classical ionic liquids, in which the vehicle conduction is the only mechanism controlling the charge transport. This result suggests that the fast proton hopping within the Grotthuss conduction gives a contribution to charge transport in the LID:DA compositions. Consequently, viscosity is no longer the main factor controlling charge transport in these systems. To verify this hypothesis, rheological measurements of LID_{0.5}:C_{50.5} and LID_{0.5}:C_{70.5} (**Figures 2.8.C and 2.8.D**) were performed and the conducting and viscoelastic properties of the PILs over a broad temperature range on the Walden plot (**Figure 2.9.**) compared. For the construction of the Walden graph the dc-conductivity needs to be presented as molar conductivity. The following equation was employed for this purpose (**Equation 5**):

$$\Lambda = \sigma_{dc} \cdot M \cdot \rho^{-1} \quad (\text{Eq. 5})$$

where M denotes molecular mass and ρ is density of sample. The molar conductivity data of LID_{0.5}:C_{50.5} and LID_{0.5}:C_{70.5} plotted vs inverse of viscosity in a double-logarithmic scale form a line with the slope k of 0.74 and 0.76, respectively, and importantly, both of them cross the ideal KCl line around room temperature (**Figure 2.9.**). Specifically, LID_{0.5}:C_{70.5} reveals an ideal conductivity at 293 K while LID_{0.5}:C_{50.5} needs to be heated to 313 K to fall

on the ideal line. Additionally, at $T < T_{\text{room}}$ both examined PIL fall into the superionic regime, i.e. above the KCl line. A similar behaviour was found for phosphoric acid, an almost ideal proton conductor with confirmed Grotthuss conduction,¹⁶⁷ thus one can conclude that fast proton hopping involving the H-bonding network gives a contribution to charge transport in the LID:DA samples. The proton hopping is the most efficient at low temperatures, i.e. in the vicinity of liquid-glass transition. On the other hand, with increasing temperature, when the mobility of ions becomes faster and H-bonds can be disrupted, the contribution of Grotthuss conduction to the overall charge transport is markedly reduced in LID_{0.5}:C5_{0.5} and LID_{0.5}:C7_{0.5}. The Walden points collected at high temperature can also be used for assessing the ionicity of studied systems. As seen in **Figure 2.9.** at 363 K $\log \Lambda(\log \eta^{-1})$ point of LID_{0.5}:C7_{0.5} falls on the line denoting 10% of system ionisation. At the same time, LID_{0.5}:C5_{0.5} reveals much higher ionisation in the order of 50%. Therefore, it can be concluded that the neutral species are active donors in the fast proton conduction process in the examined LID:DA systems.

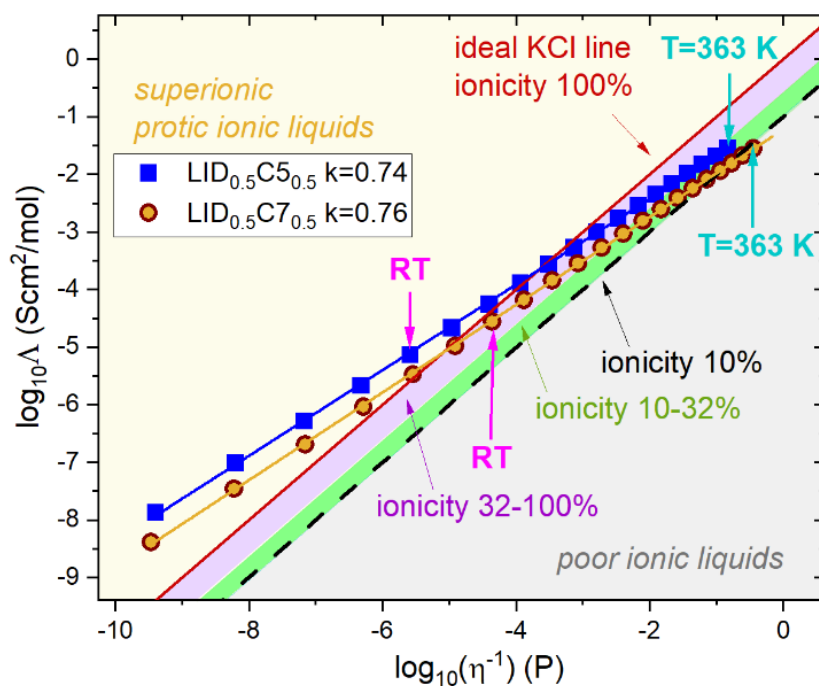


Figure 2.9. Walden plot of LID_{0.5}:C5_{0.5} and LID_{0.5}:C7_{0.5}.

2.3.5 Crystallographic analysis

The molecular structures of LID_{0.5}:C5_{0.5}, LID_{0.5}:C6_{0.5}, LID_{0.5}:C7_{0.5} and LID_{0.5}:C8_{0.5} are shown in **Figure 2.10** (details can be found in **Table AI.1**). The two shorter chain DA molecules crystallise in the monoclinic system, and the longer chain DA's in the triclinic system. In all structures, the amino group hydrogen and the DA acid hydrogen atoms were located on the difference map and refined with distance restraints. The single deprotonation of the DA is also confirmed by analysis of the bond lengths (*vide infra*) resulting in the corresponding lidocainium hemiglutarate, lidocaininium hemiadipate, lidocaininum hemipimelate and lidocainium hemisuberate salt formation, respectively. Theoretical PXRD patterns generated from the SXRD data closely match experimental PXRD patterns by visual inspection and were fitted using Le Bail Reitveld refinement (**Figures AI.5-AI.8**) showing good phase purity in LID_{0.5}:C6_{0.5}- LID_{0.5}:C8_{0.5}. LID_{0.5}:C5_{0.5} is not phase pure, with poor fitting parameters and shows the incorporation of LID predominately (confirmed by single crystal diffraction).

The asymmetric units of the four complexes, (**Figure 2.10.**), show the 1:1 ratio of LID to DA. In all structures there is a strong hydrogen bond between the amino group in LID and the DA ranging from 2.6118(15) Å in LID_{0.5}:C7_{0.5} to 2.6968(11) Å in LID_{0.5}:C6_{0.5}. Hydrogen bonding between the DA's feature in all the structures (**Figures AI.9-AI.12** and **Tables AI.2-AI.5**). It is notable that in the C6-C8 extended structures that the DA's align in a chain with head to tail acid hydrogen bonding as a homosynthon. The anionic acid moiety is also hydrogen bonded to the amino group (*vide supra*). There is also weak CH $\cdots$ O hydrogen bonding to both the acidic and anionic DA oxygen atoms. These hydrogen bonding arrangements align the packing into lidocaineH⁺:DA stacks, **Figure 2.10. (E-H)**. However, this regular head to tail DA arrangement is not observed in the C5 structure. In this case, the DA's are aligned in a staggered side-to-side hydrogen bonding homosynthon. This is assisted with strong amino hydrogen bonding to the anionic acid end and weaker C-H $\cdots$ O hydrogen bonding (chelate forming) to the carboxylic acid C5 moiety.

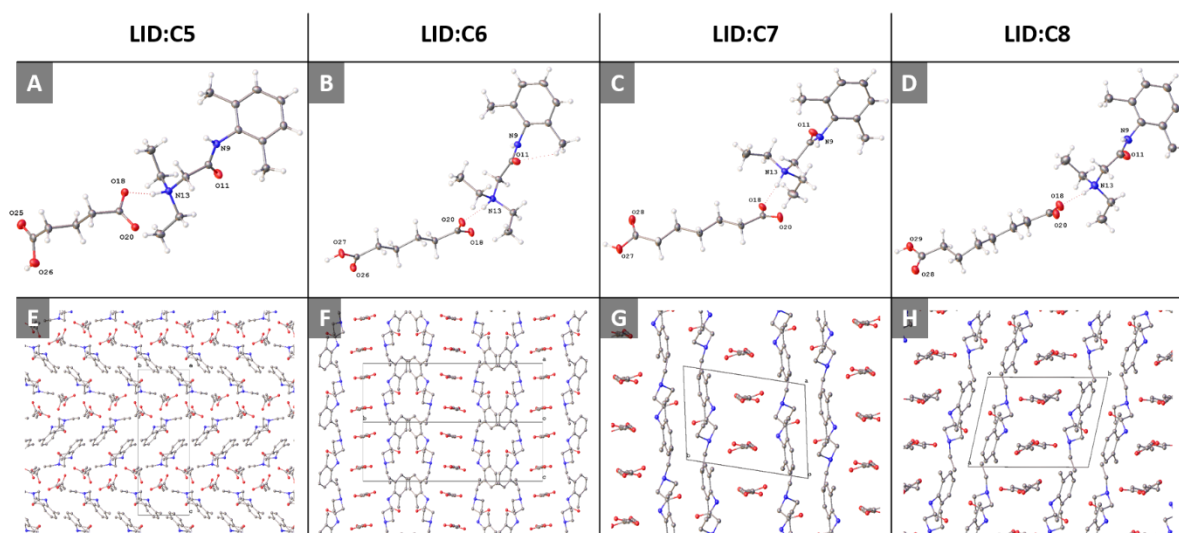


Figure 2.10. Molecular structures of the ion pairs (A) LID:C5 (B) LID:C6 (C) LID:C7 and (D) LID:C8 with heteroatoms labelled only and atomic displacement shown at 50% probability. Red dotted lines show hydrogen bonding from LID to the DA. Packing diagrams of (E) LID:C5 viewed normal to (100) showing the staggered DA homosynthon, (F) LID:C6 viewed normal to (101), (D) LID:C7 viewed normal to (001) and (H) LID:C8 viewed normal to (001) with linear homosynths. All are viewed perpendicular to the stack direction and hydrogen atoms omitted for clarity.

The evidence for N(13)-H(13) ionic bond formation is deduced from the carboxylic acid C-O bond lengths (D_{C-O}). It has been shown that in complexes where carboxylic acid deprotonation takes place the resulting carboxylate ion possesses two C-O bonds with similar D_{C-O} , i.e. the $\Delta D_{C-O} < 0.03 \text{ \AA}$, where ΔD_{C-O} is the difference in length between the two C-O bonds within a carboxylate moiety. On the other end of the ionisation spectrum, neutral carboxylic acids would possess two distinct C-O bonds with $\Delta D_{C-O} > 0.08 \text{ \AA}$.⁴ The ΔD_{C-O} values obtained for all 4 complexes were $\leq 0.04 \text{ \AA}$ indicating carboxylate ion formation (**Table AI.6**). The calculated values correlate well with expected salt formation based on ΔpK_a between an acid and a base (i.e. salt formation is expected if $\Delta pK_a > 3$).⁵⁰

Crystal structure and crystal packing profoundly affect the molecular-loosening and molecular-change steps of a solid state reaction.^{168,169} The influence of crystal packing on solid-state reactivity is described by topochemical postulates. It is generally accepted that a reaction is topochemical if the structure of the product can be explained by the crystal packing of the reactant crystal.¹⁶⁸ Crystal voids were calculated in an attempt to correlate

crystal packing efficiency to the observed melting point variation. It has been shown previously that ratios of volume occupied by molecules to unit cell, known as Kitaigorodskii Packing Indices (KPIs)¹⁷⁰, allow to compare packing efficiency and predict the T_m of the solid. However, opposite crystal packing effects have also been recognised.¹⁵² **Table 2.3.** reveals that the predicted trend is not followed in the parent DAs. Therefore, the efficiency of the crystal packing of the parent components is not the main determinant of the T_m and crystal packing trends in the salt products. However, an alternating trend was observed in the KPI values of the LID:DA systems which corroborates their crystallisation tendencies. The systems with lower KPIs and greater void spaces were slow-crystallisation systems that tend to stay liquid at room temperature.

Table 2.3. Void spaces calculated using contact surface with probe radius of 0.2 Å and approximate grid spacing of 0.2 Å. KPIs – Kitaigorodskii Packing Indices.

Compound	Melting point (°C)	Voids (% of unit cell)	KPIs (%)	ref
<i>C5</i>	98	25.1	74.9	¹⁴⁸
<i>LID</i> _{0.5} : <i>C5</i> _{0.5}	55	27.0	73.0	this work
<i>C6</i>	152	26.3	73.7	¹⁴⁸
<i>LID</i> _{0.5} : <i>C6</i> _{0.5}	114	26.7	73.3	this work
<i>C7</i>	105	28.3	71.7	¹⁴⁸
<i>LID</i> _{0.5} : <i>C7</i> _{0.5}	66	27.8	72.2	this work
<i>C8</i>	144	27.9	72.1	¹⁴⁸
<i>LID</i> _{0.5} : <i>C8</i> _{0.5}	58	26.4	73.6	this work

The effect of salt formation on the molecular conformations of each molecule within the complexes was investigated. Molecular overlays of the experimental and reference crystal structures were calculated and the similarity is expressed in terms of Root-Mean-Square-Deviation (RMSD) values, where large RMSD values indicate greater differences between the molecules. LID molecules from the LID:DA single crystals were overlaid with reference LID structure (CSD ID LIDCAN11), however, no obvious trends were discerned. Furthermore, Hirshfeld analysis of LID within the new salt complexes have not revealed significant variations that could explain the alternation in physicochemical properties of the systems. The only notable difference is the diffuse blue regions observed in *LID*_{0.5}:*C6*_{0.5} and

LID_{0.5}:C8_{0.5} crystals as seen in **Figure 2.11**. This region suggests that a part of a molecular surface has large distances to the nearest atoms which is generally characteristic of less than ideal packing arrangement.⁹⁴ The breakdown of the close-contact intermolecular contributions to the Hirshfeld surface area display no significant variation for the four salt complexes as seen in **Figure 2.11.I**.

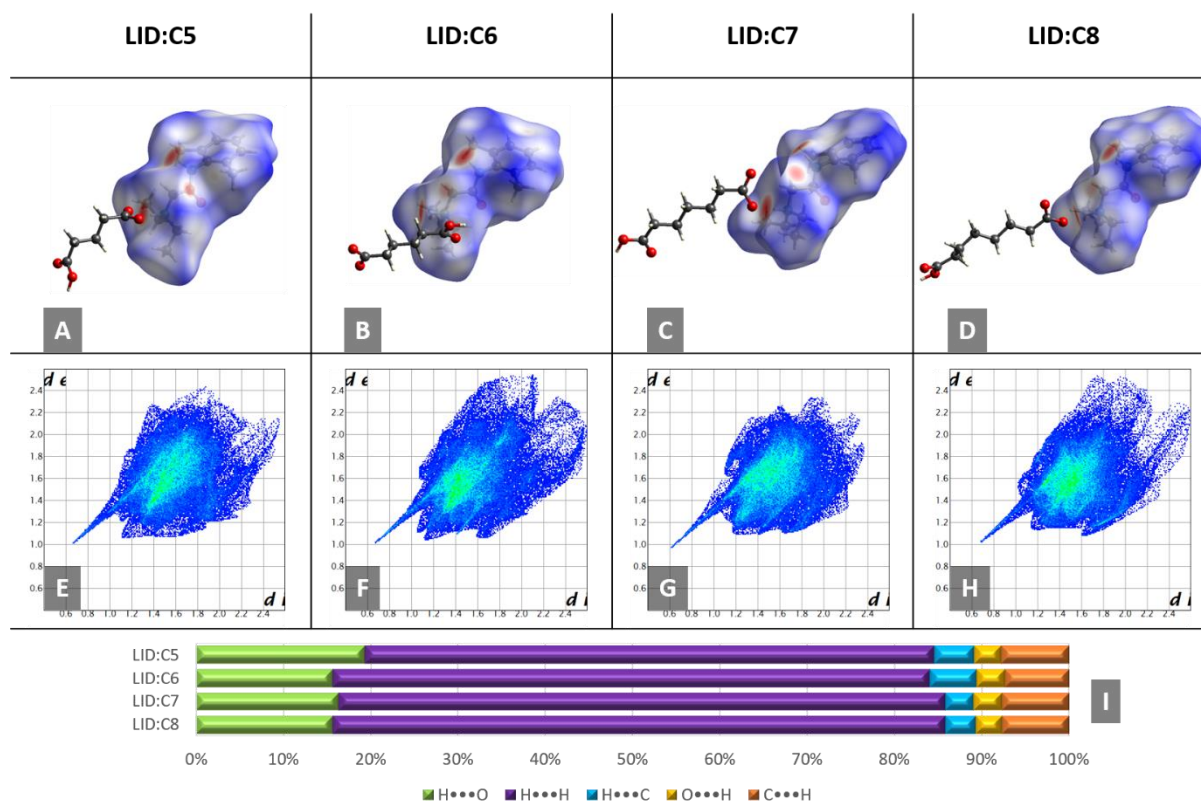


Figure 2.11. A-D: Hirshfeld surfaces for LID_{0.5}:C5_{0.5}, LID_{0.5}:C6_{0.5}, LID_{0.5}:C7_{0.5} and LID_{0.5}:C8_{0.5} mapped with d_{norm} . E-H: Corresponding 2D fingerprint plots. I: Percentage contributions to the Hirshfeld surface area for close-contact intermolecular interactions. The colour-coding is indicated in the figure.

Figure 2.12 presents overlays of reference parent DA structures (CSD ID: HITSAG, ADIPAC14, PIMELA08, SUBRAC06) with ionised DA structures obtained from SXRD data. It is interesting to observe that the longer the DA chain, the greater is the RMSD value. It appears that DAs undergo conformational changes in order to adapt to the length of the LID molecule in order to form the required number of crystal-stabilising hydrogen bonds. However, LID_{0.5}:C5_{0.5} does not follow this trend. This exception is consistent with the different crystal packing of this system. The carboxyl moieties are rotated in order to form

both carboxyl - carboxyl H-bonds with another single C5 molecule ($O(26)-H(26)\cdots O(18)$, symmetry operation $-x+2, y-1/2, -z+1/2$). As a result, this system lacks the ribbon-like crystal packing found in the rest of the series.

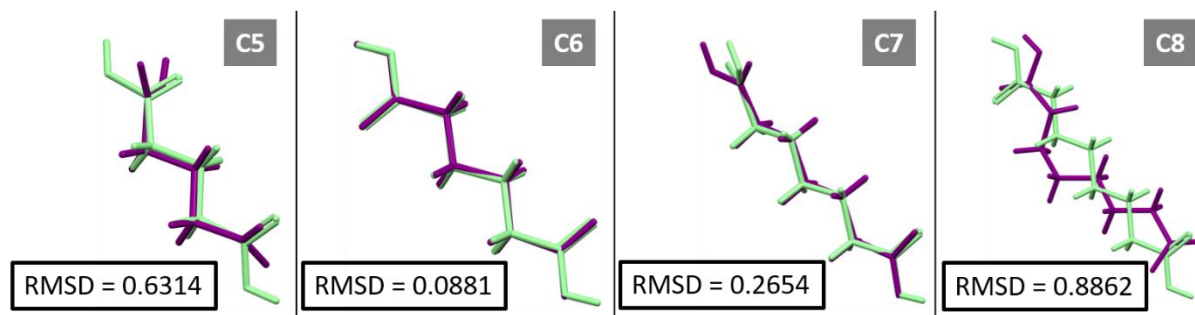
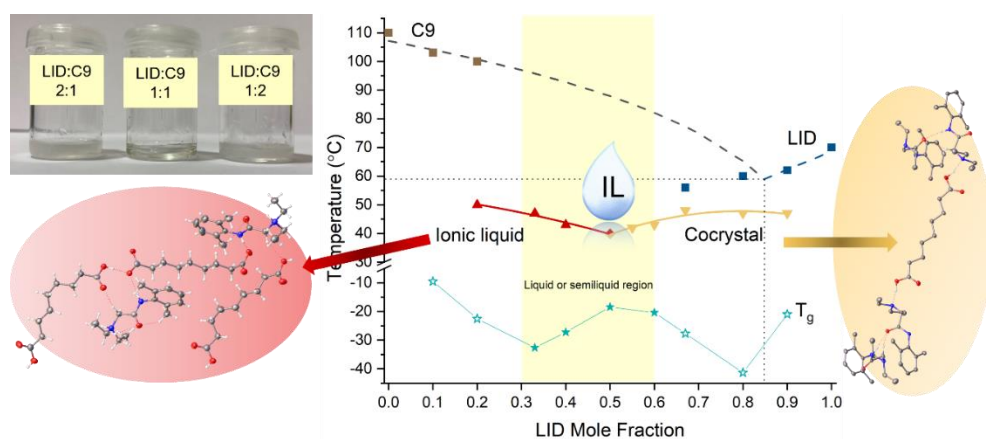


Figure 2.12. Molecular overlay of C5 - HITSAG (green) with LID_{0.5}:C5_{0.5} (purple); C6 - ADIPAC08 (green) with LID_{0.5}:C6_{0.5} (purple); C7 - PIMELA06 (green) with LID_{0.5}:C7_{0.5} (purple); C8 - SUBRAC05 (green) with LID_{0.5}:C8_{0.5} (purple). Corresponding Root-Mean-Square-Deviation (RMSD) values for the overlays are presented in boxes.

2.4 Conclusions

Lidocainium hemiadipate solid salt and lidocainium hemiglutarate, lidocainium hemipimelate, lidocainium hemsuberate ILs were successfully prepared by a simple mechanochemical solvent-free grinding. The thermal and ionisation behaviour of the systems have been investigated in detail. Upon examination of the trends in physicochemical properties it was found that the even-odd melting point alternation of DAs is generally retained in LID:DA complexes. In-depth investigation into the crystallographic properties of the DAs and the synthesised salts provided some explanations on the alternating variability of the physicochemical properties among the series. This study brought us closer to understanding the mechanisms of ILs formation and contributed to the current aim of the ILs community to devise a systematic approach for IL discovery and development.

Chapter 3: Formation of stoichiometric and non-stoichiometric ionic liquid and cocrystal multicomponent phases of lidocaine with azelaic acid by changing counterion ratios



3.1 Introduction

A number of interesting works have been published very recently raising awareness on the continuum that exists between ionised and neutral pharmaceutical multicomponent systems.^{5,13,171} A change in preparation methods, temperature or stoichiometry can modulate the ionic character of the system and yield different products as a result of complex interrelationship of kinetic and thermodynamic aspects.^{171–174} In particular, there are examples illustrating that distinct crystalline structures obtained by varying stoichiometry of co-formers or counterions can tune the solid state properties and performance of an active pharmaceutical ingredient (API).^{11,12,14}

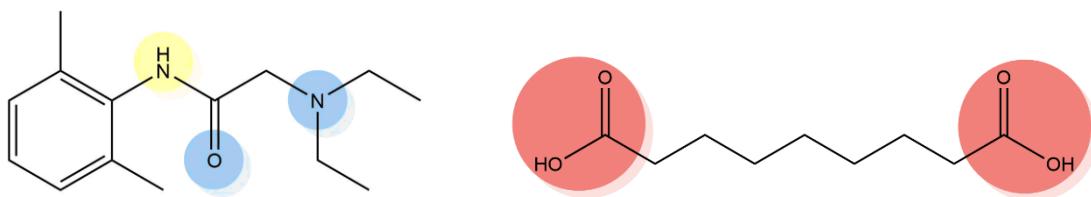
Although the majority of the investigated pharmaceutically-relevant API multicomponent systems are crystalline, the rising significance of low-melting point solids or even liquid forms of such systems has been recognised.^{8,38,65,134,175,176} They include, but are not limited to ionic liquids, deep eutectic mixtures, ionic cocrystals and oligomeric ionic liquids. Until recently, the intermolecular interactions that play the major role in the classification of the liquid forms were mainly considered at simple 1:1 stoichiometric ratios and stoichiometries dictated by the counterion of choice.^{177,178} On the other hand, non-stoichiometric ratios were viewed as systems containing excess of either of the starting materials.¹⁷⁹ However, it has been shown that mixtures of the counterions or the co-formers at different stoichiometric ratios can potentially form distinct multicomponent systems not just in the solid but also in the liquid state.^{13,26}

Chapter 2 concentrated on a range of API-ILs incorporating lidocaine and medium-chain dicarboxylic acids as the counterions. LID is an aminoamide drug used as a local anaesthetic with some antibacterial properties¹³⁸ and the molecule possesses one H-bond donor -NH group and 3 H-bond acceptor groups (**Scheme 3.1**). LID is practically insoluble in water and is formulated as a salt to overcome the solubility constraints. The tertiary amine group has a pKa value of 7.9 rendering it a weak base and most of the known LID salts undergo ionisation at this site.^{122,123} However, in an ionised form LID's membrane permeability is severely impeded.¹²⁷ Careful co-former or counterion selection for a new LID multicomponent phase formation can greatly improve the API's performance without undergoing chemical modification.^{65,180,181} The LID ionic liquids (ILs) based on medium-chain dicarboxylic acids were evaluated in terms of their thermal and dynamic behaviour supported by crystallographic analysis in an attempt to devise a prediction tool for the structure–property relationship. Alternating trends in morphology, melting points, glass

transition temperatures and crystallographic properties of the new phases were observed depending on the acid used.

The work performed in Chapter 3 investigated the influence of changing stoichiometry of LID and azelaic acid (C9), another medium-chain dicarboxylic acid on the physicochemical properties of their corresponding multicomponent systems using a thermodynamics-based approach, which includes the construction of the solid-liquid binary phase diagrams. Microscopy, X-ray diffraction analysis, infrared spectroscopy, nuclear magnetic resonance, and thermogravimetric analysis provide complimentary characterisation. The molecular structures of LID and the dicarboxylic acid investigated in the study are shown in **Scheme 3.1**. C9 is a dicarboxylic acid commonly used as a topical bactericidal, antioxidant and anti-inflammatory agent.^{182–184} C9 is a weak acid with 2 carboxylic acid moieties at both ends of the alkyl chain with pK_a values of 4.550 and 5.498. The differences in pK_a values (i.e. $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$) are 3.35 and 2.4 meaning that both, salts and cocrystals could potentially be formed.⁵⁰ Other known LID:dicarboxylic acid multicomponent systems reported to date were solely ionized systems.^{123,124} It was thus hypothesised that the LID:C9 combination would yield a similar LID:dicarboxylic acid system.

Scheme 3.1. Molecular structures of LID (left) and C9 (right). Yellow- H-bond donor and acceptor; blue- H-bond acceptor; red- carboxylic acid groups.



3.2 Experimental section

3.2.1 Materials

LID (as a base) and azelaic acid (C9) were purchased from Sigma-Aldrich (Ireland). Potassium bromide for Infrared analysis was obtained from Honeywell Fluka and was dried in a vacuum oven at room temperature prior to use. The purity of the compounds was at least 98%. All compounds were used as obtained. Absolute ethanol used was of HPLC grade (Fisher Scientific, UK).

3.2.2 Methods

3.2.2.1 Sample preparation

LID and C9 was processed at a range of molar fractions between 0.1:0.9 to 0.9:0.1 (LID:C9). The constituents were accurately weighted with a Mettler Toledo MT5 microbalance (Mettler Toledo, Switzerland) and ground in an agate mortar and pestle until homogenous mixtures were obtained. A total of 200 mg of each sample was produced. A sample of each mixture was immediately analysed by DSC, TGA and PXRD and the remaining mixtures were transferred to 2 mL microcentrifuge tubes and kept at 4 °C until further analysis.

3.2.2.2. Polarised optical microscopy (POM)

POM experiments were performed as described in Chapter 2.

3.2.2.3 Thermogravimetric analysis (TGA)

TGA was performed using Mettler TG50 measuring module coupled to a Mettler Toledo MT5 balance (Switzerland). Samples were weighed into an open aluminium pan (sample size approximately 5-11 mg) and heated from 25 °C to 200 °C at a rate of 10 K min⁻¹ under nitrogen as a purge gas. Upon completion the samples were visually inspected and the thermograms were analysed for degradation using Mettler Toledo STARe software (version 6.10).

3.2.2.4 Differential scanning calorimetry (DSC)

DSC measurements were performed as described in Chapter 2. The samples were heated from 25 °C to 115 °C at the rate of 10 K min⁻¹. The samples were then supercooled to -60 °C at 300 K min⁻¹ cooling rate and a second heating cycle was performed.

3.2.2.5 Fourier-transform infrared spectroscopy (FTIR)

Prior to analysis LID:C9 mixtures at selected compositions were heated at 60 °C under nitrogen gas for 30 min to remove moisture. FTIR measurements were performed as described in Chapter 2.

3.2.2.6 Powder X-ray diffraction (PXRD)

The LID:C9 samples were prepared at room temperature and were kept at 4 °C prior to analysis. PXRD was carried out at room temperature as described in Chapter 2.

3.2.2.7 Single crystal X-ray diffraction (SXR)

Preparation of Phase 1 (2:1 LID:C9 cocrystal) - A sample of LID:C9 at equimolar composition was heated until freely flowing liquid was obtained. The liquid sample was poured inside an NMR tube and was kept in the fridge until crystals were observed.

Preparation of Phase 2 (2:3 LID:C9 ionic liquid) - Solidified polycrystalline powder at 1:1 molar composition was obtained upon prolonged storage for 6 months at room temperature. A few crystals were removed with a needle to be seeded onto a drop of liquefied 1:2 LID:C9 mixture on a glass slide and kept at room temperature. Larger crystals of satisfactory quality for SXR analysis were harvested after a week.

SXR measurements were performed and structures were solved by Dr Brendan Twamley, TCD School of Chemistry. Data for 2:1 LID:C9 cocrystal and 2:3 LID:C9 salt samples were collected on a Bruker Apex Kappa Duo using Cu K α radiation ($\lambda = 1.54178$ Å) using a MiTeGen microloop and at 100(2) K (Oxford Cobra Cryosystem). Bruker APEX¹⁸⁵ software was used to collect, correct (Lorentz and polarization) and reduce data. Absorption corrections were applied using SADABS.¹⁸⁶ The structure was solved with the SHELXT¹⁴⁴ structure solution program using Intrinsic Phasing and refined with the SHELXL¹⁴⁵ refinement package using Least Squares minimisation with Olex2¹⁴⁶, using the space group P2₁, with Z = 2 for the formula unit, C₃₇H₆₀N₄O₆. Details of the data and refinement are given in **Table AII.1.** All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters; donor hydrogen atoms (H9a, H9b, 18, H30) were located and refined with restraints (DFIX). The absolute configuration was determined and confirmed by refining the Flack parameter as 0.3(2). The pXRD and SXR were compared using EXPO2014¹⁸⁷ with a final Le Bail refinement using the Pearson VII peak shape function with a w = 1.0/count weighting scheme. Final agreement factors, 2:1

LID:C9 cocrystal : $R_p = 10.017$, $R_{wp} = 14.605$, $R_e = 4.926$ and $\chi^2 = 8.791$; 2:3 LID:C9 salt : $R_p = 7.525$, $R_{wp} = 10.284$, $R_e = 6.203$, $\chi^2 = 2.748$.

3.2.2.8 Proton nuclear magnetic resonance (^1H -NMR)

^1H -NMR measurements were performed by Dr John O'Brien, TCD School of Chemistry, using Bruker Avance III 400 MHz spectrometer. The NMR Crystalline 1:1 LID:C9 sample obtained upon prolonged storage at room temperature and 2:1 LID:C9 sample freshly prepared by neat grinding were dissolved in DMSO-d_6 . ^1H -NMR measurements were performed using Bruker Avance III 400 MHz spectrometer. The NMR spectra were analysed using TopSpin 4.0.9 software. See **Appendix II and Figure AII.1** for the ^1H -NMR peak assignment.

3.3 Results and discussion

3.3.1 Morphology of samples

The study was initiated by solvent-free neat grinding mechanochemical synthesis of the LID:C9 systems at 0.1:0.9 – 0.9:0.1 molar compositions. Samples in the $\chi_{\text{LID}} = 0.33$ to 0.66 range yielded semiliquid or soft solid (paste) samples at room temperature (**Figure 3.1A**). In contrast, systems at extreme molar LID or C9 molar fractions were solid powders. POM analysis was performed to visually examine the process of liquefaction. The POM images in **Figure 3.1B** display the solid fusion experiment where recrystallised LID and C9 were placed side by side and solid-state reactivity was observed. Crystalline regions that were in a direct contact started undergoing liquefaction at room temperature almost immediately and a noticeable change was observed at $t = 10$ min. At $t = 7$ days the entire interface has liquefied. This observation indicates that the melting point of the product of the solid-state reaction is below room temperature and such behaviour is characteristic of a liquid, or a “deep”, eutectic formation.⁸⁴ The remaining crystalline material that was not in direct contact has not been altered signifying the liquid eutectic does not diffuse nor dissolve parent materials further. POM image in **Figure 3.1C** obtained at $t = 14$ days displays the formation of new dendritic structures. These structures may suggest an irregular eutectic morphology of this phase and/or a new phase formation.¹⁸⁸ In Chapter 2, POM demonstrated that LID reacted with glutaric acid (C5) or pimelic acid (C7) showed a similar behaviour and these LID:dicarboxylic acid mixtures underwent solid interdiffusion, while LID and suberic acid (C8) displayed true solid-state reactivity with the formation of a solid eutectic at the interface.

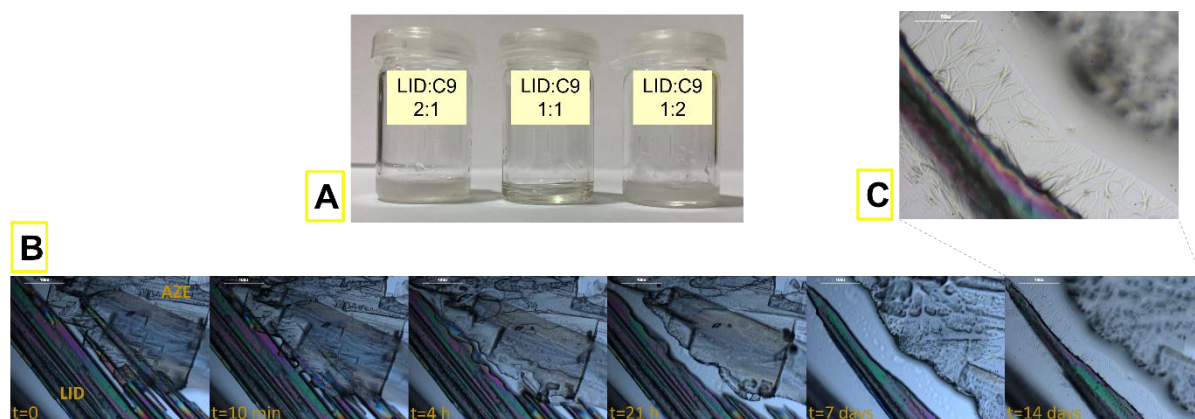


Figure 3.1. **A:** Photographs of the LID:C9 samples immediately upon grinding. **B:** POM images of the solid fusion experiment. **C:** Interphase at a greater magnification showing dendritic formations.

3.3.2 Thermal analysis

Starting materials LID and C9 as well as their mixtures at three different molar compositions (2:1, 1:1 and 2:1 LID:C9) were analysed for thermal degradation by TGA (**Figure 3.2a**). The results showed that the weight loss upon heating up to 120 °C did not exceed 2%, see **Figure 3.2b**. Heating of the materials up to 120 °C generally results in dehydration or solvent evaporation. A very slight increase in weight loss exhibited by the binary mixtures might be associated with increased hygroscopicity of the samples following mixing. This observation is not unusual as it has been shown that low melting systems generally display elevated hygroscopicity.³⁸ On the other hand, upon heating to 200 °C the % weight loss is mainly caused by sample degradation. In this case LID and 2:1 LID:C9 underwent extensive degradation. However, upon addition of increased amount of C9 the degradation was decreased. These results are also illustrated by the sample colour change after the analysis. As seen in **Figure 2a** 2:1 LID:C9 mixture turned very dark brown as compared to lighter brown colours of 1:1 and 1:2 samples.

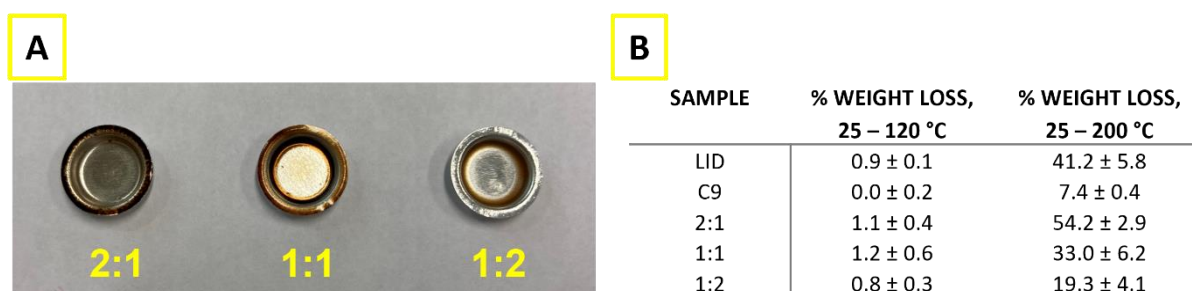


Figure 3.2. **A:** Photographs of the TGA pans after analysis. **B:** Values of % weight loss of LID, C9 and freshly ground binary mixtures upon heating up to 120 and 200 °C.

DSC analysis of freshly prepared samples was carried out to study the phase change behaviour of the LID:C9 systems at various molar compositions. **Figure 3.3A** presents a stack of DSC thermograms of the first heating cycle at different LID:C9 molar compositions. LID and C9 exhibit sharp endothermic peaks corresponding to their melting points of 69 °C and 106 °C, respectively. The melting point depression of LID is observed and is indicated by a blue arrow as increasing molar concentrations of C9 are added to the binary mixtures. A similar melting point depression is observed in C9 (indicated by a brown arrow) with increasing LID content. This observation follows simple binary phase behaviour as a result of decreasing purity of the starting components and has been observed in numerous

multicomponent systems previously.^{189,190} In addition to the endothermic peaks corresponding to the fusion events of the starting components the presence of new endothermic peaks in LID:C9 mixtures indicates the formation of new crystalline arrangements. As visible from the endothermic peaks in the yellow box the mechanochemical grinding of LID and C9 at high LID molar concentrations leads to a new phase formation, referred to as Phase 1. At $\chi_{\text{LID}} = 0.6$ and 0.55 a melting point depression of this Phase 1 is observed. The evolution of a double peak unique to 1:1 molar composition infers the coexistence of two distinct crystalline arrangements. However, the second peak is not easily discerned in samples with higher C9 content, probably due to the creation of additional hydrogen bonds between the new crystalline structure and free diacid which leads to further sample liquefaction. This phenomenon has been described previously in the formation of deep eutectic mixtures (DEMs) and oligomeric ionic liquids.^{67,106} It has been shown, but not generally recognised, that other forms of ionic liquids and DEMs can form at non-stoichiometric compositions and it is not just a 1:1 ionic liquid with excess carboxylic acid.^{6,26,66,191} It has been proposed that such arrangement in the liquid phase can be described as $[\text{BH}^+][(\text{RCOO})_2\text{H}^-]$.¹⁷⁹ The inherent slow crystallisation kinetics of these systems hinders phase identification. In an attempt to curtail liquefaction samples in the range of $\chi_{\text{LID}} = 0.9$ to 0.2 were prepared and stored in the fridge for 1 day prior to analysis. As indicated by a red box and arrow in **Figure 3.3B**, this sample treatment method enhanced new phase crystallisation, referred to as Phase 2.

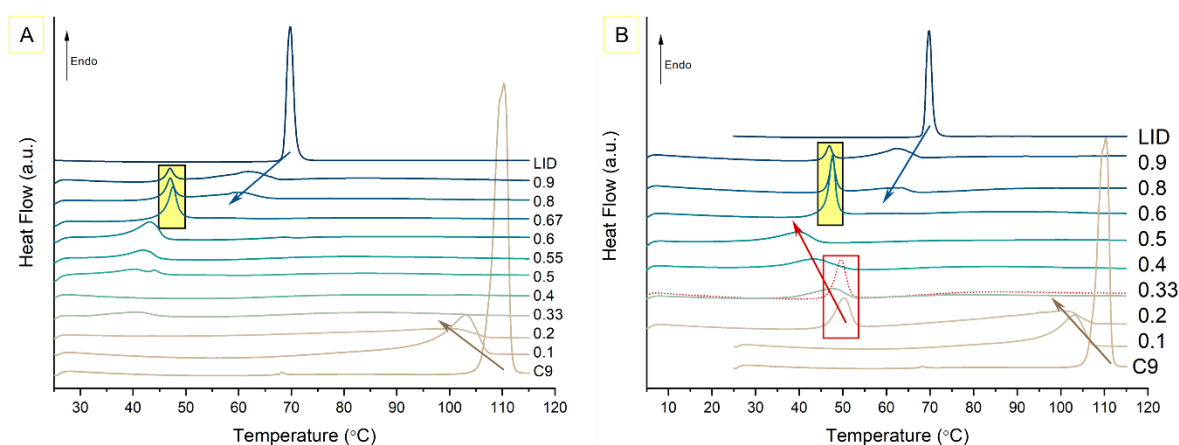


Figure 3.3. **A** - First heating DSC thermograms of the samples prepared at room temperature; **B** – additional first heating DSC thermograms of the samples prepared at 4 °C. The red dotted line indicates a sample prepared at room temperature and cooled at 4 °C.

Experimental T_m values were plotted as a function of LID molar fraction as seen in **Figure 3.4**. Dashed lines represent theoretical Schroeder van Laar solubility curves calculated using **Equation 2**, where T_{fus} (K) denotes the temperature of fusion and ΔH_{fus} (J mol⁻¹) denotes the enthalpy of fusion of the pure starting component, χ is the mole fraction of the pure starting component at a specified temperature T (K), and R is the gas constant.

$$T = \left(\frac{1}{T_{fus}} - \frac{R \ln \chi}{\Delta H_{fus}} \right) \quad (\text{Eq. 2})$$

It is evident that the melting points of the parent components can be reasonably predicted at their corresponding extreme molar fractions. This agreement suggests that the unreacted starting components remain in the mixture in their unchanged form and no additional intermolecular interactions are depressing their corresponding T_m . However, the T_m of the parent components disappear at 0.3:0.7 – 0.6:0.4 LID:C9 molar compositions. This region is highlighted in **Figure 3.4**. This observation suggests new intermolecular interactions being created within the system and is corroborated by the appearance of melting events of Phase 1 and Phase 2. It is interesting to note that at the equimolar composition the melting events of these phases merge, thus creating a sensitive equilibrium where the identity of phase formation depends on sample preparation and storage variables.

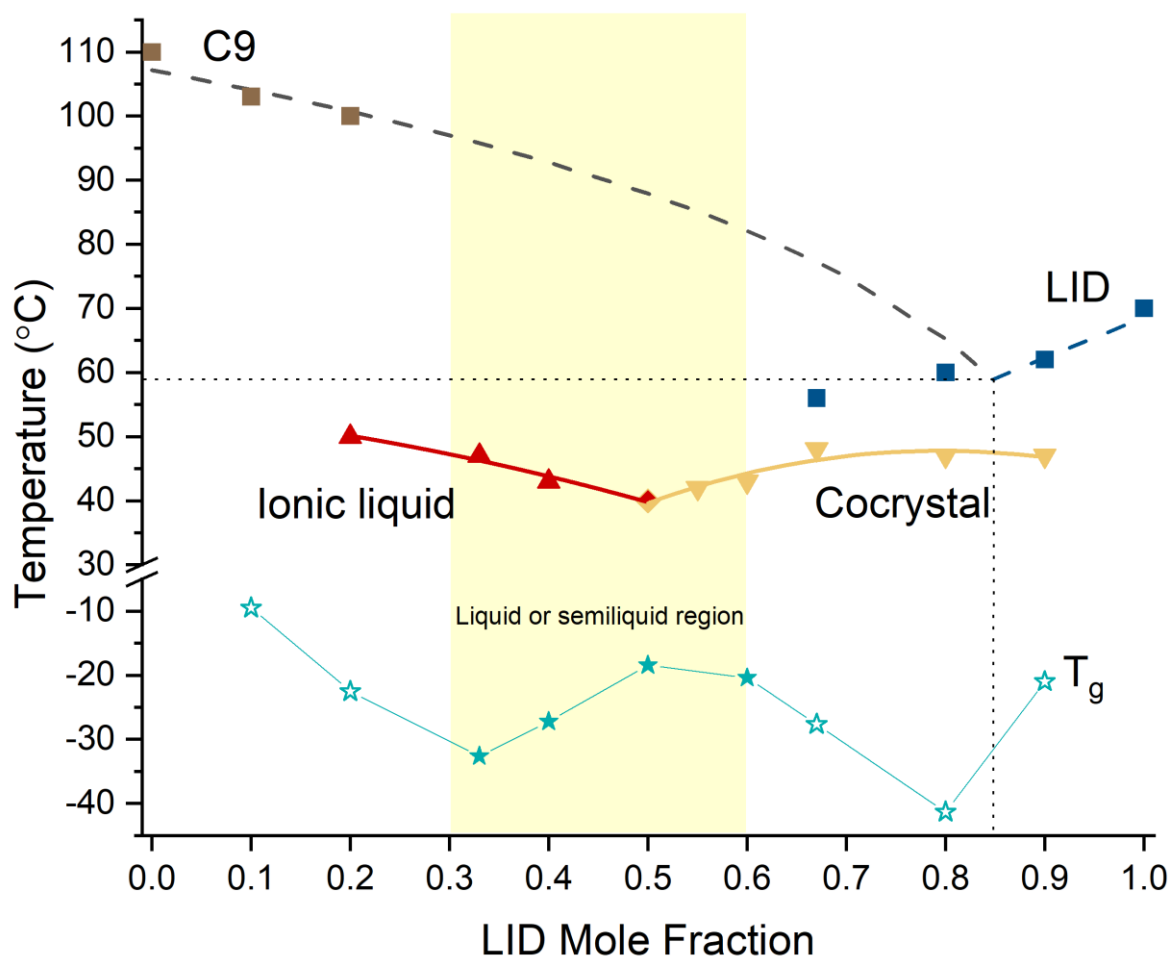


Figure 3.4 Thermodynamic phase diagram, where T_m of Phase 1 (cocystal) were obtained from samples prepared at room temperature, while T_m of Phase 2 (ionic liquid) were obtained from samples prepared at 4 °C. Dashed lines represent theoretical Schroeder van Laar solubility lines. Black dotted lines indicate theoretical eutectic composition and T_m . Open star symbols indicate T_g values of the samples that have undergone crystallisation on cooling.

Upon completion of the first heating step the samples over the entire range of compositions were fast cooled at a nominal rate of 300 K/min and then subjected to a second heating step. **Figure SII.2** presents a stack of second heating DSC thermograms which reveal the presence of glass transition events (T_g) in LID:C9 mixtures which implies the ability of the systems to be supercooled. Pure starting components do not exhibit T_g transitions as they crystallise during the cooling step. It is important to note that the samples at the extreme LID and C9 compositions also undergo partial crystallisation upon cooling and the T_g values of these systems are indicated by open star symbols in **Figure 3.4**. As can be seen from **Figure 3.4**, there is a clear maximum in T_g at the equimolar composition of the acid and the base.

The observed extremum in T_g behaviour can be explained in terms of ionicity degree. Previously, a marked increase in T_g has been correlated with the conversion of a given API into its corresponding salt form e.g. hydrochloride, sulphate or phosphate.^{67,160} Moreover, it has been established that an increase in the T_g and melting point of classical aprotic ionic liquids is observed when the electrostatic interactions start to dominate van der Waals forces.¹⁶¹ Consequently, it is expected that the supercooled equimolar LID:C9 system exhibits the most efficient proton transfer and thus, comprises the highest concentration of ionised species.

3.3.3 Investigation of ionicity in the supercooled state

FTIR spectroscopy was employed to investigate the changes in intermolecular interactions within the liquid systems as a function of LID:C9 molar composition (**Figure 3.5a**) to corroborate the results obtained by thermal analysis. The systems were melted and analysed by FTIR immediately to mimic the supercooled state investigated by the second DSC heating cycle. The clear T_g maximum observed at the equimolar LID:C9 composition suggests the highest degree of ionisation and thus, ionic liquid formation. One of the most prominent peaks observed corresponds to the carbonyl stretching vibration and appears at 1664 cm^{-1} and 1694 cm^{-1} in LID and C9 spectra, respectively. The magnified carbonyl region is presented as an inset in **Figure 3.5b** for clearer visualisation. However, spectra obtained for the binary LID:C9 mixtures exhibit an additional carbonyl signal not attributable to parent materials. This phenomenon is most clearly visible in the mixtures with higher LID content. In the 2:1 LID:C9 supercooled sample the signal is found at 1717 cm^{-1} and its position is shifted to 1724 cm^{-1} in 1:1 supercooled LID:C9 mixture. In $\chi_{\text{LID}} = 0.4$ mixture the peak appears as a shoulder at around 1717 cm^{-1} . The emergence of this peak may imply the formation of intermolecular H-bonds between the -NH moiety of the LID's amide group and the carbonyl group of the C9. As a result of -NH group participating in the creation the new H-bond, the C=O bond is strengthened and a shift to higher wavenumbers is observed. The greatest shift at the 1:1 composition suggests the strongest amide-carbonyl H-bond formation, most probably due to formation of the homogenous 1:1 molecular arrangement. This reasoning is corroborated by the complete disappearance of pure LID signal as a result of being entirely used up in the 1:1 complex formation, hence, giving rise to the observed T_g maximum. On the other hand, C9 C=O signal persists in the spectrum, which can be explained by the availability of 2 carbonyl groups and 1 being left unchanged. In addition, a prominent symmetric stretching carboxylate ion peak at 1540 cm^{-1} appears in the spectra of

mixtures, which provides an indication that ionisation in the form of proton transfer between LID and C9 has taken place.

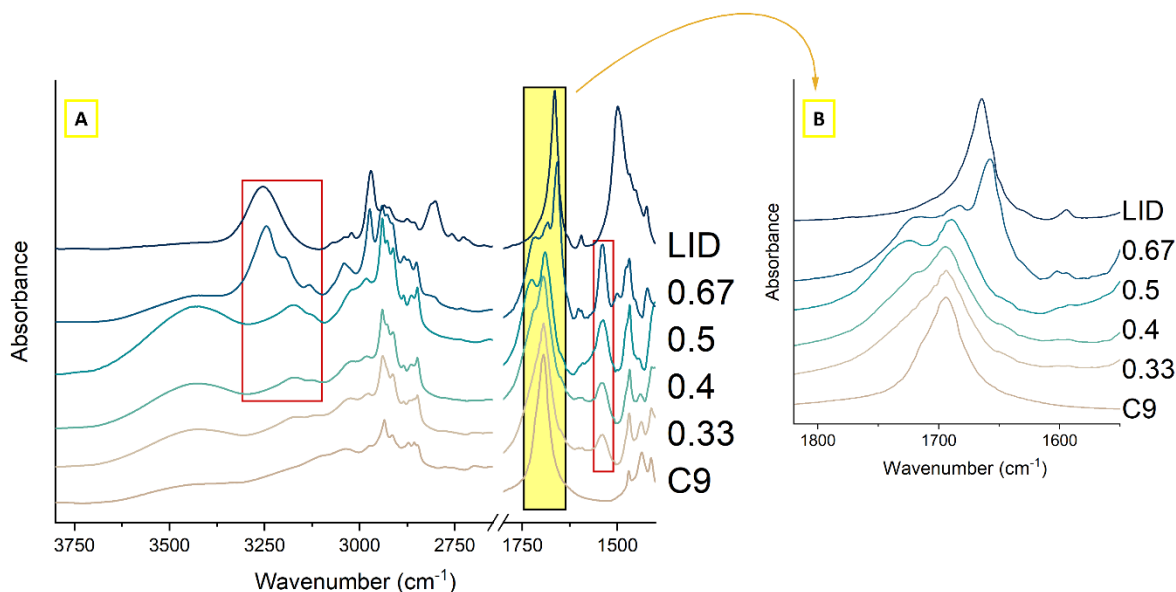


Figure 3.5. A: FTIR spectra of the LID:C9 systems at various molar compositions. B: Inset with magnified carbonyl region of the LID:C9 systems.

The decreased intensity and wavenumber of the amide N-H stretch at 3250 - 3170 cm^{-1} region is caused by the dilution of LID in C9 and the formation of the H-bond (*vide supra*). A peak assignment table is presented in **Table 3.1**. The presence of proton transfer in the 1:1 complex implies the formation of an ionic liquid. The systems with the higher acid content, i.e. in the range $\chi_{\text{LID}} = 0.4$ to 0.33 possess a greater number of hydrogen bonds formed within the complexes and, as a result, the systems are further liquefied. Depending on the arrangement of these additional H-bonds formed the compositions may be classified as either oligomeric ionic liquids or deep eutectic mixtures.

Table 3.1. FTIR peak assignment for parent compounds and LID:C9 binary mixtures.

Compound	Wavenumber (cm ⁻¹)		
	$\nu(\text{NH})$	$\nu(\text{C=O})$	$\nu(\text{COO}^-)$
<i>LID</i>	3254	1664	-
<i>0.67:0.33</i>	3245, 3198	1717, 1683, 1658	1540
<i>0.5:0.5</i>	3173, 3129	1725, 1690	1540
<i>0.4:0.6</i>	3170	1717, 1694	1540
<i>0.33:0.67</i>	3170	1694	1540
<i>C9</i>	-	1694	-

3.3.4 Investigation of crystalline phases

PXRD analysis of the samples prepared as described in Section 2.2.1 revealed the formation of a new crystalline phase at $\chi_{\text{LID}} = 0.5$ to 0.2 range of compositions, as seen in **Figure 3.6**. On melting of this new system, Phase 2 was first observed by thermal analysis (**Figure 3.4**). The PXRD pattern corresponding to the new phase displays peaks that do not appear in the patterns of the parent materials, such as at $2\theta = 6^\circ$, 11° , 14° and 16° . Low intensities of the peaks were observed due to the sample being partially liquid. A peak at $2\theta = 6^\circ$ appears at a lower position as compared to the first peaks of the parent materials, signifying the formation of a larger crystal lattice.

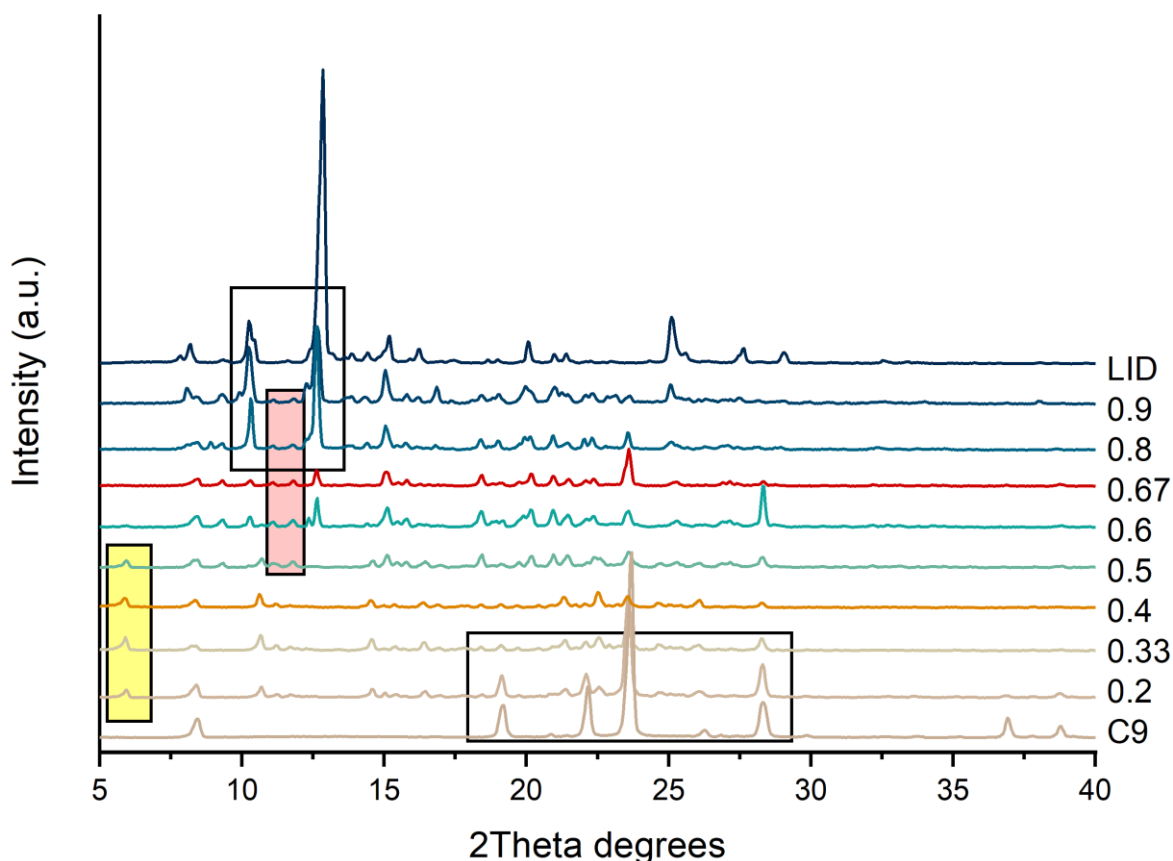


Figure 3.6. A stack of PXRD traces at the range of LID molar fractions χ_{LID} . The pattern highlighted in red corresponds to Phase 1 and the pattern highlighted in orange corresponds to Phase 2.

An attempt to obtain a single crystal of Phase 2 has unexpectedly resulted in an identification of a second, new crystalline phase, Phase 1. The PXRD pattern of this system is highlighted in red colour in **Figure 3.6** and appears to be very similar to pure LID with some differences. In particular, the 2:1 system displays a peak at $2\theta = 8.4^\circ$ as compared to a peak at $2\theta = 8.2^\circ$ seen in LID, and displays unique peaks at $2\theta = 11^\circ$, 18° , 24° , 27° and 28° . These peaks are also visible in the pattern of the $\chi_{\text{LID}} = 0.5$ mixture implying sample heterogeneity, where both new crystalline products coexist in equilibrium.

3.3.5 Effects of sample preparation and storage on systems speciation

It is important to note the impact of method of sample preparation and storage conditions on the LID:C9 complex formation. DSC analysis was performed using freshly ground samples without preheating in order to capture any thermal transitions that occur at lower temperatures. For example, a freshly ground 1:1 LID:C9 sample appears as a liquid

(**Figure 3.1A**) with a small amount of solid particles suspended within the liquid matrix. These particles were later identified as nucleation sites for the formation of the new crystalline complexes (Phase 2) and DSC thermograms of these samples allowed to their melting points to be captured. However, preheating 1:1 LID:C9 samples up to 60 °C in an oven destroyed these crystallisation nucleation sites resulting in a stable, for at least 6 months, ionic liquid that did not crystallise on storage at room temperature. PXRD analysis of the freshly ground samples allowed identification of the new crystalline structures being formed from these nucleation sites, these crystals showed distinct PXRD patterns, as seen in **Figure 3.6**. PXRD analysis of the equimolar sample performed after preheating did not display any diffraction peaks and resulted in a disordered “halo”. The samples with the higher C9 content exhibited analogous behaviour. Therefore, it is possible to conclude that LID:C9 molten mixtures form distinct ionic liquid phases at a range of equimolar and non-stoichiometric ratios with greater acid content.

On the other hand, the base-rich 2:1 LID:C9 mixture was not as sensitive to environmental variables. Crystalline Phase 1 was successfully obtained by both methods, neat grinding at room temperature and co-melting parent components in an oven. Another important observation to note is the equilibrium of the 2:1 and 1:1 complex formation in the LID:C9 equimolar mixtures. Depending on the preparation and storage conditions different crystalline phases were observed and the summary of the observations is presented in **Table 3.2**. The bulk synthesis of Phase 2 was not successful. A range of seeding experiments were also attempted, where Phase 1 was seeded in a molten equimolar LID:C9 mixture, in a molten 1:2 LID:C9 mixture and in multiple organic solvents. The seeding material containing Phase 1 was impure polycrystalline and contained traces of crystalline LID and crystalline Phase 2. As a result, in most cases an identical impure polycrystalline material was obtained. These results can be explained by the differences in the stability and solubility exhibited by these complexes, where the least soluble and most stable system crystallises out first. This phenomenon has been identified and investigated in other binary systems with LID¹²⁸ and other APIs^{171,192,193}. However, seeding in a molten acid-rich 1:2 mixture yielded a pure Phase 2 crystal with quality satisfactory for SXRD analysis. The crystallisation work performed with LID:C9 mixtures was very challenging and before single crystals were obtained a suspicion was raised that one of the crystalline phases might actually be a degradation product. To check for sample degradation ¹H-NMR analysis was performed. The peak assignment presented in **Table 3.1** indicates that Phase 1 and Phase 2 differ in the

solid state, but degradation products were not observed in the ^1H -NMR spectra, see peak assignment in **Figure AII.1**.

Table 3.2. Impact of preparation and storage variables on phase crystallisation in equimolar LID:C9 mixtures. * Phase 2 was only identified upon prolonged storage (about 3-6 months after sample preparation). ** Only once has this sample crystallised as Phase 2 in an NMR tube and this sample was used for SXRD analysis.

		Preparation				
		Neat grinding, RT	Neat grinding, 4°C	Co- melting at 60 °C	Seeding in molten 1:1 mixture	Seeding in molten 1:2 mixture
Storage	At RT	Impure polycrystalline	Not performed	Liquid	Impure polycrystalline	Phase 2
	At 4 °C	Impure polycrystalline	Impure polycrystalline*	Liquid**	Not performed	Not performed
	Under vacuum	Phase 1	Not performed	Phase 1	Impure polycrystalline	Not performed

3.3.6 Single crystal X-ray diffraction analysis

Single crystals of the two distinct crystalline phases, Phase 1 and Phase 2, were obtained and analysed. Phase 1, the 2:1 LID:C9 complex with a melting point of 47 °C and crystallising in a monoclinic $P2_1$ space group was identified as a cocrystal. The theoretical PXRD pattern generated from the SXRD data closely matched experimental PXRD patterns by visual inspection and a Le Bail refinement with difference pattern shown in **Figure AII.3**. The asymmetric unit contains 2 LID molecules and 1 C9 molecule held together by H-bonding interactions as seen in **Figure 3.7A**. The strongest H-bonds are formed between the LID tertiary amine moiety and both C9 carboxylic groups with $d(\text{D}\cdots\text{A}) = 2.583(3)$ and $2.603(3)$ Å. The formation of a cocrystal, rather than a salt is also evidenced by the C9 carboxylic C-O bond length analysis. In salts, the deprotonation of a carboxylic acid results in a carboxylate ion possessing two C-O bonds with similar $D_{\text{C-O}}$, i.e. the $\Delta D_{\text{C-O}} < 0.03$ Å, where $\Delta D_{\text{C-O}}$ is the difference in length between the two C-O bonds within a carboxylate moiety. In cocrystals, neutral carboxylic acids would possess two distinct C-O bonds with $\Delta D_{\text{C-O}} > 0.08$ Å.⁴ The 2:1 LID:C9 complex exhibits high $\Delta D_{\text{C-O}}$ values of 0.119 and 0.125 Å confirming cocrystal formation. The crystal structure is further stabilised by the hydrogen-bonded NH...O heterosynthons ($d(\text{D}\cdots\text{A}) = 2.900(3)$ and $2.932(3)$ Å) formed between the LID amide moieties and further weak CH...O interactions ($d(\text{D}\cdots\text{A}) = 3.243(3)$ Å). The

resulting structure forms zig-zag crystallisation patterns as seen in **Figure 3.7B**. See **Figure AII.5** and **Table AII.2** for atom labels and a list of all hydrogen bonds present within the system.

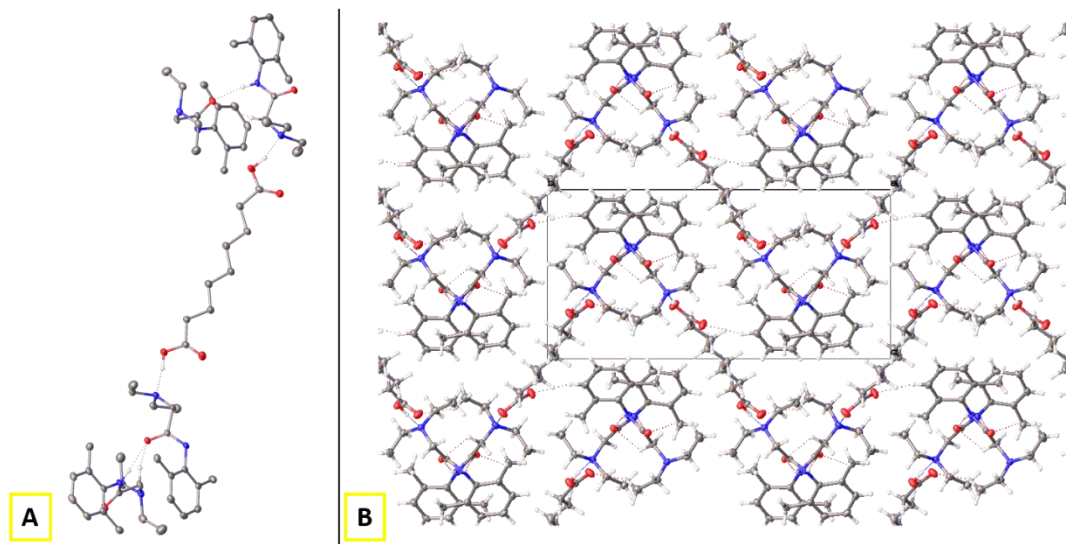


Figure 3.7. A: Primary hydrogen bonding motif (dotted lines) in the 2:1 LID:C9 cocrystal (Phase 1). Displacement shown at 50% probability. Only hydrogen atoms involved in the H-bonding motif are shown. **B:** Packing diagram of 2:1 LID:C9 viewed normal to the a-axis. Dotted lines indicate hydrogen bonding interactions. Displacement shown at 50% probability.

Interestingly, despite the fact that the crystalline 2:1 LID:C9 system is a cocrystal, FTIR analysis showed that the carboxylate ion peak was also visible in the supercooled mixture of the same composition (**Figure 3.5**). This is due to the ability of the system to be partially liquefied as indicated by the presence of a T_g transition observed by DSC (**Figure 3.4**). Hence, the supercooled fraction of the sample exhibits proton transfer due to increased molecular mobility.

The second crystalline phase, Phase 2, comprises a highly unusual 2:3 LID:C9 ratio and it is characterised by a melting point onset of 50 °C. No other crystalline structures involving LID at such ratio with other counterions or co-formers has been deposited in the CSD database to date. The complex crystallises in a triclinic $P\bar{1}$ space group with 2 LID and 3 C9 molecules constituting an asymmetric unit. Theoretical PXRD patterns generated from the SXRD data closely match experimental PXRD patterns by visual inspection and a Le

Bail refinement with difference pattern shown in **Figure AII.4**. The crystalline structure is composed of 2 unionised C9 molecules, 1 doubly ionised C9 anion and 2 ionised LID cations which are held together via a complex network of hydrogen bonding interactions as seen in **Figure 3.8.A-B**. The 2 LID molecules are ionised at the tertiary amine sites via a proton transfer from both carboxyl moieties of a single C9 molecule. The complete deprotonation of C9 is supported by C-O bond analysis, where the two carboxyl moieties possess ΔD_{C-O} of 0.004 and 0.006 Å. The deprotonated carboxylate anions form hydrogen bonding interactions with $LIDH^+$ cations via all possible amine and amide H-bond donors, the strongest of which occurs between the carboxylate anion and an amide moiety $COO\cdots NH$ with $d(D\cdots A) = 2.811(6)$ Å. The doubly deprotonated C9 anion is further stabilised by H-bonds arising from unionised C9 carboxyl donors with $d(D\cdots A)$ distances ranging from 2.559(6) to 2.633(6) Å. See **Figure AII.6** and **Table AII.3** for atom labels and a list of all hydrogen bonds present within the system. The structure is highly complex which explains the great difficulty faced during crystallisation efforts.

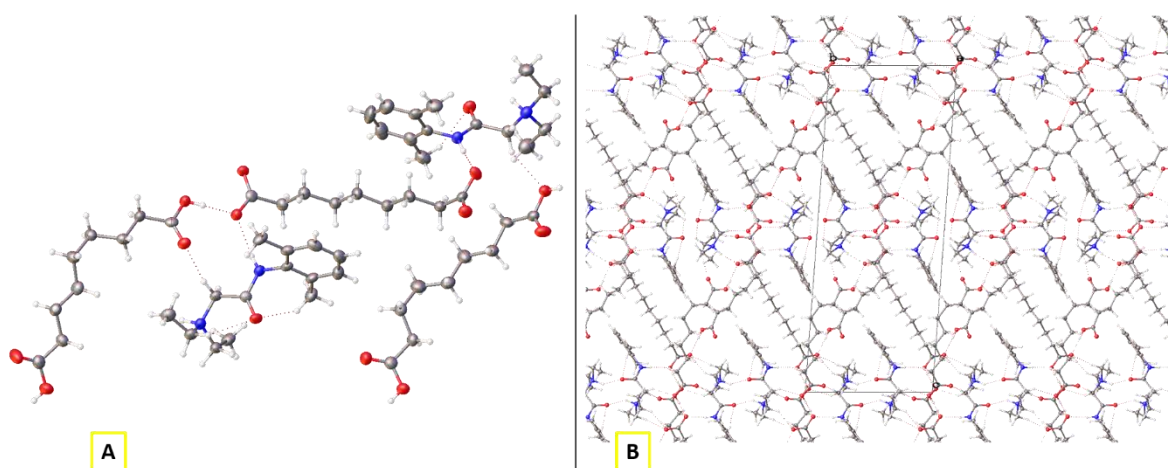


Figure 3.8. A: Primary hydrogen bonding motif (dotted lines) in the 2:3 LID:C9 IL (Phase 2). Displacement shown at 50% probability. Only hydrogen atoms involved in the H-bonding motif are shown. **B:** Packing diagram of 2:3 LID:C9 viewed normal to the a-axis. Dotted lines indicate hydrogen bonding interactions. Displacement shown at 50% probability.

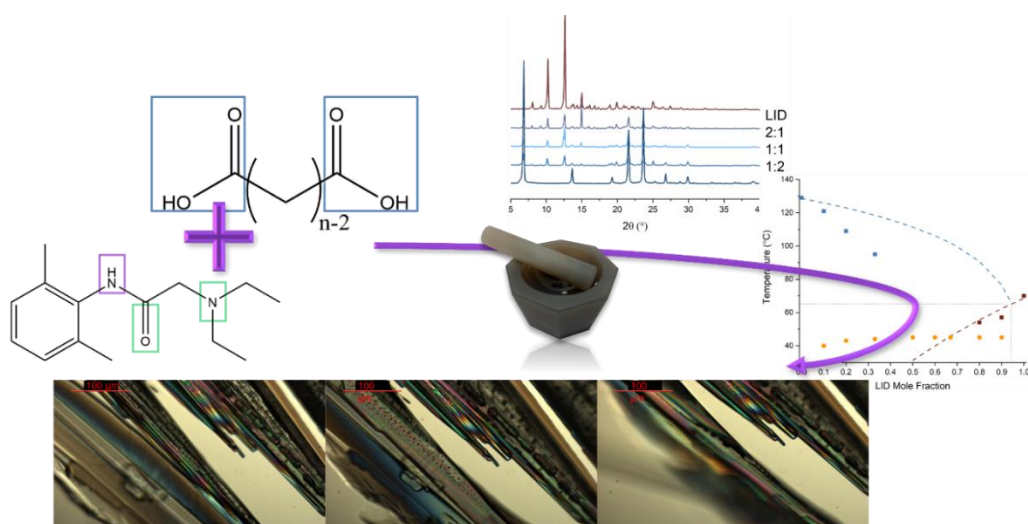
The molecular arrangement resembles the bonding pattern characteristic of oligomeric ionic liquids. However, all oligomeric ILs reported to date are formed from monocarboxylic acids and the generalised molecular formula is generally accepted as

$[\text{BH}^+][(\text{RCOO})_2\text{H}^-]$.¹⁷⁹ The LID:C9 complex presented in this paper is the first example of oligomeric ionic liquid composed of anions derived from dicarboxylic acids. The molecular formula of the crystalline oligomeric complex may be written as $[(\text{BH}^+)_2][(\text{HOOCRCOOH})_2(\text{OOCRCOO})^{2-}]$. Due to the presence of a greater number of H-bonding donors and resultant increased complexity of the potential ion patterns the molecular formula characterising this crystalline complex may or may not be applicable to other dimeric or higher order oligomeric anions and ionic liquids. It is also important to note that the crystalline structure corroborates the interactions in the solid state and these findings support the presence of analogous interactions in the liquid phase. Therefore, the 2:3 crystalline salt is the equivalent solid structure to the 2:3 oligomeric ionic liquid in the liquid phase. In this context, the molecular formula of the 1:2 LID:C9 oligomeric ionic liquid is $[\text{BH}^+][(\text{HOOCRCOO})_2\text{H}^-]$.

3.4 Conclusions

This work has highlighted the importance of considering a range of stoichiometric ratios for the formation of multicomponent systems incorporating acid-base pairs. Despite a series of equimolar LID:dicarboxylic acid salts published previously we have demonstrated that LID and C9 binary mixtures at various molar compositions can form a range of distinct multicomponent phases. This approach allows for fine-tuning of physicochemical and crystallisation properties of a binary system without altering its constituents. Neat grinding of LID and C9 has resulted in the formation of liquid or semiliquid systems at the $\chi_{\text{LID}} = 0.33$ to 0.66 molar fractions, where 1:1 composition exhibited the highest ionicity attributable to an ionic liquid formation. The greatest extent of liquefaction at $\chi_{\text{LID}} = 0.4$ was attributed to an oligomeric ionic formation, the crystal structure of which was solved to be a 2:3 oligomeric crystalline ionic liquid. To the best of our knowledge, such system is the first example of an oligomeric ionic liquid composed of anions derived from dicarboxylic acids with a $[(\text{BH}^+)_2][(\text{HOOCRCOOH})_2(\text{OOCRCOO})^{2-}]$ general molecular formula. In addition, a crystal structure of 2:1 LID:C9 cocrystal was also successfully obtained. These results suggest that prediction of acid-base multicomponent systems formation is more challenging when variable stoichiometric ratios are considered. However, addressing the non-stoichiometric approach allows for a better understanding, modification and visualisation of alternative forms of multicomponent phases.

Chapter 4: Impact of the Dicarboxylic Acid Chain Length on Intermolecular Interactions with Lidocaine



4.1 Introduction

Active pharmaceutical ingredients can exist in a variety of morphological forms ranging from solids to liquids, from crystals to amorphous materials, from single molecular structures to complicated multicomponent systems.^{132,2} Moreover, they can be found in a wide spectrum of ionisation states comprising fully ionised salts, partially ionised and “confused” eutectic solvents and neutral cocrystals, among a vast array of others.^{66,4} Altering and fine-tuning of the physical form of APIs can greatly affect drug formulation strategies and drug performance.¹⁹⁴

Principles of crystal engineering have permitted a more systematic approach to be taken to engineer the desired properties of pharmaceutical materials.^{30,32,195} These principles have been employed in a new concept, called anticrystal engineering, to obtain alternative forms of APIs with inhibited crystallisation.^{37,8} Anticrystal engineering has initially been defined as a method of identifying and intentionally avoiding the pairing of cations and anions with the goal of inhibiting salt crystallisation.³⁷ Later, it has been shown that the presence of hydrogen bonds is fundamental in liquefaction of multicomponent phases and subsequently, the scope of anticrystal engineering has expanded to include neutral non-ionic species.^{106,8} Other factors, such as low symmetry and charge delocalisation contribute to inefficient packing of counterions or co-formers contributing to decreased likelihood of crystallisation.³⁸

However, current prediction tools cannot always accurately predict the nature of a multicomponent system as small changes in physicochemical parameters of parent components lead to significantly different outcomes and many salt, cocrystal and ionic liquid forms are still being discovered empirically.³⁹ One of the popular discovery approaches employed is mechanochemical screening. It involves a variety of techniques, including neat grinding, solvent assisted grinding and milling.^{19,196,17,23,21} In addition to ease of experimental design and high screening efficiency mechanochemical synthesis is also generally considered as a green alternative to conventional synthetic methods due to minimisation of organic solvent use and reduced need for product purification steps.¹⁶

Anticrystal engineering approach was employed in Chapter 2 to investigate the effect of a range of crystal and physicochemical parameters in the formation of multicomponent systems comprising lidocaine (LID) and a series of short- and medium-chain aliphatic dicarboxylic acids (DA). LID, 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide, is an aminoamide drug used as an active pharmaceutical ingredient in local anaesthetic formulations. It is often selected as a model compound for investigation of physicochemical

properties of multicomponent phase formation.^{128,106,15,124} In Chapter 2 we have observed alternating trends in morphology, melting points, glass transition temperatures, and crystallographic properties of the new phases across the LID:DA series. In addition, in Chapter 3 we have investigated the influence of changing counterion ratio on the nature of intermolecular interactions and the identity of new phase formation. Upon addition of excess LID base component to azelaic acid, a neutral cocrystal multicomponent phase was obtained. Alternatively, the presence of excess acid component has resulted in the formation of a range of proton-transferred ionic liquids.

In Chapter 4 we are diving deeper into the aliphatic dicarboxylic acid homologous series with the aim to establish structural consistency in the extended series of LID:DA systems and to explore how the length and the flexibility of the long carbon backbone affect molecular recognition, crystallisation and thermal behaviour of the expected binary systems. Decanedioic (sebacic), undecanedioic, dodecanedioic and tridecanedioic acids used in the current study have been symbolised as C10, C11, C12 and C13, where a number denotes the number of carbon atoms in the acid backbone. Such designation has been adopted to follow a series of works investigating the even-odd alternation of physicochemical properties of saturated aliphatic dicarboxylic acids.^{153,154,148} While shorter DAs is a popular choice for the use as constituents in multicomponent systems,^{197,198} longer-chain DAs are much less explored. C10 has been employed for the formation of multicomponent phases in combination with propranolol⁸⁷, apatinib¹⁹⁹ and isonicotinamide²⁰⁰. C12 has been investigated as a possible coformer in combination with praziquantel²⁰¹ and pyridinecarboxamide-based potential cancer drugs²⁰². To the best of our knowledge, API:C11 or API:C13 systems have not been reported to date.

4.2 Materials and Methods

4.2.1 Materials

LID (as a base), sebacic acid (C10), dodecanedioic acid (C12) and 1,11-undecanedicarboxylic acid (C13) were purchased from Aldrich (Ireland). 1,9-nonanedicarboxylic acid was purchased from TCI (Belgium). HPLC grade ethanol was obtained from Fisher Chemical (Ireland). All chemicals were used as supplied.

4.2.2 Methods

4.2.2.1 Sample preparation

The binary mixtures were prepared by accurately weighing LID and each of the acids using Mettler Toledo MT5 microbalance (Mettler Toledo, Switzerland) at a range of molar fractions. The powders were then co-ground using an agate pestle and mortar until homogenous mixtures were obtained. The samples were transferred into microcentrifuge tubes and were kept at 4 °C for 24 h before being analysed.

4.2.2.2 Differential Scanning Calorimetry (DSC)

DSC scans were carried out as described in Chapter 2. The samples were subjected to a 1st heating cycle at a 10 K min⁻¹ rate, followed by a fast-cooling step to -60 °C at 300 K min⁻¹ rate, and finally a 2nd heating cycle at 10 K min⁻¹ rate.

4.2.2.3 Polarised Optical Microscopy (POM)

Prior to analysis, LID and C11 were dissolved in ethanol and were left at room temperature until complete solvent evaporation. A small crystal of each, LID and C11, were placed on a glass slide in direct contact with one another. The solid fusion experiment was performed as described in Chapter 2.

4.2.2.4 Powder X-Ray Diffraction (PXRD)

PXRD analysis was performed as described in Chapter 2. Freshly-ground LID:DA at a range of molar compositions were analysed. In addition, equimolar LID:DA compositions were heated in an oven at 60 °C until molten followed by slow cooling and drying under vacuum at room temperature for 60 h. The melt-cool samples were then analysed by PXRD.

4.2.2.5 Attenuated Total Reflectance Fourier-Transform Infrared Spectroscopy (ATR-FTIR)

ATR-FTIR spectra were obtained with Spectrum One spectrophotometer (Perkin Elmer, USA) equipped with a diamond ATR accessory and Spectrum v. 5.0.1 software. The samples were dried in an oven at 60 °C for 30 min prior to analysis. A spectral range of 650-

4000 cm⁻¹ and accumulation of 8 scans were used. Deconvolution of infrared bands was conducted using the Gauss function fitting module in OriginLab ver. 7.5.

4.2.2.6. Single Crystal X-Ray Diffraction (SXRD)

A powdered sample of LID:C13 at 1:1 molar ratio was dissolved in a minimum amount of ethanol and was allowed to stand at room temperature until complete solvent evaporation. Colourless crystals of the C13 acid of satisfactory quality for SXRD analysis were obtained.

SXRD analysis and structure elucidation were performed by Dr Brendan Twamley, TCD School of Chemistry. Data for the C13 were collected on a Bruker APEX DUO using Cu K α radiation ($\lambda = 1.54178$ Å). The sample was mounted on a MiTeGen cryoloop and data collected at 100(2) K using an Oxford Cobra cryosystem. Bruker APEX¹⁴² software was used to collect and reduce data. Absorption corrections were applied using SADABS.¹⁴³ Structures were solved with the SHELXT structure solution program¹⁴⁴ using Intrinsic Phasing. Data were refined using Least Squares method on F² with SHELXL.¹⁴⁵ All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters. Molecular graphics were generated using OLEX2.¹⁴⁶ Crystal data, details of data collection and refinement are given in **Table AIII.1**.

The acid group hydrogen H1 was located on the difference map and refined.

Crystallographic data for the structure in this chapter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 2168827. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.uk).

4.2.2.7 Crystallographic analysis

Mercury (version 2020.2.0)¹⁴⁷ was used for structure visualisation, crystal packing analysis, molecule overlay calculations and unified pair-potential (UNI) force-field calculations.^{203,204} Reference structures used for calculations were obtained from Cambridge Structural Database (CSD): LIDCAN11¹⁴⁹, SEBAAC06¹⁴⁸, UNDEAC11²⁰⁵, UNDEAC12²⁰⁵, DECDAC02²⁰⁶, BRASAC11²⁰⁷. Void spaces within crystal lattices were calculated using contact surface with probe radius of 0.2 Å and approximate grid spacing of 0.2 Å.

4.2.2.8 Density Functional Theory (DFT) Calculations

DFT calculations were performed by Dr Lidia Tajber, TCD School of Pharmacy. A Gaussian03 program was employed to calculate the total energy of fully optimised structures of C10, C11, C12 and C13, extracted from the single crystal structures SEBAAC06¹⁴⁸,

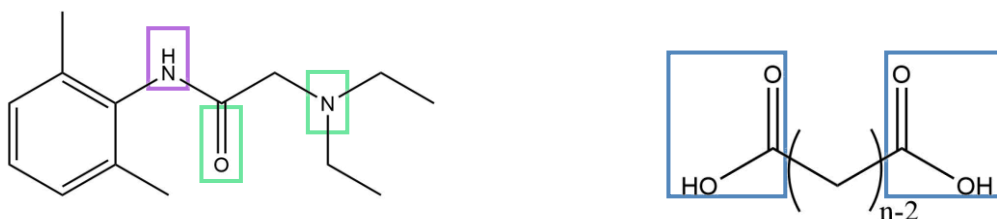
UNDEAC11²⁰⁵, UNDEAC12²⁰⁵, DECDAC02²⁰⁶, BRASAC11²⁰⁷ and the new form of C13 obtained in this work.²⁰⁸ The B3LYP/6-31++G(d,p) level of density functional theory (DFT) was used. Wavefunction analysis was conducted using Multiwfn 3.6 as described previously.^{8,209,210}

4.3 Results and discussion

4.3.1 Anticrystal engineering considerations

LID is a weak base with a pK_a of approximately 8.0.¹²¹ It possesses one H-donor and three H-acceptor groups as shown in **Scheme 4.1**. Upon sufficient difference in pK_a (ΔpK_a) values, which is defined as $\Delta pK_a = pK_{a_{base}} - pK_{a_{acid}}$, LID may form molecular salts via ionisation at the tertiary amine site. The sufficient ΔpK_a is commonly accepted to be > 3 units.⁵⁰ The pK_a value for C10 was experimentally determined and the pK_a values for C11, C12 and C13 were theoretically calculated to be 4.7,^{211–214} thus, generating sufficient ΔpK_a to facilitate proton transfer. However, due to flexibility and bulkiness of DAs the access to the H-bonding active sites may be sterically hindered. As a result, the degree of proton transfer may not be derived theoretically in a reliable fashion and experimental characterisation is crucial for the characterisation of multicomponent phases. The principles of molecular complementarity applicable to crystal engineering complicate the possibilities of molecular interactions further. It is well known that acid carboxyl moieties tend to form supramolecular heterosynthons with amide moieties of basic compounds.³³ Therefore, LID possessing an amide group has a potential to form additional hydrogen bonds via amide-carboxyl synthon formation.

Scheme 4.1. Molecular structures of LID (left) and a general molecular structure of a DA (right), where n = number of carbon atoms in the backbone. Purple: H-bond donor and acceptor; green: H-bond acceptor; blue: carboxylic acid groups.



In anticrystal engineering approach the aim of a counterion or a co-former is to lower the melting point (T_m) of an API. It has been shown that, in general, the T_m of a salt or a cocrystal is influenced by the melting point of the parent materials.^{39,40} The T_m of the DAs investigated alternate with even-odd number of carbons in the carbon backbone. The thermal data in **Table 4.1** was obtained for the parent DAs and is in a good agreement with previously published data.²¹⁵ Therefore, it is anticipated that the melting points of any multicomponent systems formed will also alternate in a similar fashion.

Table 4.1. Physicochemical and crystallographic properties of the investigated molecules. Melting point and enthalpy of fusion (ΔH) data was determined by DSC analysis. Kitaigorodskii Packing Indices (KPIs) were calculated from the void space measurements. Packing energies were calculated using Mercury software. It was not possible to calculate the packing energy of LID due to disorder present in the crystal structure.

Molecule	Molar mass (g/mol)	Melting point (° C)	ΔH (kJ/mol)	Polymorphic form	KPIs (%)	Packing energy (kJ/mol)	Ref.
LID	234.34	69-70	16.0	P2 ₁ /c	70.2	-	149
C10	202.25	133-136	45.4	P2 ₁ /c	70.7	-156.5	148
C11	216.28	109-112	43.7	C2/c (form I)	76.4	-174.4	205
				P2 ₁ /c (form II)	75.6	-172.8	205
C12	230.3	129-131	51.6	P2 ₁ /c	71.3	-171.7	206
C13	244.33	112-115	52.9	C2/c (form I)	76.1	-189.6	This work
				P2 ₁ /n (form II)	74.5	-187.0	207

Higher torsion angles, twisting of the carbon chain and overall greater distortion from the equilibrium conformation of the odd dicarboxylic acids lead to energetically unfavourable molecular conformations.¹⁵³ **Table 4.1** presents a summary of crystallographic properties of LID and DAs, their determined polymorphic forms and corresponding packing energies. It is hypothesised that the energy difference between an ideal isolated state and the energy released upon grinding or melting of the solid state could influence the tendency of the acids to form multicomponent systems with bases. It means, that upon mechanochemical synthesis, odd-chain DAs would display preference for forming multicomponent phases with LID rather than retaining or reforming highly-strained parent acid structures. It was discussed in Chapters 2 and 3 that LID:DA systems with glutaric, pimelic and azelaic acids displayed poor crystallisation tendency and readily formed ionic liquids upon physical contact. In contrast, LID with adipic acid required heat treatment for the formation of lidocaine hemiadipate salt and LID with suberic acid formed a mixture of acid-base eutectic and lidocaine hemisuberate salt upon grinding.

Kitaigorodskii's Packing Indices (KPIs) is another useful measure that can aid in prediction of counterion interaction tendency.¹⁷⁰ It is linked with the theory that parent materials with less efficient packing have larger cavities providing enhanced availability of

active sites required for solid state reactions.¹⁷⁰ According to these postulates, less efficiently packed DAs (i.e. characterised by lower KPIs) are predicted to exhibit a greater tendency to undergo solid state reactivity upon grinding and should form multicomponent systems more readily.

Supporting information was also obtained via molecular modelling using DFT method. Individual DA molecules were isolated from their crystalline structures, optimised and energies of the molecules were calculated. Mapping of the calculated electrostatic potential (ESP) on the molecular van der Waals surface of the DAs (C10-C13) showed that the minimum ESP values were comparable and ranged from -38.00 to -36.50 kcal/mol (**Table 4.2**). The location of this minimum was on the carbonyl moiety of the -COOH group indicating its electrophilic nature. The maxima were slightly more dissimilar and varied between 49.09 and 53.92 kcal/mol with said maxima located on the hydrogen atom of the -OH moiety of the carboxylic group and representing the nucleophilic part of the molecule. Considering the values, the DAs are expected to interact with LID via hydrogen bonds driven by electrostatic attraction between the molecules.^{216,8} However, considering the values of σ_{tot}^2 , C10 and C12 should interact with LID more strongly, as the higher the σ_{tot}^2 value the stronger tendency to interact electrostatically with another molecule (**Table 4.2**).²¹⁷

Table 4.2. The values of general interaction properties function (GIPF) descriptors, as defined by the molecular vdW isosurface at $\rho = 0.001 \text{ e/Bohr}^3$ and V_{min} – global ESP minimum, V_{max} – global ESP maximum and σ_{tot}^2 - total ESP variance.

DA	V_{min} (kcal/mol)	V_{max} (kcal/mol)	σ_{tot}^2 (kcal/mol) ²
C10	-38.00	53.92	235.2
C11 (form I)	-35.91	49.17	189.5
C11 (form II)	-37.55	49.57	192.7
C12	-37.83	53.01	232.0
C13 (form I)	-36.50	50.51	196.8
C13 (form II)	-37.41	49.09	188.0

Summarising, based on the KPIs, C11 and C13 should display a greater tendency to undergo solid state reactivity considering grinding processed, while C10 and C12 should interact with LID more strongly, thus form multicomponent systems more readily.

4.3.2 Mechanochemical synthesis and crystallisation studies

Upon manual neat grinding, homogenous binary mixtures of LID:DAs in the form of white solid powders were obtained. Mixtures of LID:C11 in the range of $\chi_{\text{LID}} = 0.67 - 0.33$ molar fractions were obtained as a white semi-liquid paste. Solid fusion experiment performed using POM revealed that single crystals of LID and C11 undergo solid interdiffusion at room temperature and form a liquid eutectic at temperatures below room temperature, as evident in **Figure 4.1**. The observation resembles solid-state reactivity of LID with glutaric, pimelic and azelaic acids, discussed in Chapters 2 and 3.

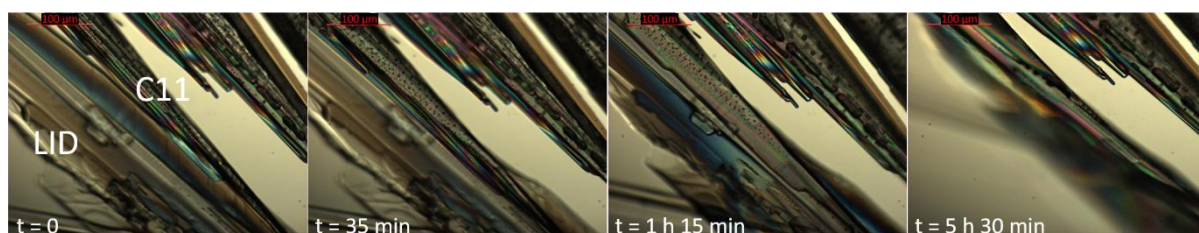


Figure 4.1. A solid fusion experiment performed with recrystallised LID (bottom left: plate-like crystal) and recrystallised C11 (top right and centre: needle-like crystals). After 5 h 30 min most of LID has dissolved within the eutectic, while most of C11 that has not been in direct contact with LID has remained unchanged.

PXRD analysis of the parent materials and freshly ground binary mixtures reveals combinations of the parent diffractograms without new Bragg peaks in any of the four systems (**Figure 4.2A-C**). Thus, no new crystalline phases were created upon neat grinding. The binary mixtures at 1:1 molar ratio were then heated at 60 °C until molten followed by slow cooling and drying under vacuum at room temperature in an attempt to promote formation of intermolecular interactions. The melt-cool crystallisation experiments yielded diffractograms with a combination of peaks stemming from the parent materials. The diffractograms for the melt-cool samples are highlighted in orange colour in **Figure 4.2**. However, it is important to note that partial liquefaction of LID:C11 samples in the range of $\chi_{\text{LID}} = 0.67 - 0.33$ molar fractions provides a likely indication for a new phase formation characterised by a melting point that is lower than room temperature. Solvent-evaporation crystallisation from water, methanol, ethanol and acetonitrile also proved to be unsuccessful and only parent dicarboxylic acids crystallised out. The data for solvent-evaporation crystallisation experiments is not presented. This contrasts with the observations made for

shorter-chain LID:DA systems with oxalic, malonic, succinic, glutaric, adipic, pimelic, suberic and azelaic acids, which were obtained by both, mechanochemistry and solution-based methods.¹²³

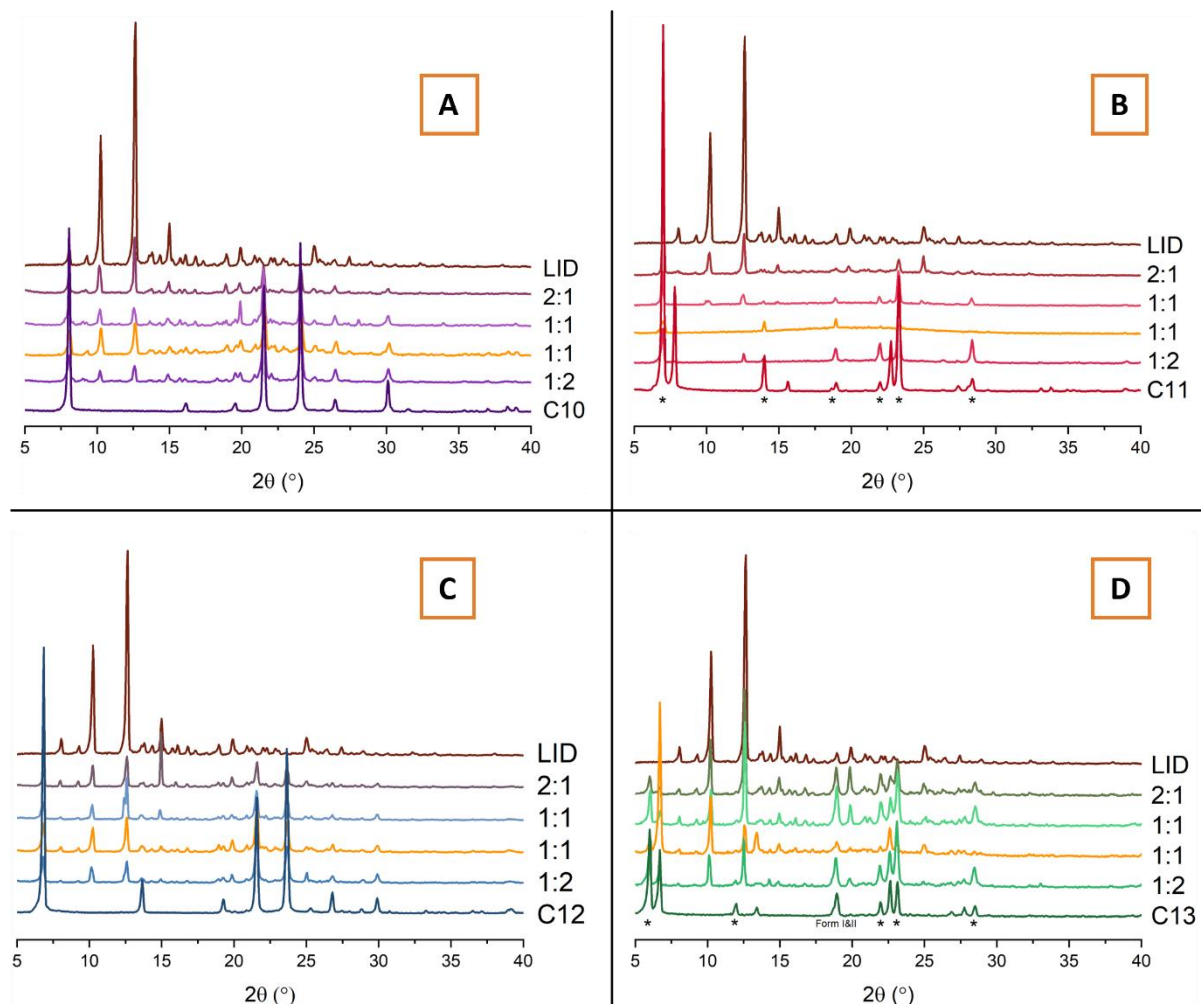


Figure 4.2. Stacks of PXRD diffractograms at different molar compositions of **A:** LID:C10; **B:** LID:C11, where stars under the diffractogram of the pure C11 sample denote peaks corresponding to the C 2/c polymorph (Form I). Unmarked peaks correspond to the P 2₁/c polymorph (Form II); **C:** LID:C12; **D:** LID:C13, where stars under the diffractogram of the pure C13 sample denote peaks corresponding to the C 2/c polymorph (Form I). Unmarked peaks correspond to the P 2₁/n polymorph (Form II). Diffractograms marked with orange colour represent equimolar samples that were heated until completely molten and then dried under vacuum at room temperature for 60 h.

During crystallisation efforts a previously undetermined low-temperature form I (β -form) of C13 acid was isolated and analysed by SXRD. Full crystallographic characterisation may be found in **Table AIII.1**. The high-temperature form II (α -form), on the other hand, has been previously determined and characterised by multiple research groups.^{218,207} The PXRD patterns of the two forms are presented in **Figure 4.3A**.

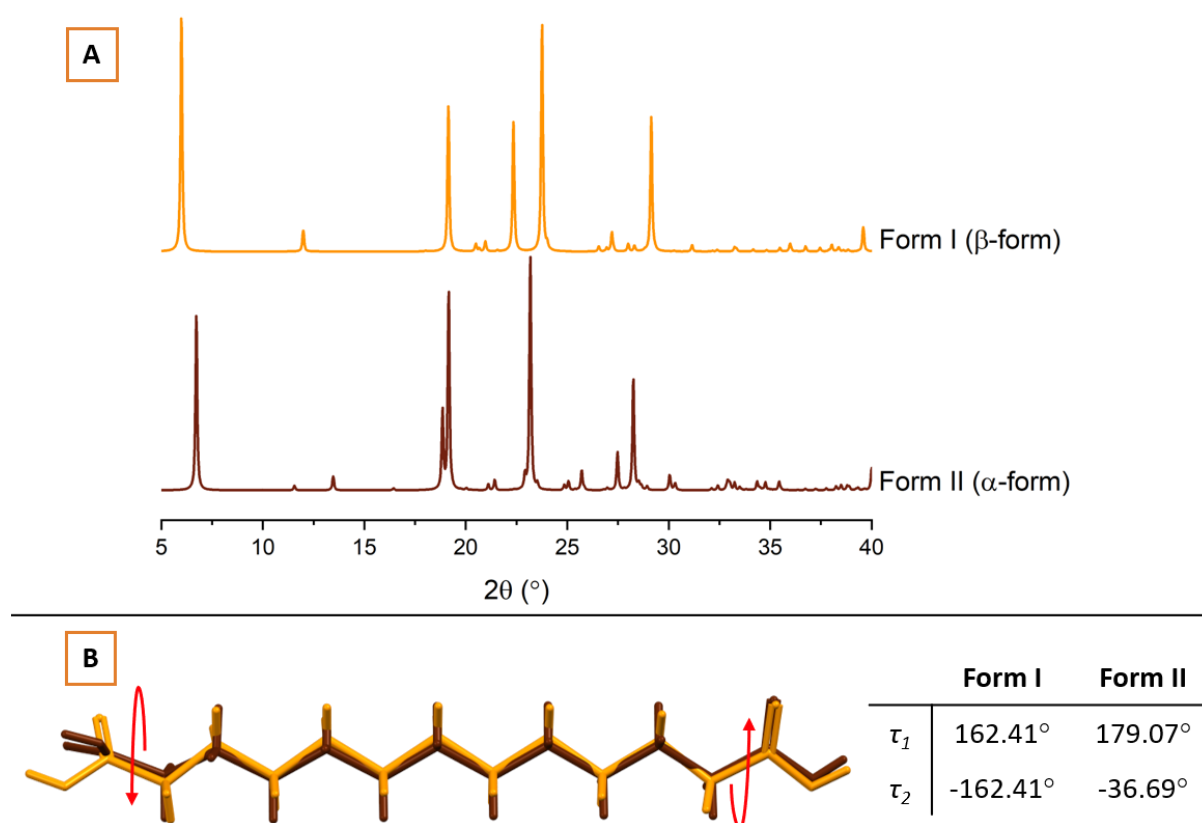


Figure 4.3. A: Calculated PXRD patterns of forms I and II of C13 dicarboxylic acid. Crystal structure of form II was obtained from CSD.²⁰⁷ **B:** Molecular overlay of form I and form II of the C13 dicarboxylic acid displaying the differences in torsion angles.

It is interesting to note that medium and long odd-chain dicarboxylic acids with carbon chain length in the range of C7-C15 only crystallise as a form II from solvents with H-bond donating ability.²⁰⁷ However, in the current study the presence of LID molecules in ethanolic solution has opposed the solvent-dependent polymorph selectivity pattern within the acid homologous series and form I of C13 has crystallised out.

Analogous to other odd-chain dicarboxylic acids within the homologous series, form I of C13 crystallises as a monoclinic crystal system and is assigned to the C2/c space group.

The molecules within the crystal are arranged as carboxylic acid dimers formed via OH...O hydrogen bonding with $d(D...A) = 2.6619(16) \text{ \AA}$, which are further assembled into stacked molecular chains as shown in **Figure 4.4**. To avoid the unfavourable O...O repulsion between the carboxyl groups of the neighbouring chains the C13 molecules are found in a twisted conformation with torsion angles for $O_1-C_1-C_2-C_3$ and $O_1^i-C_1^i-C_2^i-C_3^i$ being $\tau_1 = \tau_2 = \pm 162.41(10)^\circ$. In contrast, the torsion angles in the form II are different at both ends of the molecule, as shown in **Figure 4.3B**. This observation is consistent with the general trend followed by the series of odd-chain dicarboxylic acids.

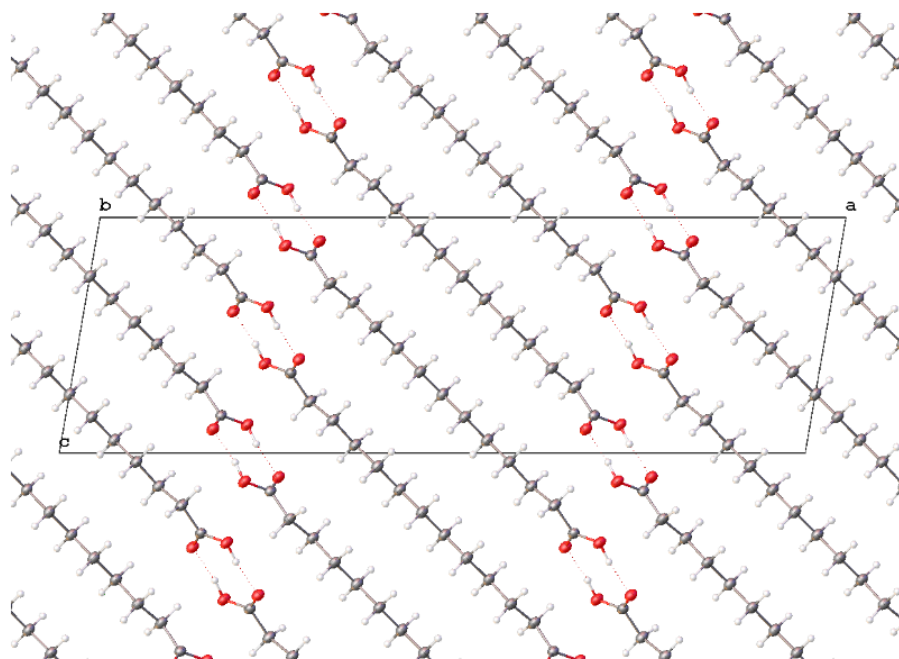


Figure 4.4. Packing diagram of form I of C13 viewed normal to the b-axis showing the acid hydrogen bonding motif. Displacement at 50% probability.

4.3.3 Thermal analysis of the binary mixtures

The binary mixtures at a range of molar compositions were analysed by DSC and the data obtained from the 1st heating cycle was used to construct thermodynamic phase diagrams. Theoretical solubility curves were constructed using the Schroeder van Laar equation (**Equation 2**), where T_{fus} (K) is the temperature of fusion and ΔH_{fus} (J mol^{-1}) is the enthalpy of fusion of the pure starting component, χ is the mole fraction of the pure starting component at a specified temperature T (K), and R denotes the universal gas constant. The

Schroeder van Laar model describes the solid solubility behaviour of the starting components that do not interact and form an ideal eutectic mixture.⁸⁴

$$T = \left(\frac{1}{T_{fus}} - \frac{R \ln \chi}{\Delta H_{fus}} \right) \quad (\text{Eq. 2})$$

The thermal data for the parent materials presented in **Table 4.1** was obtained from the 1st heating cycle, where LID, C10 and C12 displayed a single endothermic transition at 69, 133 and 129 °C, respectively. These transitions were ascribed to the melting events of the pure materials that are only found as a single polymorphic form. Endothermic transitions for the C11 and C13 dicarboxylic acids at 109 and 112 °C, respectively, appeared as merged peaks due to the odd dicarboxylic acids possessing two distinct polymorphic configurations each.^{207,215} However, due to the closeness of the melting points of the different polymorphs it is not possible to separate the overlapping peaks.

In all four systems studied and presented in **Figures 4.5** and **4.6** the expected melting point depression of the parent materials is observed. However, the extent of the melting point depression deviates from the ideal solubility curve predicted by the Schroeder van Laar model. This deviation from ideality implies the formation of intermolecular interactions between the parent components that contribute to the further lowering of the melting point. Eventually, at certain molar compositions no peaks are observed for residual LID and dicarboxylic acid endothermic transitions.

The analysis of LID:C10 binary mixtures presented in **Figures 4.5A** and **4.6A** indicate the presence of two distinct endothermic peaks at 58 °C and 61 °C, most visible at the 1:1 molar composition. A slight shifting of the endotherm at 61 °C in the samples with a higher molar fraction of C10 acid suggests that it may indeed be a new distinct phase, such as a salt or a co-crystal. Such double peak phenomenon was observed in LID systems with other even-chain DAs, adipic and suberic, where the peaks were attributed to a salt and a eutectic melting events, as described in Chapter 2. In both systems, LID:adipic acid and LID:suberic acid, crystal structures of fully-ionised salts were solved. However, crystallisation efforts of the LID:C10 system did not yield definite evidence for the formation of such phase. Binary mixtures of the LID:C11 system also exhibit a eutectic formation in the samples with a higher molar fraction of LID, as seen in the phase diagram in **Figure 4.6B**. The peaks for the fusion events of the eutectic appear at 42 °C but are not visible in the stack of the DSC traces in **Figure 4.5B** due to peak broadness and low ΔH_{fus} values. A

stack of DSC thermograms with the magnified 40 – 60 °C region is presented in **Figure AIII.1**. This observation is not unusual for the semi-liquid paste sample morphology and has been observed in other LID:DA systems with odd-chain dicarboxylic acids discussed in Chapter 2. It can be explained by the dispersion of the solid particles within a liquid matrix that gradually dissolve upon melting as a result of slower heat transfer processes. LID:C12 and LID:13 exhibit similar thermal behaviour as shown in **Figures 4.5C-D** and **4.6C-D**. A single eutectic is formed in both systems at 45 °C and 40 °C, respectively.

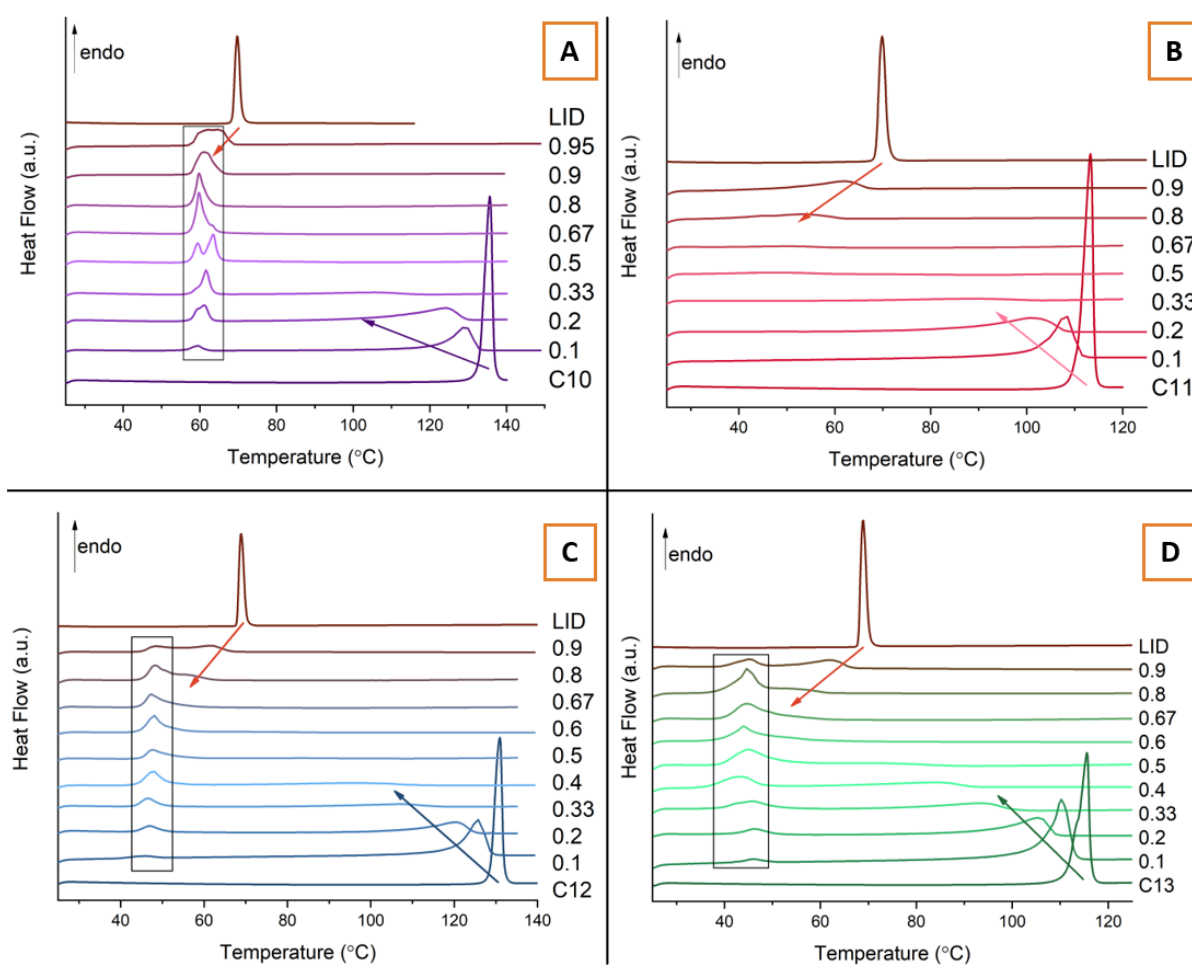


Figure 4.5. Stacks of 1st heating cycle DSC thermograms at different molar compositions of **A:** LID:C10, **B:** LID:C11, **C:** LID:C12 and **D:** LID:C13. Red arrows indicate LID melting point depression with increasing DA molar fraction. Purple, pink, blue and green arrows indicate melting point depression of C10, C11, C12 and C13, respectively.

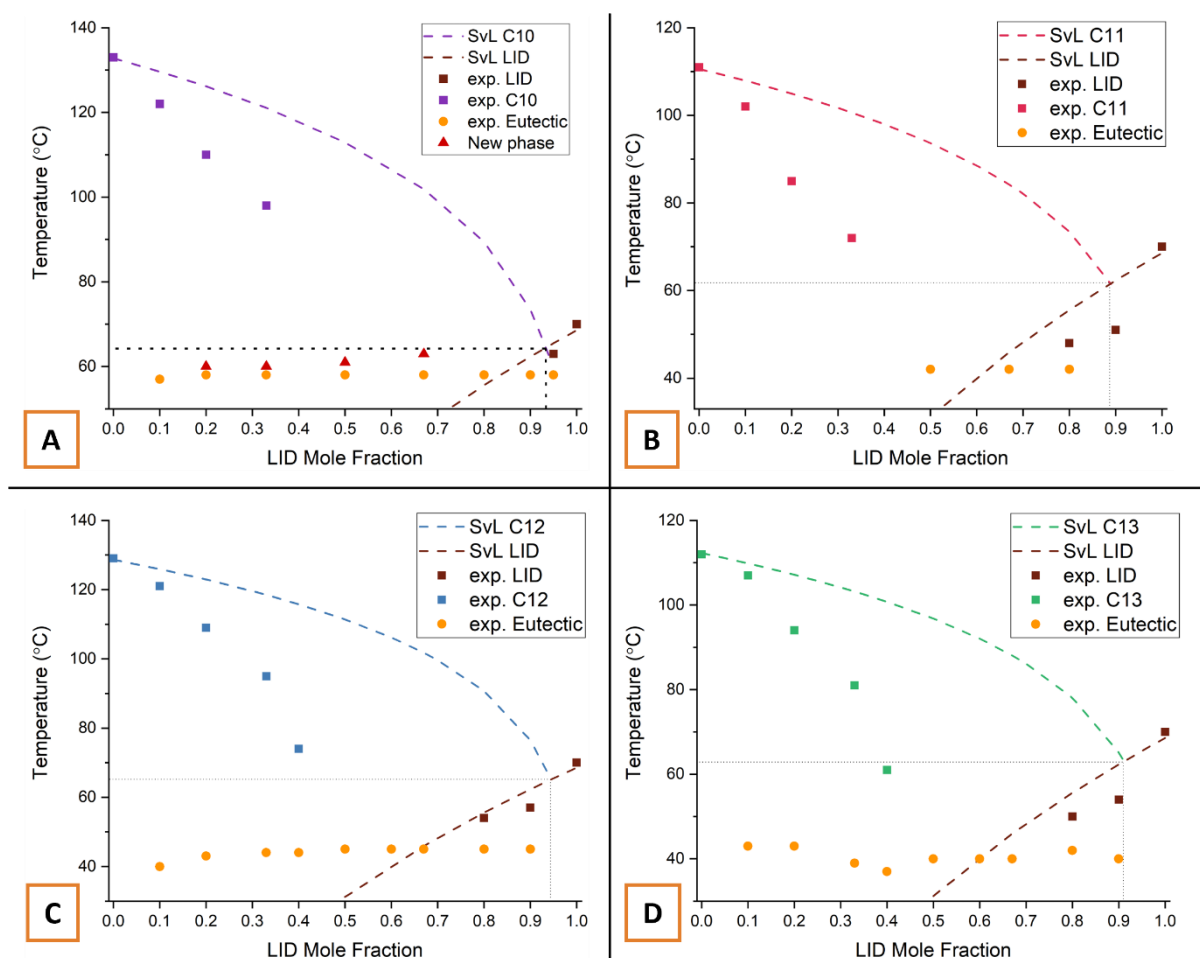


Figure 4.6. Phase diagrams of the four systems studied. A: LID:C10, B: LID:C11, C: LID:C12, D: LID:C13. Dashed lines were calculated using the Schroeder van Laar (SvL) equation. Dotted lines represent the theoretical temperature and composition of the eutectic as determined by the Schroeder van Laar equation.

The melting points of the eutectics in all of the four systems studied exhibit deviation from the theoretical eutectic temperature predicted by the Schroeder van Laar model. One of the suggested definitions of a “deep eutectic solvent” states that DES is a mixture of pure compounds for which the eutectic point temperature is below that of an ideal liquid mixture.⁸⁴ The melting point depression between the ideal and the observed eutectic point is used to measure how “deep” the eutectic is. The calculated deviations for the systems studied summarised in **Table 4.3** show that only LID:C10 could be reasonably predicted as the differences in the eutectic melting points for other systems are ≥ 20 °C. Analogous to the melting point depression of the parent components, the formation of intermolecular interactions, such as hydrogen bonds, within the eutectics contribute to the observed “deepening” of the melting points.²¹⁹ Therefore, FTIR spectroscopy, as described below,

was employed to investigate the nature of these intermolecular interactions. It is interesting to note that even though the observed eutectic points follow the expected even-odd alternating pattern, the calculated deviations ΔT_e do not. The Schroeder van Laar model can also predict ideal eutectic composition, χ_e . The theoretical χ_e calculated for the LID:DA systems also exhibit even-odd alternating pattern, although the values are very similar, see **Table 4.3**.

Table 4.3. Calculated differences ΔT_e between the predicted ideal eutectic melting temperature T_e , **ideal** and an observed experimental eutectic melting temperature T_e , **observed**.

System	χ_e , ideal	T_e , ideal (° C)	T_e , observed (° C)	ΔT_e (° C)
<i>LID:C10</i>	0.93:0.07	64	58	6
<i>LID:C11</i>	0.89:0.11	62	42	20
<i>LID:C12</i>	0.94:0.06	65	45	20
<i>LID:C13</i>	0.91:0.09	63	40	23

Following the first heating the 1:1 LID:DA samples were fast-cooled at a nominal rate of 300 °C/min and subjected to a second heating cycle. **Figure 4.7A** presents a stack of DSC thermograms for the 2nd heating cycle which reveal good glass-forming ability of LID:DA equimolar samples manifested by their ability to be supercooled, i.e. no melting or crystallisation events are observed upon cooling and/or before heating to the glass transition temperature (T_g). In contrast, pure starting components do not exhibit T_g transitions as they crystallise during the cooling step. The observed T_g values of the equimolar binary mixtures follow the usual even-odd alternating pattern as shown in **Figure 4.7B**. It has been suggested that the nature of intermolecular interactions in the supercooled state impacts the position of the T_g .²²⁰ Therefore, 1:1 LID:C10 characterised by the highest T_g value of -18 °C is expected to form the strongest electrostatic interactions in the supercooled state and LID:C11 with the T_g value of -25 °C forming the weakest. However, the nature of the proton-transfer mechanism and the presence of other intermolecular interactions (e.g. van der Waals forces) can also shift the position of the glass transition temperature.²²¹

In addition, 1:1 LID:C12 sample also exhibits crystallisation and melting peaks upon heating past the glass transition temperature. PXRD analysis of the crystallised material revealed that it was composed of both, LID and C12 parent materials (**Figure 4.2c**).

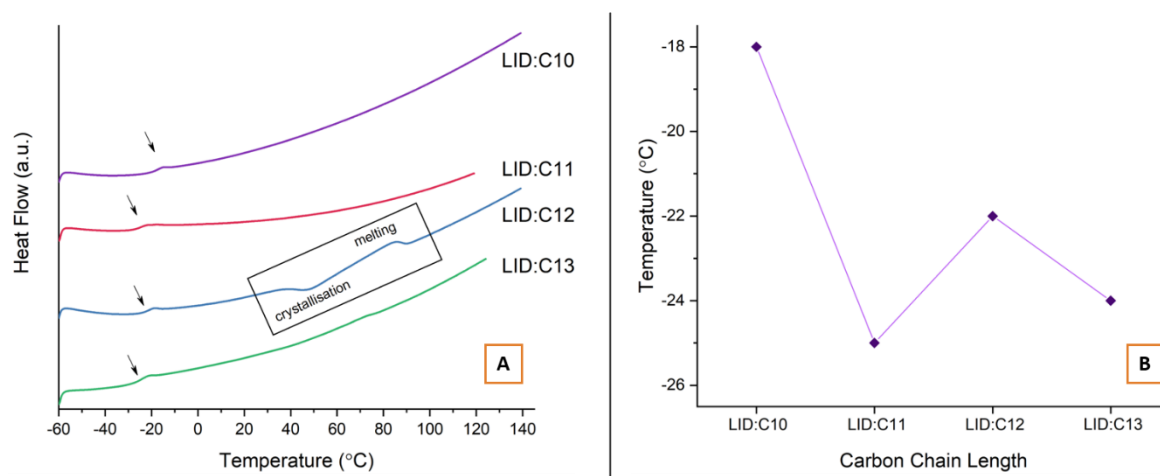


Figure 4.7. The alternating trend in T_g values of the equimolar LID:DA mixtures.

4.3.4 Investigation of intermolecular interactions

ATR-FTIR was employed to elucidate the nature of molecular interactions within the systems that contributed to the deviation of the experimental data from the solid solubility curves predicted by the Schroeder van Laar model. The stacks of ATR-FTIR spectra of the raw materials and the binary mixtures are shown in **Figure 4.8**. The two spectral regions presented display peaks corresponding to the stretching vibrations of the hydrogen bond donor and acceptor groups of the parent materials. A single broad peak observed in the region of $3300 - 3200 \text{ cm}^{-1}$ corresponds to the amide N-H stretching vibration in LID. Upon dilution in the dicarboxylic acids the peak gradually diminishes. A series of peaks found in the $1800 - 1500 \text{ cm}^{-1}$ region is assigned to carbonyl stretching vibrations. However, carbonyl peak assignment in samples involving dicarboxylic acids is complex due to the presence of free and hydrogen-bonded carboxyl groups, in addition to the presence of multiple polymorphs of odd dicarboxylic acids. Gaussian peak fitting was used to deconvolute the peak overlap observed in the carbonyl region to facilitate a more accurate assignment of peak maxima, see **Figure AIII.2**.

Deconvolution of carbonyl signals yielded three bands in all dicarboxylic acids. The major band is found at around 1689 cm^{-1} and is assigned to a hydrogen-bonded C=O stretching vibration. A small shoulder at 1713 cm^{-1} is assigned to a non hydrogen-bonded carbonyl group. This band is most prominent in odd dicarboxylic acids possibly due to coexistence of two different polymorphs within the samples. An additional signal is observed

in the region of $1677 - 1661\text{ cm}^{-1}$ in each of the acids. LID possesses a major peak at 1662 cm^{-1} and a shoulder at 1637 cm^{-1} .

The evidence for the formation of intermolecular interactions between LID and C10 comes from the appearance of a peak at 1540 cm^{-1} ascribed to a carboxylate ion asymmetric stretching vibration (**Figure 4.8A**). This band is most clearly observed at 1:1 composition indicating strongest intermolecular attraction. The appearance of this band does not necessarily mean complete acid ionisation and it has been shown previously that carboxylate peaks may also be observed upon partial proton transfer in “poor” ionic liquids and systems with a “confused” proton.^{222,6} Increased prominence of non hydrogen-bonded carbonyl band of C10 also supports the formation of intermolecular interactions between LID and C10. The deconvolution of the LID:C11 spectrum reveals processes very similar to the ones observed in the LID:C10 system. However, the carboxylate ion band at 1540 cm^{-1} in **Figure 4.8B** is much more prominent in the 1:1 LID:C11 binary mixture indicating a greater extent of proton transfer. The semi-liquid nature of the ground sample and the appearance of this band suggest a possibility of ionic liquid formation.

In contrast, very weak signals corresponding to a carboxylate stretching vibration are observed in LID:12 and LID:C13 systems indicating that the acids may not interact with LID at the carboxyl sites primarily via a proton transfer. In addition, **Figure 4.8C** reveals that the non hydrogen-bonded signal of the C12 carbonyl group does not increase in prominence upon mixing with LID. This finding suggests that the melting point depression observed in the LID:C12 system and the deviation from the ideal behaviour predicted by the Schroeder van Laar model is mainly caused by dipole-dipole interactions and/or Van der Waals forces. The interactions in LID:C13 system are analogous to the interactions observed in the LID:C12 binary mixtures. However, as seen in **Figure 4.8D**, the non hydrogen-bonded carbonyl signal of C13 does become more prominent upon mixing with LID. This is possibly due to the crystal lattice of C13 being broken during mechanical grinding.

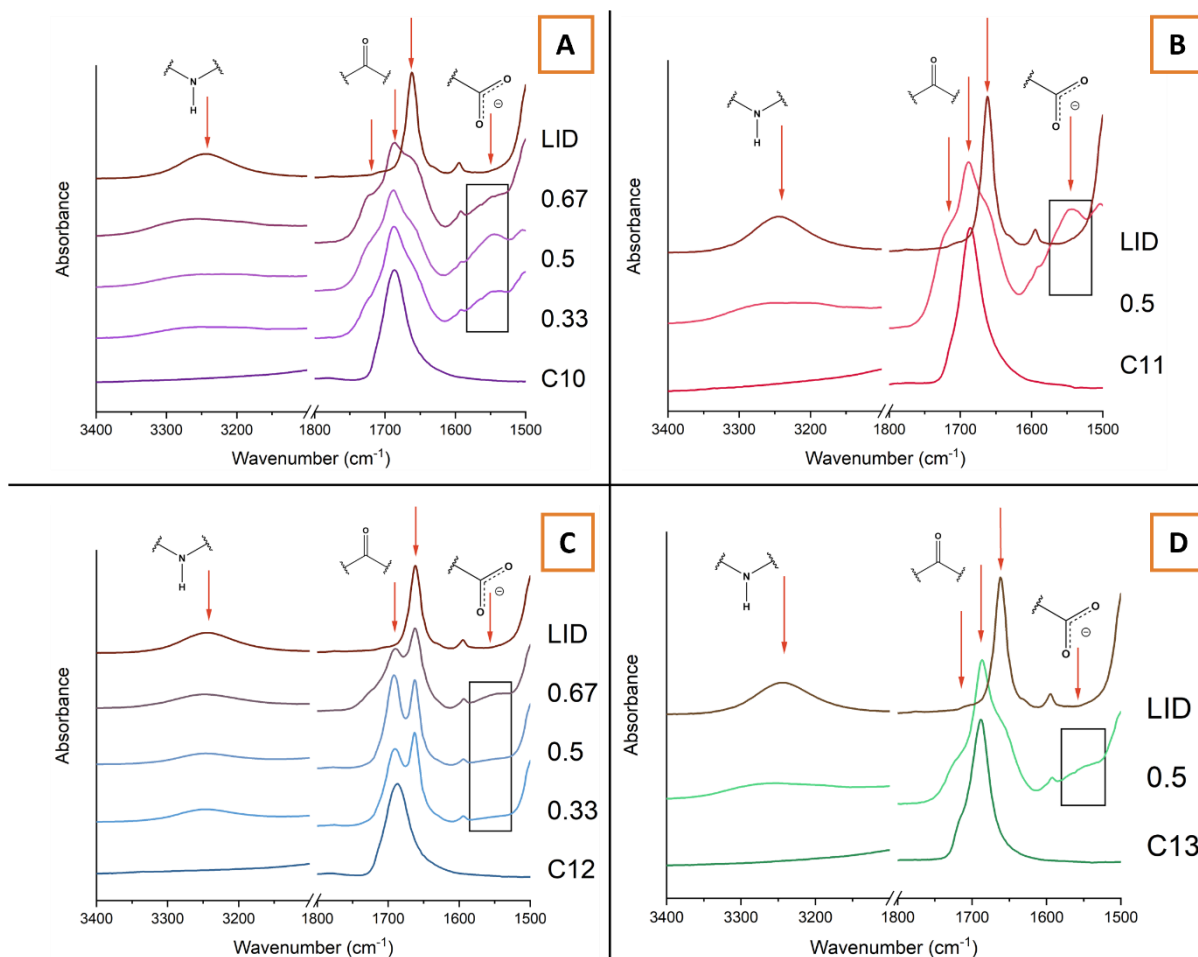


Figure 4.8. Stacks of IR spectra at different molar compositions of **A:** LID:C10, **B:** LID:C11, **C:** LID:C12 and **D:** LID:C13. Red arrows indicate FTIR signals of interest. Black box indicates carboxylate ion region.

4.4 Conclusions

Binary mixtures of LID with C10, C11, C12 and C13 DAs were investigated by thermal, spectroscopic, crystallographic analysis and theoretical modelling and calculations. It was concluded that LID forms hydrogen-bonding interactions with the DAs investigated, but the interactions are not sufficient for the complete transformation into new homogenous multicomponent phases. DSC analysis has revealed the formation of eutectic phases in all LID:DA systems. The observed eutectic melting points deviate from the ideal eutectic temperatures calculated by Schroeder van Laar equation as a result of intermolecular interactions between the reacting components. The appearance of 2 new endothermic peaks in the DSC thermograms of the LID:C10 system were attributed to a eutectic and an unknown new crystalline phase formation. Mechanochemical grinding induces partial liquefaction of the LID:C11 system signifying a possible new phase formation characterised

by a lower than room temperature melting point. Intermolecular interactions between LID and the longest DAs, C12 and C13, were found to be the weakest. However, deconvolution of the FTIR spectra has provided evidence for partial ionisation in all of the systems investigated. The presence of a single glass transition event in all systems at equimolar LID:DA compositions implies a formation of a homogenous phase in a supercooled state. The even-odd alternating pattern in physicochemical and crystalline properties that are characteristic of the DA homologous series was observed in thermal properties of the LID:DA systems. It was demonstrated that eutectic melting points and glass transition temperatures alternate as a function of acid carbon chain length. In addition, a previously undetermined form I of the C13 DA has been solved by SXRD. This work has enhanced our understanding of the influence of increasing dicarboxylic acid chain length on the formation of intermolecular interactions with LID as a possible strategy to fine-tune physicochemical properties of multicomponent systems for pharmaceutical applications.

[illegible]

5.1 Introduction

Pharmaceutical strategies aiming to alter physical forms of drugs without modification of the chemical structure of an API have been shown to successfully address challenges associated with poor drug solubility, dissolution, permeability, thermal stability, hygroscopicity and crystallinity.^{132,223,224} Examples of such strategies include disturbing or disrupting the crystal lattice via salt, cocrystal and other multicomponent phase formation.²²⁵ Melting point depression in such multicomponent phases may lead to the formation of neutral deep eutectic mixtures (DEMs) or low-melting point salts, such as ionic liquids (ILs). If a drug is an ionisable substance, turning it into a salt is usually the most preferred approach to significantly improve its essential physicochemical properties.¹¹⁰ Synthesis of a protic IL incorporating an API and a counterion which, by definition, melts at temperatures below 100 °C,¹³³ allows to achieve greater API solubility and dissolution rates through reduction of the interaction between the API molecules and increase in ionicity due to salification. Furthermore, due to the liquid nature of ILs such a strategy helps to prevent the issue of polymorphic interconversion.¹¹⁴

Generally, salts of ionisable APIs exhibit higher solubilities than their respective free acid or base forms.¹¹⁰ In turn, the increase in solubility in the aqueous diffusion layer surrounding the solid contributes to higher dissolution rate of the salt.²²⁶ Increased solubility often leads to increased hygroscopicity, which compromises stability of a drug product. The assessment of chemical and physical stability of an API based on its susceptibility to absorb atmospheric water or moisture serves as a crucial measure of the drug's performance.²²⁷ The solubility of salts is directly influenced by lipophilicity of the chosen counterions, where an increase in lipophilicity leads to a decrease in solubility.³⁸ Hence, the evaluation of water-octanol partition coefficient is necessary. This is particularly relevant for local anaesthetics, as the drug diffusion in tissues depends on its partition coefficient.¹²⁷ With increased permeability, the overall API bioavailability can be enhanced. The intriguing interplay of these parameters governs the performance of a selected formulation design strategy.

Transdermal and topical drug delivery remains challenged by the impervious stratum corneum posing as a main barrier to absorption of most APIs. ILs have increasingly attracted attention as a strategy to enhance transdermal and cellular membrane permeability.^{175,228,229,15} It is well known that ionised drugs do not readily cross these barriers due to their lack of sufficient lipophilicity.^{127,44} However, ILs have a potential to cross membranes as hydrogen-bonded complexes or ion-pairs behaving like neutral species.^{229,230}

Moreover, high tunability of IL systems allows to select a counterion with the most desired properties to achieve a required solubility-lipophilicity balance.

The main aim of this study was to evaluate solubility, dissolution, lipophilicity, permeability and stability parameters of the previously synthesized and characterized systems incorporating lidocaine (LID) and a medium-chain dicarboxylic acid (DA) as a counterion to assess the adopted pharmaceutical formulation strategy discussed in Chapters 2 and 3. The molecular structures of LID and glutaric (C5), adipic (C6), pimelic (C7), suberic (C8) and azelaic (C9) DAs investigated are presented in **Scheme 5.1** and their relevant physicochemical properties are summarized in **Table 5.1**.

Scheme 5.1. Molecular structures of LID (left) and a general molecular structure of a DA (right), where n = number of carbon atoms in the backbone.

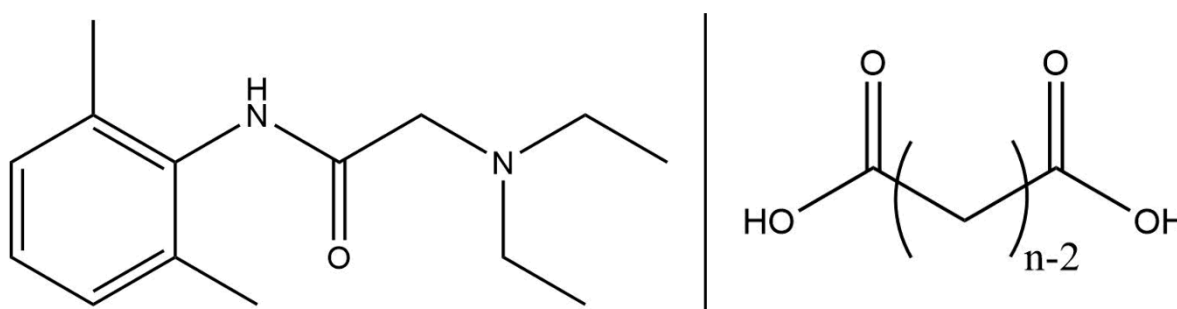


Table 5.1. Relevant physicochemical properties of LID and the series of DAs studied.

Parameter	LID	C5	C6	C7	C8	C9	Ref.
Molar mass (g/mol)	234.34	132.11	146.14	160.17	174.20	188.22	
Melting point (°C)	68	99	153	106	144	106.5	231,153
pK_a^*	8.0	4.34	4.41	5.50	4.53	4.55	121,232
Solubility (M, 25 °C)	2.0×10^{-2}	4.1	1.7×10^{-1}	3.9×10^{-1}	1.4×10^{-2}	9.5×10^{-3}	126
LogP	2.45	-0.29	0.08	0.61	0.69	1.57	233,234

* pK_a values for LID base and for the most acidic group of the dicarboxylic acid counterion.

5.2 Materials and Methods

5.2.1 Materials

Lidocaine (LID), lidocaine hydrochloride monohydrate, glutaric acid (C5), adipic acid (C6), pimelic acid (C7), suberic acid (C8), azelaic acid (C9), n-octanol, isopropyl myristate, silicon oil, disodium hydrogen phosphate dihydrate, magnesium chloride and sodium chloride were purchased from Sigma-Aldrich (Ireland). Hydrochloric acid 35%, citric acid anhydrous, potassium dihydrogen phosphate, phosphoric acid and sodium hydroxide were purchased from Penta (Czech Republic). Acetonitrile was obtained from J.T.Baker (US).

5.2.2 Methods

5.2.2.1 Sample preparation

IL samples were prepared via a mechanosynthetic process as described previously in Chapters 2 and 3.

5.2.2.2 Equilibrium solubility determination using shake-flask method

All pH measurements of the media used were performed using SevenCompact pH meter (Mettler Toledo, USA) equipped with InLab Expert pH electrode (Mettler Toledo, USA). Water was purified by Milli-Q IQ 7003/7005/7010/7015 fully-integrated water purification system. Excess solid of LID base and LID:DA mixtures were added to 0.5 mL of aqueous media in 2 mL Eppendorf vials. The vials were placed on an Eppendorf Thermomixer at 25 °C, 1000 rpm for 24 h. pH values of the solutions containing excess solid material were measured using SevenCompact pH meter (Mettler Toledo) equipped with InLab Micro Pro-ISM pH electrode (Mettler Toledo) after 24 h of incubation. The samples were diluted with HPLC mobile phase which was prepared at 60:40 ratio of acetonitrile:KH₂PO₄ pH 8.0 buffer adjusted with concentrated NaOH and analysed by Waters Alliance 2695 HPLC equipped with a Waters 2998 PDA detector on a ProntoSIL 120-3-C18 ace-EPS 150x3 mm column. The temperature of the column was maintained at 30 °C. The isocratic flow with 0.75 mL/min rate and detection at $\lambda = 220$ nm were used. Each sample was prepared in triplicate.

5.2.2.3 Intrinsic Dissolution Rate (IDR) determination

An attempt to measure Intrinsic Dissolution Rates of LID:DA systems was made. However, the applicability of the term IDR might be questionable for semiliquid samples. This is because the real surface area of the sample cannot be determined accurately. In addition, the dissolution rate is influenced by viscosity (as more liquid samples expose greater surface area faster). IDR measurements were performed using PION InForm (Pion, UK). The discs with defined surface of 0.07 cm² were prepared by compressing 8-15 mg of powdered

sample under a weight of 110 kg for 2 min using a manual hydraulic tablet press. The discs were visually examined to ensure their surfaces were free of visible defects. For liquid and semiliquid samples the disc preparation involved careful placement of 8-10 mg of sample inside the disc holder in order to fill the $d = 3$ mm cavity. The reverse side of the disc holder was stoppered with a rubber bung to prevent the exposure of the reverse side of the disc to the dissolution medium. The measurements were performed in 40 mL hydrochloric acid continuously adjusted to maintain pH=2.0 medium at 25 °C. The solution was stirred at 100 rpm. UV spectra were recorded at 30 s intervals using the 5 mm UV pathlength window and $\lambda = 214$ -308 nm detection range during 30 min run time. All measurements were performed in triplicate.

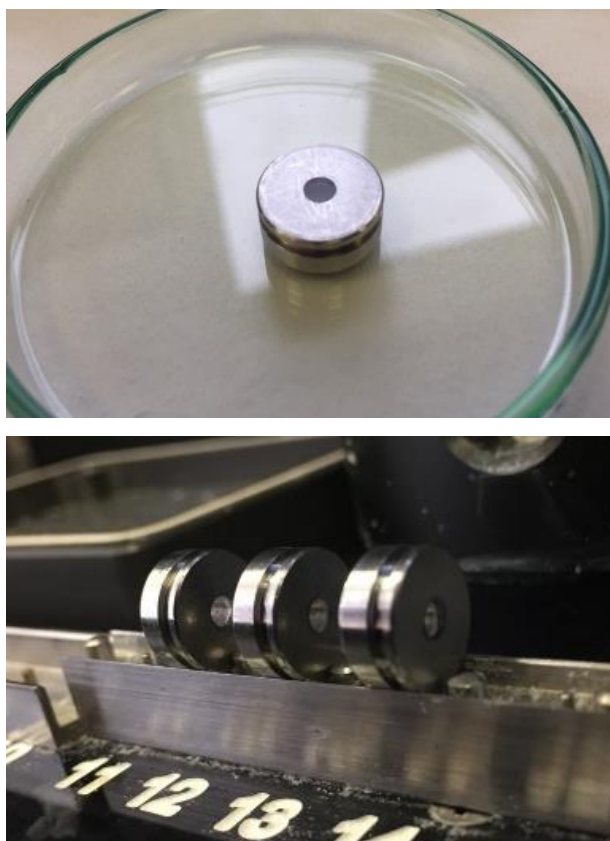


Figure 5.1. Photographs of the discs used in dissolution studies.

5.2.2.4 Powder X-Ray Diffraction (PXRD)

PXRD was performed by Dr Michal Simek, Zentiva, Czech Republic. PXRD was carried out at room temperature using PANalytical X'Pert Pro equipped with Cu K α radiation

(1.54 Å) X-ray source. The samples were scanned over a 2θ degrees range of 2–40° with a 0.017 2θ degrees step between the measured points.

5.2.2.5 *Dynamic Vapour Sorption (DVS)*

DVS measurements were performed with assistance of Dr Anita Umerska, TCD School of Pharmacy. DVS measurements were performed using an Advantage-1 automated gravimetric vapor sorption analyser (Surface Measurement Systems Ltd., U.K.) at a constant temperature of 25.0 ± 0.1 °C using water as the sorbing vapour. Samples weighing 20–35 mg were placed in a sample basket and were equilibrated at 0% relative humidity (RH) until a constant mass, defined as $dm/dt \leq 0.002$ mg/min, was attained. The sample mass change during the sorption-desorption cycle was then measured at 10% increments in the 0 and 90% RH range until a constant mass ($dm/dt \leq 0.002$ mg/min) or until the maximum step length (8 h) was reached. Following DVS analysis the samples were removed and analysed by PXRD as described in Chapter 2.

5.2.2.6 *Determination of distribution coefficient (LogD)*

LogD determinations were performed by Dr Anita Umerska, TCD School of Pharmacy. Samples were dissolved in PBS pH=7.4, which was previously equilibrated with either 1-octanol or isopropyl myristate to achieve a concentration of 5 mg/ml. The exception was lidocaine base, which showed lower solubility, and undissolved lidocaine base was separated from the aqueous phase by filtration (25 mm syringe filter, PTFE hydrophilic, 0.45 μ m; Fisher Scientific). An aliquot of 4 ml of the aqueous phase was then mixed with 4 ml of either 1-octanol or isopropyl myristate and equilibrated in a shaking bath at 25 °C at 100 rpm. After 24 hours the samples were left to stand for 1 hour and the aqueous phase was sampled, diluted suitably with the mobile phase and the amount of LID quantified by HPLC (Section 2.2.10 below). The equilibrated concentration in the organic phase was calculated as the difference between the total amount of LID used and the quantity of LID determined in the aqueous layer following equilibration.

5.2.2.7 *Parallel artificial membrane permeability assay (PAMPA)*

PAMPA analysis was performed by Dr Anita Umerska, TCD School of Pharmacy. A 96-well MultiScreen Filter Plate (Millipore Corporation, Billerica, MA, USA), with the underdrain removed, was used as the donor plate, and a 96-well MultiScreen Transport Receiver Plate (Millipore Corporation, Billerica, MA, USA) as the acceptor plate. An aliquot of 3.5 mL of the artificial membrane solution comprising 30% isopropyl myristate/70%

silicone (v/v) was transferred into a 10 mL volumetric flask and made up to the mark with n-hexane. Each well of the donor plate was coated with 17 μ L of the 35% (v/v) solution of the artificial membrane dissolved in n-hexane and left for 20 min to completely evaporate the solvent.²³⁵ Then, 0.3 ml of PBS pH=7.4 was added to each well of the acceptor plate and 0.2 ml of sample (5 mg/ml) were added to each well of the donor plate in triplicate. The donor plate was then placed into the acceptor plate and incubated at room temperature for 4 hours. Following incubation, the contents of each well of the acceptor plate was analysed by HPLC (Section 2.2.10 below).

5.2.2.8 Dynamic Light Scattering and Conductivity Measurements (DLS)

Zetasizer Nano ZS (Malvern Instruments, UK) equipped with Malvern Zetasizer v. 8.02 software was used to measure conductivity and hydrodynamic diameter of particles in saturated LID:DA aqueous solutions. The measurements were performed in DTS1070 disposable folded capillary cells at 25 °C and each sample was measured 7 times. Particle size was corrected for viscosity of the dispersant. Dynamic viscosity of the dispersant was measured at 25 °C using a Vibro Viscometer SV-10 (Japan).

5.2.2.9 Thermogravimetric Analysis (TGA)

TGA analysis was carried out as described in Chapter 3. Approximately 6-11 mg of each sample was accurately weighed into an open aluminium pan and subjected to a heating cycle from 25 °C to 300 °C at a rate of 10 K min⁻¹ under nitrogen as a purge gas.

5.2.2.10 HPLC method for LID determination following logD and PAMPA experiments

HPLC analysis was performed by Dr Anita Umerska, TCD School of Pharmacy. The amount of LID was measured with a Waters Alliance 2695 Separations Module (Milford, Massachusetts, USA). A Capcell Pak SG120 C18 column, with a length of 250 mm, internal diameter of 4.6 mm and 5 μ m particle size (Shiseido, Tokyo, Japan) was used. The instrument was controlled by Empower® 3 software. The mobile phase consisted of two phases: acetonitrile and 0.1% v/v solution of trifluoroacetic acid (TFA) in water. Standard solutions of LID were prepared in the mobile phase. An injection volume of 10 μ l and a gradient flow (**Table 5.2**) with a rate of 1.0 ml/min was used. The separation was carried out at room temperature. A Waters 2487 dual λ absorbance detector at 208 nm was used to detect LID and the drug had a retention time of 18.3 min.

Table 5.2. Gradient conditions for the HPLC method (flow rate of 1 ml/min was used).

Time (min)	0.1% v/v TFA in water	Acetonitrile
	70	30
5	70	30
20	30	70
25	30	70
30	70	30
36	70	30

5.2.2.11 Statistical analysis

Statistical analysis was performed using Origin version 7.5 software. Data was analysed using two-sample t-tests. Significance levels were denoted as: *** for $p < 0.001$, ** for $p < 0.01$, * for $p < 0.05$ and *ns* for non-significance.

5.3 Results and Discussion

5.3.1 Equilibrium solubility study

Sample preparation and physicochemical characterisation has been reported previously in Chapters 2 and 3. In summary, a series of ionic liquids and one conventional salt of LID with DAs have been synthesised. The ionic liquids in a liquid supercooled state at 1:1 LID:DA compositions were lidocainium hemiglutarate (LID:C5), lidocaininum hemipimelate (LID:C7), lidocaininum hemisuberate (LID:C8) and lidocainium hemiazelate (LID:C9). In addition, a 1:1 conventional salt lidocainium hemiadipate (LID:C6) was included in the study to complete the series for comparative purposes. A cocrystal incorporating lidocaine:azelaic acid at 2:1 molar composition (2LID:C9) which was described in Chapter 3 has been included in the determination of distribution coefficient, permeability and hygroscopicity. Other LID:C9 multicomponent forms, as identified in previous chapters, have not been included in this study.

Equilibrium solubility of LID forms was determined for LID base and 1:1 LID:C6 and LID:C8 samples. The solubility study was performed in ultrapure water. Upon addition of excess amounts of the sample, changes in pH of the media were observed immediately.

Table 5.3. Equilibrium solubility results in ultrapure water.

Sample	Final pH	Solubility mg/ml	Solubility M
<i>LID base</i>	9.4 ± 0.2	3.66 ± 0.16	0.02 ± 0.000
<i>LID:C6</i>	4.7 ± 0.0	73.41 ± 0.10	0.31 ± 0.004
<i>LID:C8</i>	5.2 ± 0.0	82.36 ± 0.61	0.35 ± 0.003

An experiment was set up for the ILs with odd dicarboxylic acids (LID:C5, LID:C7 and LID:C9), where the amount of sample was added to reach 1M target concentration. Upon addition of this amount viscous liquid samples were obtained with no solid precipitation visible after 24 h of incubation, as seen in **Figure 5.2**. Increased solubility of the low melting ILs likely stems from weak intermolecular interactions between the components.¹¹⁰ Consequently, saturated solutions could not be obtained due to complete IL-water miscibility. This observation is in agreement with previous studies of multicomponent systems incorporating a series of dicarboxylic acids, where systems with odd dicarboxylic

acids exhibited higher solubility than their even counterparts as a result of strained geometry and higher lattice energy in the solid state.¹⁹⁸

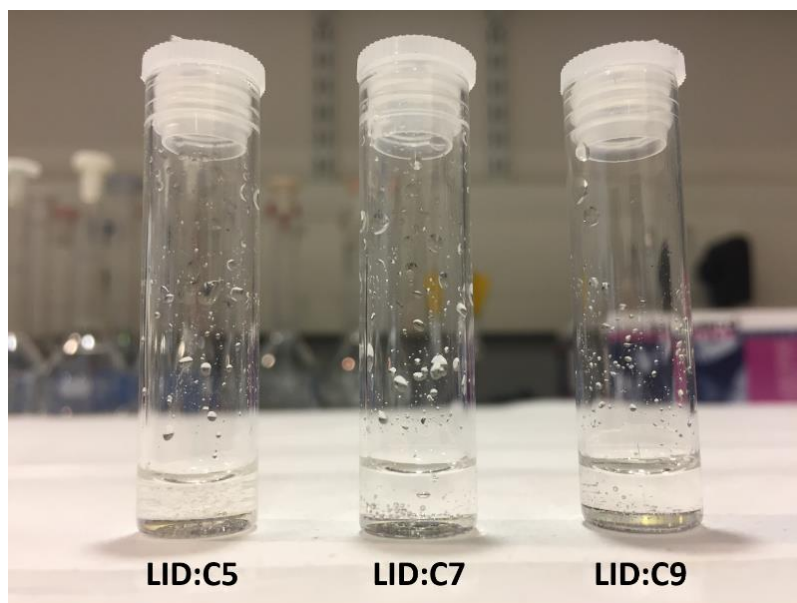


Figure 5.2. Viscous liquid samples of LID:C5, LID:C7 and LID:C9 at 1M concentration exhibiting IL-water miscibility.

The solubility study results presented in **Table 5.3** reveal that LID solubility is greatly improved when prepared as LID:DA salts. The solubility values were corrected as equivalent to the solubility of LID base and were determined to be 73.41 ± 0.10 mg/ml and 82.36 ± 0.61 mg/ml for LID:C6 and LID:C8, correspondingly. However, PXRD diffractograms of the solid precipitate collected following the solubility study have revealed a different sample behaviour in solution; the PXRD patterns identified were attributed to the intact LID:C6 salt and disproportionated precursor C8 dicarboxylic acid, see **Figure 5.3**. Considering PXRD diffractograms of the freshly-ground LID:C8 systems presented in Chapter 2 and the aqueous behaviour reported here it is suggested that upon dissolution the LID:C8 system adopts a more favourable 2:1 stoichiometry and excess C8 acid being the least soluble species precipitates out of the solution. The formation of a cocrystal at this stoichiometry is probable and a similar system has been reported in the LID:C9 mixtures in Chapter 3. Unfortunately, no single crystal of adequate quality suitable for single crystal XRD of the 2:1 LID:C8 system was obtained.

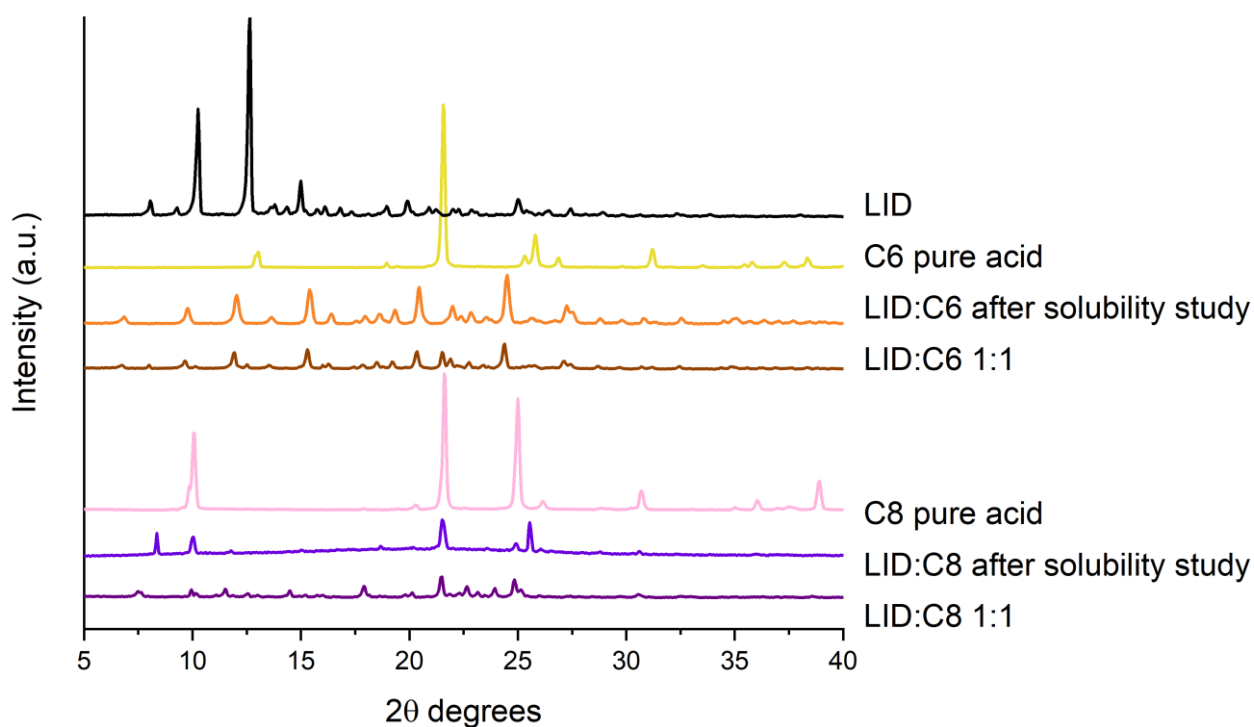


Figure 5.3. PXRD diffractograms of the solid precipitate collected after the solubility study of LID:C6 and LID:C8.

DLS analysis was performed to determine whether aggregation has an influence on the solubility/ dissolution behaviour of LID:DA systems in aqueous media. Measurement of the hydrodynamic diameter (D_h) in saturated LID:DA solutions did not reveal any effect of changing counterion on aggregate formation, see **Table 5.4**. The D_h values of all the samples are not statistically significantly different with only LID:C9 exhibiting slightly larger D_h . Solution conductivity measurements have only revealed a decreasing conductivity trend with increasing carbon chain length of the dicarboxylic acid. The data obtained does not provide any evidence for the systems' self-association and formation of aggregates in saturated or highly concentrated aqueous IL solutions.

Table 5.4. DLS and conductivity data obtained for the saturated LID:DA aqueous samples.

Sample	Hydrodynamic diameter, D_h (nm)	Conductivity (mS/cm)
LID:C5	1.161 ± 0.495	9.46 ± 0.22
LID:C6	1.165 ± 0.433	8.20 ± 0.16
LID:C7	1.510 ± 0.511	7.65 ± 0.17
LID:C8	1.308 ± 0.415	6.25 ± 1.07
LID:C9	4.074 ± 2.484	6.07 ± 0.14

5.3.2 Intrinsic dissolution rate measurements

Dissolution tests were performed for LID base, LID HCl and equimolar mixtures of LID:C5, LID:C6, LID:C7, LID:C8 and LID:C9. The experiment was designed with a low target concentration to attain sink conditions in order to mitigate solubility constraints. Aqueous dissolution medium at pH=2 was chosen to investigate dissolution in salt form and to prevent conversion to the free base form. Intrinsic dissolution rates (IDR) rates were derived using zero-order kinetics model applied to the first linear part of the dissolution curve using zero order type calculation (**Equation 6**) and are presented as the weight of the dissolved substance in μg (m) per unit time in min (t) per unit area in cm^2 (A_{disc}).²³⁶

$$IDR = \frac{dm}{dt} \frac{1}{A_{disc}} = V \frac{dc}{dt} \frac{1}{A_{disc}} \quad (\text{Eq.6})$$

Where V is the volume of the medium in mL and dc/dt denotes the slope of the linear part of the dissolution profile. The results are presented in **Table 5.5**. It is important to note that the IDR is measured as a function of a defined unit area of a disc. This means that the unit area must remain constant during the first linear part of the dissolution profile. Experimentally, it is facilitated by pressing solid powder into a disc with a defined radius using a hydraulic press. However, such method is not applicable to liquid and semi-liquid samples. A careful placement of a sample into the sample holder cavity as described in the methods section was deemed adequate as the samples were not displaced upon handling and a defined unit area was exposed to the dissolution medium. Nonetheless, one must be careful when defining the dissolution rates of liquid samples as intrinsic.

The results presented in **Table 5.5** reveal that the IDR values of the LID:DA salts were considerably greater as compared to LID base. The greatest dissolution rate improvement was achieved with LID:C5 where the IDR was increased 9-fold when compared to the free base form. The least increase was observed in the dissolution of LID:C6 which only improved 3-fold when compared to the free base form. In addition, it was observed that IDR values alternate with DAs chain length. The IDRs of the solid salts were lower as compared to liquid ILs. Note, that LID:C9 exhibits a greater standard deviation due to the sample being the most liquid out of the whole range. However, upon visual examination the sample occupied the disc holder cavity with a defined diameter without being displaced.

Table 5.5. IDR results.

Sample	IDR ($\mu\text{g}/\text{min}/\text{cm}^2$)	IDR enhancement over LID base
<i>LID base</i>	34.3 ± 0.80	-
<i>LID:C5</i>	304.5 ± 8.63	9-fold
<i>LID:C6</i>	112.4 ± 2.96	3-fold
<i>LID:C7</i>	183.1 ± 3.63	5-fold
<i>LID:C8</i>	151.9 ± 1.77	4-fold
<i>LID:C9</i>	212.0 ± 26.74	6-fold

The observed alternating trend in the dissolution rates can be explained by simple diffusion model consisting of an API surface, surrounded by a thin aqueous boundary layer (ABL) and the bulk solution.⁴⁴ The dissolution of a drug within the API and ABL interface is initiated by the breaking of intermolecular interactions within the salt structure and the ease with which these interactions are broken is correlated with the crystallinity of the solid substance.¹¹² In general, it has been shown that counterions which facilitate the formation of low-melting salts with reduced packing efficiency and lattice enthalpy lead to the improvement in the dissolution rates.¹¹² Therefore, odd ILs which are liquid or semiliquid at room temperature exhibit higher IDRs compared to highly crystalline even counterparts. The trend observed in the LID:DA range is in agreement with other multicomponent systems incorporating dicarboxylic acid counterions. For example, berberine:dicarboxylic acid cocrystals follow a similar odd-even alternating trend in dissolution values, where

berberine:glutaric acid and berberine:pimelic acid exhibit faster dissolution rates compared to berberine:succinic acid and berberine:adipic acid systems.²³⁷

5.3.3 Determination of distribution coefficient

Drugs intended for use in topical formulations need to possess a suitable solubility balance between the water and oil phase to effectively permeate through the lipophilic stratum corneum layer of the skin barrier. Partitioning of a drug within biphasic oil-aqueous solubility media allow to measure its partitioning coefficient (LogP) between the two phases as an indicative assessment of drug permeability.²³⁸ In order to study and determine the partition coefficient of a drug water or PBS buffer are generally used to mimic the underlying hydrophilic cells of the epidermis, while organic solvents, such as octanol, hexanol or isopropyl myristate are employed to mimic the lipophilic stratum corneum.²³⁹ It is important to note that while partitioning coefficient of neutral molecules is denoted as LogP, ionisable molecules can partition either in their neutral forms or in an ionised state. Therefore, it is preferable to report their partitioning coefficient values as an apparent LogP, or a distribution coefficient LogD. The logP value can be used as an indication of a suitability of a drug to be used for transdermal applications. It has been proposed that drugs with a LogP falling in the range of $-1 < \text{LogP} < 2$ or $1 < \text{LogP} < 3$ exhibit both hydrophilic and lipophilic properties sufficient enough to obtain effective transdermal permeation, crossing both, the lipophilic and hydrophilic layers of the skin.²³⁹ It has been shown that counterion or coformer selection for multicomponent system synthesis allows to tune drug lipophilicity.²⁴⁰

Due to LID being an ionisable molecule, the partitioning of LID between aqueous and lipophilic phases is reported as LogD values. The measurements were performed in two systems using PBS as the aqueous phase and *n*-octanol and isopropyl myristate as lipophilic phases. *n*-octanol has been used as a standard organic medium for partitioning experiments because the octanol–water partition coefficient ($\log P_{o/w}$) is an important parameter for modelling biological membranes. Isopropyl myristate possesses polar and nonpolar domains that mimic complex semipolar matrix nature of human skin making it a suitable model for skin/transdermal absorption studies.²⁴¹ The results of the measurements are reported in **Table 5.6**.

Table 5.6. Distribution coefficient values determined in octanol-PBS pH7.4 and isopropyl myristate-PBS pH7.4 systems.

Sample	LogD octanol-PBS pH7.4	LogD isopropyl myristate-PBS pH7.4
<i>LID</i>	1.31±0.033	1.19±0.010
<i>LID HCl</i>	-0.08±0.052	-0.12±0.012
<i>LID:C5</i>	0.01±0.035	0.01±0.035
<i>LID:C6</i>	0.07±0.040	0.19±0.088
<i>LID:C7</i>	0.08±0.020	0.13±0.033
<i>LID:C8</i>	0.06±0.057	0.18±0.041
<i>LID:C9</i>	0.16±0.041	0.15±0.074
<i>2LID:C9</i>	0.41±0.061	0.24±0.016

The measurements performed in both *n*-octanol-PBS pH7.4 ($\text{LogD}_{\text{o/PBS}}$) and isopropyl myristate-PBS pH7.4 ($\text{LogD}_{\text{IPM/PBS}}$) systems revealed that the LogD values for the LID:DA systems were found between the values of LID base and LID HCl, see **Table 5.6**. LID:C5 exhibited the lowest LogD value of 0.1 ± 0.035 in both media systems and 2LID:C9 cocrystal exhibited the highest values of $\text{LogD}_{\text{o/PBS}}$ 0.41 ± 0.061 and $\text{LogD}_{\text{IPM/PBS}}$ 0.24 ± 0.016 . It appears that the $\text{LogD}_{\text{o/PBS}}$ values of the LID:DA systems follows an increasing trend as a function of increasing acid chain length. This trend is also observed in the LogP values of the parent dicarboxylic acids presented in **Table 5.1**. In contrast, $\text{LogD}_{\text{IPM/PBS}}$ values follow an alternating trend with even LID:DA systems exhibiting slightly higher distribution coefficient values. Statistical analysis of the results obtained indicates that the $\text{LogD}_{\text{o/PBS}}$ values determined for all of the LID:DA systems were statistically significantly different compared to LID base ($p<0.001$). This indicates that formation of LID:DA systems results in a decrease in lipophilicity that may affect membrane transport of LID. However, the decrease in lipophilicity is statistically significantly lower compared to LID HCl salt. Statistical analysis presented in **Table 5.7** shows that $\text{LogD}_{\text{o/PBS}}$ values of the LID:DA systems, with the exception of LID:C5, are significantly higher in comparison to LID HCl. These results suggest that LID:DA should be able to penetrate biological membranes more effectively than LID HCl salt which is commonly used in commercial LID formulations. Similar results were obtained in the isopropyl myristate-PBS pH7.4 media, where all of the LID:DA systems exhibited $\text{LogD}_{\text{IPM/PBS}}$ values significantly different from both, LID and LID HCl, see **Table 5.8**.

These results suggest that formation of LID:DA systems allows to achieve enhancement of aqueous solubility of LID and simultaneously, maintain suitable lipophilicity for effective membrane transport. The values obtained are within the proposed lipophilicity ranges making the systems suitable candidates for transdermal delivery of LID.

Table 5.7. Statistical analysis of the distribution coefficient values determined in octanol-PBS pH7.4.

Sample	LogD octanol-PBS 7.4	Level of significance
<i>LID</i>	p<0.001	***
<i>LID HCl</i>	(against LID HCl)	
<i>LID:C5</i>	p=0.077	ns
<i>LID:C6</i>	p=0.019	*
<i>LID:C7</i>	p=0.022	*
<i>LID:C8</i>	p=0.035	*
<i>LID:C9</i>	p=0.004	**
<i>2LID:C9</i>	p<0.001	***

Table 5.8. Statistical analysis of the distribution coefficient values determined in isopropyl myristate-PBS pH7.4.

Sample	LogD isopropyl myristate-PBS 7.4	Level of significance	LogD isopropyl myristate-PBS 7.4	Level of significance
<i>LID</i>	(against LID)		p<0.001	***
<i>LID HCl</i>	p<0.001	***	(against LID HCl)	
<i>LID:C5</i>	p<0.001	***	p=0.015	*
<i>LID:C6</i>	p=0.002	**	p=0.024	*
<i>LID:C7</i>	p<0.001	***	p=0.003	**
<i>LID:C8</i>	p<0.001	***	p=0.004	**
<i>LID:C9</i>	p=0.001	***	p=0.022	*
<i>2LID:C9</i>	p<0.001	***	p<0.001	***

5.3.4 Skin-PAMPA Permeability Study

Skin parallel artificial membrane permeability assay (skin-PAMPA) was chosen to evaluate the API's transdermal penetration by passive diffusion. The original skin-PAMPA model incorporating a membrane consisting of 30% isopropyl myristate and 70% silicon oil was employed.²⁴² This model has previously demonstrated a good correlation between the effective permeability coefficients (P_e) measured by skin-PAMPA and the corresponding human skin permeability coefficient values (K_p) available from a validated database.²⁴³ Moreover, it has also been demonstrated that various skin-PAMPA models are suitable

alternatives to the standard vertical diffusion cell assay for assessing skin permeability of formulations intended for topical application.^{244–247}

The commercially available LID HCl was included in the study for comparison. The P_e , $\text{Log}P_e$ and their corresponding final pH values determined for the samples studied are presented in **Table 5.9**. As seen in **Table 5.9**, the values were influenced by pH, thus direct comparison of the data must be carefully considered. The P_e values indicate significantly lower permeability of the LID:DA mixtures when compared to the permeability of LID base. Equimolar LID:DA systems exhibit low permeability ranging from $0.340 \pm 0.015 \times 10^{-6}$ cm/s for LID:C7 to the lowest value of $0.111 \pm 0.008 \times 10^{-6}$ cm/s for LID:C5, according to a benchmark classifying permeability of $< 1 \times 10^{-6}$ cm/s as low.²⁴⁸ The permeability of 2LID:C9 cocrystal is higher than for the equimolar mixtures but is only slightly enhanced compared to LID HCl with P_e of $7.808 \pm 0.369 \times 10^{-6}$ cm/s and $6.404 \pm 0.146 \times 10^{-6}$ cm/s for 2LID:C9 and LID HCl, respectively.

Table 5.9. PAMPA permeability values of LID base, LID HCl and LID:DA samples. P_e - effective permeability.

Sample	$P_e \times 10^{-6}$ (cm/s)	$\text{Log}P_e$	pH
<i>LID Base</i>	39.280 ± 3.373	-4.407 ± 0.036	8.7
<i>LID HCl</i>	6.404 ± 0.146	-5.194 ± 0.010	6.8
<i>LID:C5</i>	0.111 ± 0.008	-6.955 ± 0.031	5.0
<i>LID:C6</i>	0.279 ± 0.015	-6.555 ± 0.024	5.3
<i>LID:C7</i>	0.340 ± 0.015	-6.469 ± 0.020	5.4
<i>LID:C8</i>	0.321 ± 0.053	-6.500 ± 0.077	5.4
<i>LID:C9</i>	0.326 ± 0.053	-6.492 ± 0.074	5.4
<i>2LID:C9</i>	7.808 ± 0.369	-5.108 ± 0.021	6.9

There is a wide range of factors that affect the permeability of multicomponent phases comprising an API and a counterion through a membrane. These include, but are not limited to, a degree of ionisation of ionisable APIs, lipophilicity, molecular weight of counterions, choice of medium.^{15,249,250} It appears that the results obtained for the sample set investigated are consistent with the pH partition hypothesis which suggests that only unionised drugs can permeate lipid membranes.²³⁰ Consequently, a correlation between the measured pH value and observed permeability might be drawn. Counterions, such as C5, which caused the greatest decrease in pH also caused the greatest decrease in LID

permeability. These observations are consistent with other studies that established a correlation between the pH of the medium, i.e. the amount of ionised and unionised species, and permeability of lidocaine salts.²⁵¹

It is important to note that skin-PAMPA may serve as a very useful primary permeability screen during early drug development, however, it tends to underestimate permeability as it does not take into account active transport of a substance through a membrane. This consideration is particularly applicable to local anaesthetics, as their local effects have been attributed to their interactions with membranes.^{127,252} Therefore, other permeability assays also need to be considered.

5.3.5 Thermal stability

A series of TGA measurements were performed to assess thermal stability of the LID:DA systems. The TGA plots in **Figure 5.4A** show very similar decomposition profiles for LID base and all of the multicomponent mixtures studied. $T_{5\%onset}$ values presented in **Figure 5.4B** do not display any significant deviation. It is possible to conclude that the choice of the counterion from the DA series does not affect thermal stability significantly. Only a slight zig-zag trend in thermal stability data has been observed. However, a slightly higher degradation of the LID:C5, LID:C7 and LID:C9 systems could have been observed due to their liquid nature and a higher moisture content as demonstrated by DVS analysis (*vide infra*).

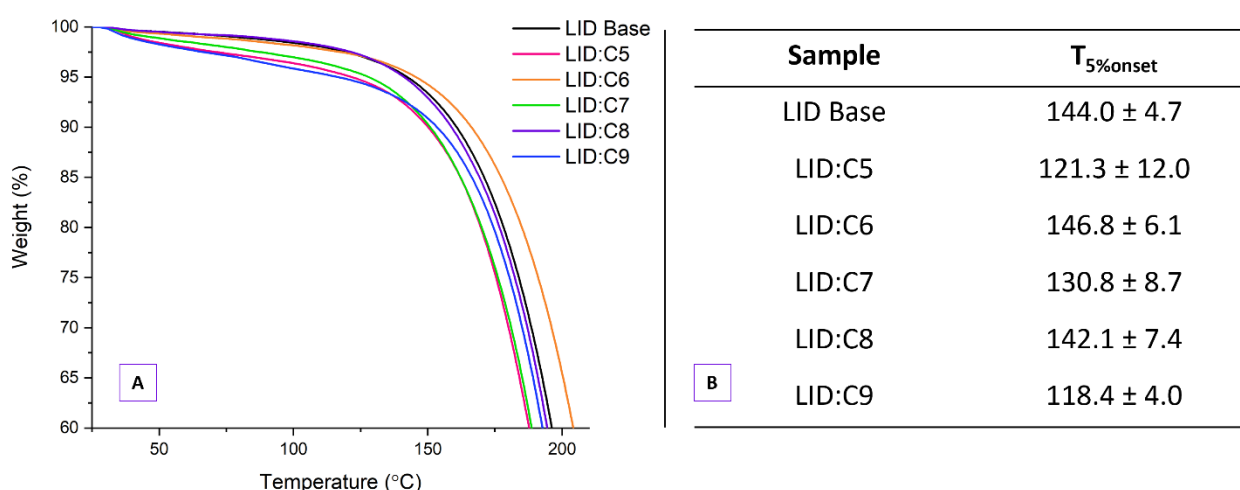


Figure 5.4. A: TGA decomposition profiles of the LID:DA systems. B: $T_{5\%}$ onset values for sample degradation determined by TGA.

5.3.6 Hygroscopicity

Another parameter that critically influences stability, solubility and dissolution rates of multicomponent phases is hygroscopicity.^{38,118} Hygroscopicity is defined as a measure of the tendency for a substance to take up water vapour from the atmosphere at constant temperature with changes in relative humidity (RH).¹¹⁸ DVS isotherms for the LID:DA systems analysed are presented in **Figure 5.5**. Vapour sorption behaviour of all of the LID:DA systems is characterised by similar concave type III sorption-desorption isotherms according to the BDDT classification system.²⁵³ The concave shape along the entire % RH range presents a characteristic low uptake at low vapour concentration and a strong increase in sorption at higher vapour concentration. In addition, all samples also exhibit hysteresis which arises as a result of retardation of vapour desorption. It arises when vapour diffuses into the bulk more quickly than it returns to the surface. Consequently, at the specified RH level, a greater amount of moisture will be present during desorption, resulting in the appearance of hysteresis. Hysteresis is commonly observed in amorphous or porous materials as vapour can permeate more readily into the bulk. Upon completion of the sorption/desorption loop all samples, with the exception of LID:C5, have approached 0% mass change indicating their return to the initial state. The mass change for LID:C5 was 1.9% indicating that some moisture was retained in the sample.

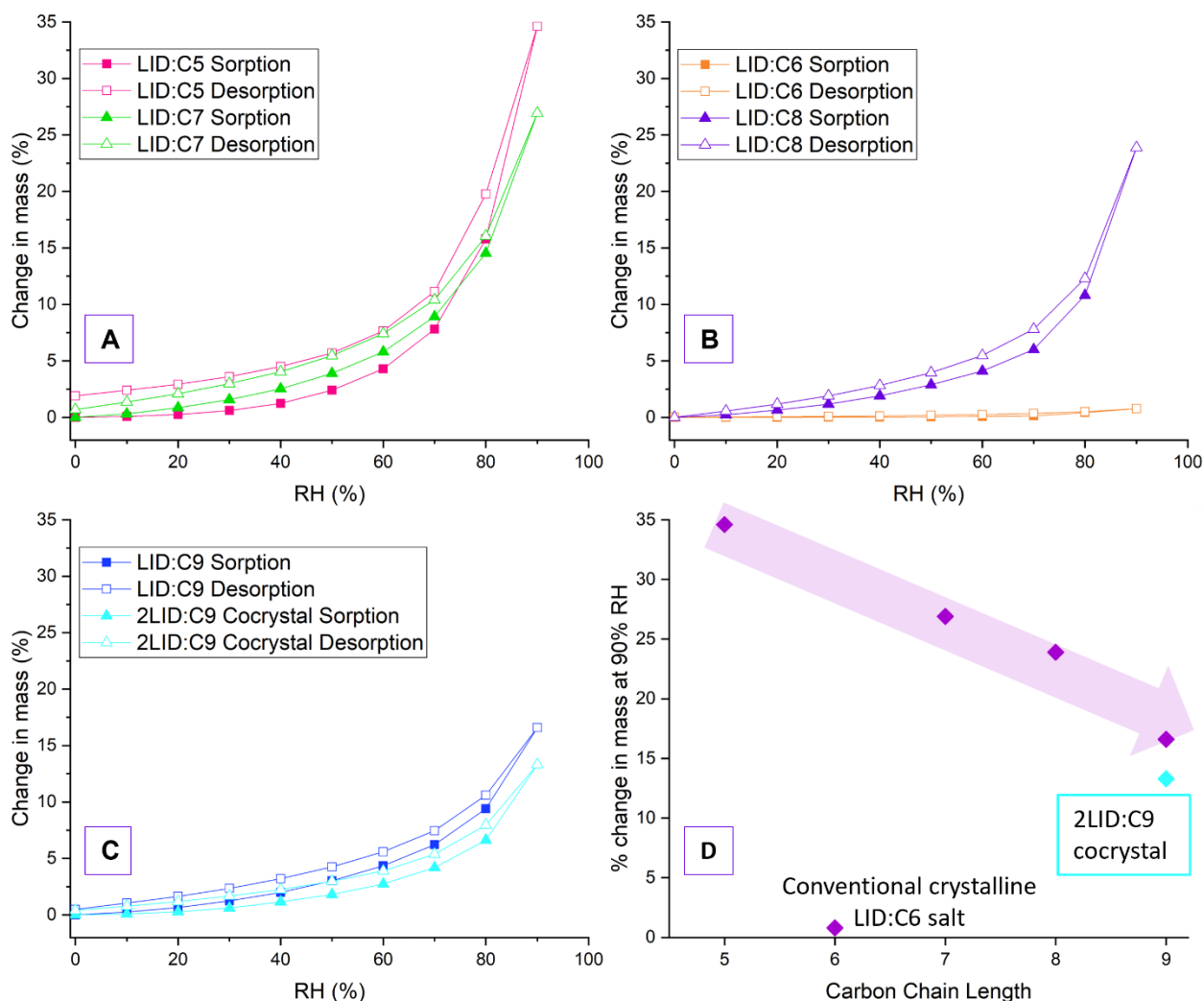


Figure 5.5. Moisture sorption data presented as plots of change in mass (%) as a function of relative humidity (%) for A: LID:C5 and LID:C7; B: LID:C6 and LID:C8; C: LID:C9 and 2LID:C9 cocrystal. D: a trend in change in mass at 90% RH observed as a function of carbon chain length.

From the selection of the LID:DA systems studied here it is evident that the choice of a counterion greatly influences their water sorption propensity. **Table 5.10** highlights a great variation in the change of mass observed upon reaching 90% RH as a function of the carbon chain length of the DAs. All ILs and 2LID:C9 cocrystal display high vapour sorption. The change in mass for the LID:C5 IL was the highest at 34.6%. In contrast, LID:C6 conventional salt displays the lowest vapour sorption at 0.8% mass change. Generally, highly soluble salts, ILs and amorphous materials exhibit high degree of hygroscopicity as moisture can easily permeate into the bulk of the substance. This is in contrast to crystalline and poorly-soluble substances, for which moisture adsorption is limited to the solid surface.³⁸ As

evident from **Figure 5.5**, the LID:DA series, with the exception of the LID:C6 conventional salt, follow a general trend of decreasing vapour sorption propensity with increasing DA carbon chain length. This observation is in agreement with a correlation discerned by Wiest et al., wherein an increased counterion lipophilicity was linked with a reduced vapour sorption.²⁵⁴ Specifically, counterions with longer alkyl chains exhibited lower hygroscopicity.

Table 5.10. DVS measurement of the mass change (%) values obtained at the end of sorption (25 °C/ 90% RH) and desorption (25 °C/ 0% RH) cycles for the samples investigated.

Sample	Mass change (%) at 25 °C/ 90% RH	Mass change (%) upon desorption to 25 °C/ 0% RH
<i>LID:C5</i>	34.6	1.9
<i>LID:C6</i>	0.8	0.0
<i>LID:C7</i>	26.9	0.7
<i>LID:C8</i>	23.9	0.0
<i>LID:C9</i>	16.6	0.5
<i>2LID:C9</i>	13.3	0.4

All samples were subjected to PXRD analysis following the DVS cycles. A stack of diffractograms presented in **Figure 5.6** reveals unchanged solid forms of LID:C6 conventional salt and LID:C7 and LID:C9. LID base has precipitated from LID:C5 IL, LID:C6 salt and 2LID:C9 cocrystal. Precipitation of LID base from the 2LID:C9 cocrystal was observed due to higher solubility of the LID:C9 IL form with LID base precipitating out as excess. LID:C8 IL is crystalline solid at room temperature, however, upon exposure to moisture it has dissolved and did not crystallise due to very slow crystallisation kinetics.

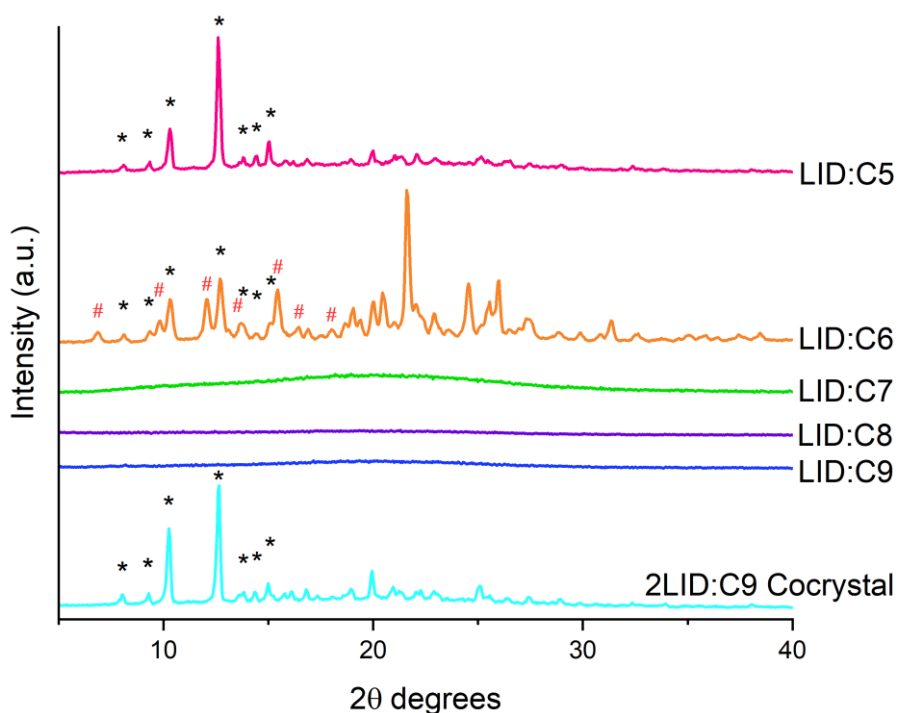


Figure 5.6. PXRD analysis of the samples removed after the completion of the DVS sorption-desorption cycle. Stars indicate peaks attributed to LID and hashes indicate peaks attributed to LID:C6 salt.

5.4 Conclusions

Multicomponent phase approach may be efficiently used to modulate or improve API's pharmaceutical performance parameters, including solubility, dissolution, lipophilicity, permeability and hygroscopicity. The preparation of LID:DA multicomponent phases has proven to be an effective strategy to increase solubility of poorly soluble LID. Even dicarboxylic acid systems LID:C6 and LID:C8 displayed a significant increase in aqueous solubility of LID when compared to LID base, while odd systems LID:C5, LID:C7 and LID:C9 were completely miscible with water. The intrinsic dissolution rates of LID were also increased when prepared as LID:DA systems with LID:C5 exhibiting the greatest enhancement over LID base. All systems have also displayed favourable lipophilicity for transdermal drug delivery. Low skin model membrane permeability may provide counterbalance to extremely high solubility by increasing drug residence time on skin. All LID:DA systems with the exception of the LID:C6 conventional solid crystalline salt have exhibited high degree of moisture sorption which may impact their stability. However, further stability studies are required to assess the effects of moisture sorption on the LID:DA systems. Overall, all systems appear to be suitable candidates for further formulation steps and skin permeability assays.

Chapter 6: General Discussion

6.1 General discussion and conclusions

The main aim of this project was to investigate multicomponent phase formation of LID with a series of dicarboxylic acids to contribute to the pool of current knowledge concerning structure-property relationship of multicomponent phases, mainly ionic liquids and salts. The emphasis was placed on determining the correlation between the physicochemical and solid state properties of parent materials and their corresponding products. The data presented in Chapters 2-5 demonstrate that the aims were generally achieved. Detailed discussion of achievements and shortcomings is presented in this chapter.

Chapter 1 presents a brief overview of the main aspects relating to the research of multicomponent phases for pharmaceutical outcome enhancement. Mechanochemical synthesis is discussed as one of the possible routes of multicomponent phase synthesis. However, it is important to remember that not all systems can be synthesised via mechanochemical activation. Also, mechanochemical synthesis tends to yield incomplete interconversion and many systems cannot be annealed due to poor thermal stability of certain precursor APIs. Therefore, solution synthesis cannot be disregarded. Prediction of a possibility to synthesise a new phase by mechanochemistry requires a thorough understanding of the solid-state reactivity. There is a wide spectrum of phases that can be synthesised. Chapter 1 presents a selection of different types of multicomponent phases that were obtained in the current work. This list is not exhaustive and new types of multicomponent phases are being discovered continually. Ultimately, the driving force for the multicomponent phase research is enhancement of the pharmaceutical outcome. Relevant pharmaceutical attributes in terms of solubility, dissolution and stability were discussed in this work.

Braga et al.¹²³ have reported a successful synthesis of LID:DA salts with oxalic, fumaric, malonic, and succinic acids, which served as a stepping stone for the current work. They have obtained conventional salts with a high melting point via water-assisted grinding and solution synthesis. According to the principles of anti-crystal engineering, the use of dicarboxylic acids that are further along the carbon chain length series should yield new salt formation with less than ideal crystal packing; thus, characterised by a lower melting point. Consequently, a series of counterions were selected for the synthesis of multicomponent phases with LID with the overall aim to understand how protonics, intermolecular interactions, crystalline and solid-state properties influence multicomponent phase formation. The investigation presented in Chapter 2 was initiated by identification and optimisation of mechanochemical reaction conditions. It was identified that LID:DA

multicomponent phases with C5, C7 and C8 counterions may be formed upon solvent-free neat grinding at room temperature as corroborated by PXRD, DSC and FTIR analysis. POM has provided further evidence that LID with odd DAs interact upon physical contact even without exertion of mechanical force. In contrast, LID:C6 mixtures had to be annealed to initiate crystallisation of the LID:C6 salt. One of the aims of Chapter 2 was to gain insight into solid-state reaction pathways. It was observed that solid-state reactivity in the LID:C5, LID:C7 and LID:C8 systems proceeds through eutectic formation followed by parent material interdiffusion within the eutectic matrix. DSC analysis of the binary mixtures has revealed that T_m of the new phases formed follow a matching alternating trend as in the T_m of the parent DAs. This trend suggests that thermal behaviour of the counterions used in LID binary systems has a direct effect on the thermal behaviour of the API. The combination of PXRD, FTIR and SXRd analytical techniques have allowed to characterise and classify the new phases. Ultimately, mechanochemical synthesis resulted in the formation of lidocainium glutarate, lidocainium adipate, lidocainium pimelate and lidocainium suberate salts. Thermal and dynamic behaviour of supercooled LID:DA systems was also investigated. The presence of glass transition events in most mixtures imply the ability of the systems to be supercooled. An alternating trend in T_g values across the DA series for the equimolar compositions of all of the LID:DA mixtures was noted. Supercooled states of the LID:C5 and LID:C7 samples were examined in greater detail as these systems exhibit a clear maximum T_g at equimolar compositions indicating the highest degree of ionicity at 1:1 stoichiometry. Analysis of the Walden Plot has shown that the conductivity of these systems increases as the temperature is decreased. This observation is representative for conductivity that is facilitated by the Grotthuss mechanism, i.e. fast proton hopping through H-bond network. Successful isolation of single crystals for the systems synthesised has allowed SXRd analysis to be performed and the data obtained was thoroughly examined to discern possible correlation between parent materials and corresponding products. The alternating trends in physicochemical properties of the binary systems were correlated with the T_m and conformational strain in the parent DAs. Another peculiar trend was observed in conformational changes of the DAs. It was found that longer DAs needed to be distorted from the equilibrium conformation to a greater extent in order to fit LID molecule for effective intermolecular interactions to form. The work discussed in Chapter 2 has enhanced current understanding of the mechanisms of ILs formation and achieved the aim of contributing towards devising a systematic approach for IL discovery and development.

Chapter 3 has focused on further investigation and fine-tuning of physicochemical properties of acid-base multicomponent systems by varying stoichiometric ratios of the components. LID and C9 counterions were chosen for the study and the synthetic method employed was identical to the method optimised previously. POM has demonstrated that LID and C9 undergo solid-state reactivity upon contact formation, similar to the LID:C5 and LID:C7 systems discussed in Chapter 2. Varying stoichiometric ratios of the components has significantly altered physicochemical properties of the mixtures. It was shown that increasing molar fraction of C9 has led to increased thermal stability of the LID:C9 system. In-depth investigation corroborated by DSC, PXRD, FTIR and SXRD analysis has shown that varying molar fraction of the components leads to formation of stoichiometric and non-stoichiometric ionic liquid and cocrystal multicomponent phases. Cocrystal formation was obtained in LID-rich samples, while acid-rich compositions yielded IL formation. A LID:C9 sample comprising counterions at 1:1 ratio resulted in a mixture of crystallised cocrystal and IL phases due to a sensitive equilibrium, where the identity of phase formation depends on sample preparation and storage variables. Different combinations of sample preparation and storage parameters were trialled which led to a range of possible outcomes, including molten ILs, impure polycrystalline solid and semi-solid samples and crystallisation of solid phases. DSC and FTIR investigation of the system in the supercooled state has shown that 1:1 stoichiometric ratio contains the highest concentration of ionised species. Thus, suggesting that the 1:1 LID:C9 system in the supercooled state is an IL. It was hypothesised that 1:1 LID:C9 IL may crystallise in the same manner as LID:DA systems investigated in Chapter 2. Numerous unsuccessful attempts were made to obtain a single crystal of the equimolar LID:C9 system. It was later inferred that C9 molecule is too long and requires unattainable distortion in order to fit LID molecule for the required H-bonding and ionisation interactions. However, crystallisation efforts led to the discovery of 2 unexpected phases at 2:1 and 2:3 stoichiometries. PXRD analysis detected that neat grinding of the LID:C9 sample at 1:1 ratio has produced new phase nuclei. These nuclei appeared as tiny white crystals suspended in the molten IL. These nuclei were seeded in a range of organic solvents but were immediately dissolved. The nuclei were also unsuccessfully seeded in a pre-heated homogenous molten 1:1 LID:C9 IL. Unexpectedly, seeding in an acid-rich 1:2 pre-heated homogenous molten 1:2 mixture resulted in a crystal growth. Crystals of satisfactory size and quality for SXRD analysis were obtained and crystal structure was solved. The crystal appeared to be a 2:3 crystallised oligomeric IL with a $[(\text{BH}^+)_2][(\text{HOOCRCOOH})_2(\text{OOCRCOO})^2]$ molecular formula. The system discovered was highly unusual. Firstly, to the best of our knowledge, it is the first reported oligomeric IL

based on a dicarboxylic acid. Secondly, it is highly unusual to obtain a crystalline oligomeric salt. Oligomerisation creates additional H-bonding within acid-base systems which leads to melting point depression and liquefaction.^{26,6} Finally, it is the first multicomponent phase of LID at such stoichiometry deposited in CSD. The 2:1 LID:C9 was discovered during preparation of the equimolar sample for neat ¹H NMR studies. Molten 1:1 IL was left in an NMR tube and 2:1 cocrystal crystallised out of the mixture. The results obtained in Chapter 3 convey the prediction of acid-base multicomponent systems formation is more challenging when variable stoichiometric ratios are considered. Addressing the non-stoichiometric approach allows for discovery, fine-tuning and enhanced understanding of alternative forms of multicomponent phases.

Chapter 4 addresses the aim to establish structural consistency in the extended series of LID:DA systems and to explore how length and flexibility of the long carbon backbone affect molecular recognition, crystallisation and thermal behaviour of the expected binary systems. It was found that only LID and C11 undergo solid-state reactivity upon contact formation and it was the only system that yielded semi-liquid samples. LID:C10, LID:C12 and LID:C13 at all molar compositions were solid powders. PXRD analysis of the systems revealed that no new phases were created upon neat grinding. Melt-cool crystallisation experiments and solvent-evaporation crystallisation experiments also proved to be unsuccessful. This outcome ceases the new phase formation trend that was observed in shorter-chain LID:DA systems discussed in Chapters 2 and 3. Unrelated to the original aim of Chapter 4, these crystallisation efforts produced a previously undetermined low-temperature form I (β -form) of C13 acid. Form II has been solved and reported previously, while form I was only hypothesised based on the availability of the equivalent form for other odd carbon chain length dicarboxylic acids within the homologous series.²⁰⁷ DSC analysis of the binary mixtures revealed formation of solid eutectic phases in all of the systems investigated. However, the T_m of the eutectic phases were lower than predicted by the Schroeder van Laar equation. This deviation was explained by FTIR spectroscopy that detected partial ionisation of the mixture components in all systems. Presence of T_g events in the second DSC heating cycles have shown the ability of the systems to be supercooled and the usual even-odd T_g alternating pattern was observed. The data gathered in Chapter 4 has shown that LID and long-chain DAs continue to exhibit alternating odd-even trend observed in medium-chain DAs from Chapters 2 and 3 to some degree. However, no new homogenous phases were isolated in this study. While the components have shown the

ability to form weak intermolecular interactions in the supercooled state, they are not sufficient for the formation of crystalline multicomponent phases.

As mentioned, the driving force for the multicomponent phase research is enhancement and optimisation of pharmaceutical outcome of the drugs. Previous chapters have focused on gaining understanding on how physicochemical properties of starting materials influence formation and physicochemical properties of the corresponding multicomponent phase products. The aim of Chapter 5 was to investigate the influence of the observed structural variation of the systems synthesised in Chapters 2 and 3 on their interactions with water and behaviour in aqueous solutions. Aqueous equilibrium solubility study has revealed that LID:DA multicomponent phase formation has greatly enhanced aqueous solubility of LID. Furthermore, an alternating trend was observed in solubility behaviour, where odd LID:DA systems with C5, C7 and C9 acids exhibited complete water miscibility. IDR measurements have also revealed enhanced dissolution rates of LID:DA systems compared to LID base. Similar to the trend in solubility behaviour, the dissolution rates also alternate with dicarboxylic acid carbon chain length, where LID:DA systems with odd dicarboxylic acids exhibit superior IDR. Measurement of logD values has indicated that all of the systems possess favourable lipophilicity characteristics required for effective delivery of the drug across human skin barrier. The results of PAMPA permeability assay were more difficult to interpret due to self-buffering effects of LID:DA systems in aqueous media. The data obtained have displayed direct correlation with the final pH values of the sample solutions. Stability of the systems was assessed via thermal degradation study performed by TGA and moisture sorption measurements carried out using DVS. The degradation plots of all the samples has shown similar profiles for LID:DA systems and LID base. $T_{5\%onset}$ values obtained do not display any significant deviation. DVS measurements revealed high vapour sorption by all the LID:DA systems studied. The change in mass for the LID:C5 IL was the highest at 34.6%. In contrast, LID:C6 conventional salt displayed the lowest vapour sorption at 0.8% mass change. The LID:DA series, with the exception of the LID:C6 conventional salt, followed a decreasing vapour sorption trend with increasing DA carbon chain length. The results obtained in this chapter have displayed how choice of a counterion can greatly influence pharmaceutical performance of a multicomponent phase. The investigation of a series of closely related LID:DA systems provided a possibility to tune and choose favourable physicochemical and aqueous behaviour characteristics. Overall, the results indicate that all the systems may be considered as suitable candidates for further formulation and development as delivery systems of LID.

6.2. Key findings of this work

- The conditions for mechanochemical synthesis of LID:DA systems were identified and optimised. Liquid and semi-liquid systems of LID:C5, LID:C7, LID:C9, LID:C11 that fall within χ_{LID} 0.33-0.67 molar compositions were obtained. On the contrary, all molar compositions of LID:C6, LID:C8, LID:C10, LID:C12 and LID:C13 yielded solid powder samples.
- The solid-state reactivity of all the systems, except LID:C6 salt, was achieved via neat mechanochemical grinding. The solid-state reactivity of LID:C5, LID:C7 and LID:C9 occurs via contact formation as manifested by liquefaction observed by POM.
- Solid-state reactivity in the LID:DA systems, except LID:C6 salt, proceeds through eutectic formation followed by parent material interdiffusion within the eutectic matrix.
- LID and C6 components undergo solid state reactivity only upon heating.
- FTIR, DSC, PXRD and SXRD analyses confirmed the formation of 1:1 lidocainium hemiglutarate, lidocainium hemiadipate, lidocainium hemipimelate and lidocainium hemisuberate salts; 2:1 LID:C9 cocrystal and 2:3 LID:C9 oligomeric ionic liquid crystal. The formation of 2:1 LID:C8 cocrystal was suspected but a SXRD elucidation was not achieved.
- The LID:C9 oligomeric ionic liquid has crystallised at a highly unusual 2:3 ratio. No other crystalline structures involving LID at such ratio with other counterions or co-formers has been deposited in the CSD database to date.
- The 2:3 LID:C9 complex has a $[(\text{BH}^+)_2][(\text{HOOCRCOOH})_2(\text{OOCRCOO})^{2-}]$ molecular formula and it is the first example of an oligomeric ionic liquid composed of anions derived from dicarboxylic acids.
- Equimolar LID:C5, LID:C7, LID:C8 and LID:C9 systems obtained were classified as ionic liquids.
- Binary mixtures of LID with long-chain DAs, i.e. C10, C11, C12 and C13, have yielded formation of eutectic phases as evidenced by the evolution of eutectic peaks in DSC thermograms.
- Binary mixtures of LID with long-chain DAs have not yielded any new crystalline phase formations. However, partial ionisation of the mixture components in the supercooled state was evidenced by DSC and FTIR analysis.

- All equimolar mixtures of LID with all the acids C5-C13 exhibit a single T_g transition during second DSC heating cycle indicating complete component mixing at the molecular level and the ability of the systems to be supercooled.
- Walden plots for the LID:C5 and LID:C7 systems revealed their superionic properties at low temperatures ($T < T_{RT}$) and low ionicity at high temperatures ($T > T_{RT}$). It was concluded that conductivity in these systems is facilitated by Grotthus mechanism, i.e. fast proton hopping through the H-bond network.
- Even-odd alternating trends as a function of the acid carbon chain length in the range of the binary systems studied were identified: alternating T_m , thermal behaviour, T_g values, crystal packing efficiencies, KPI values, solubility, intrinsic dissolution rates.
- The alternating trends were correlated with the T_m and conformational strain in the parent DAs.
- Increasing trend in conformational changes of the DAs has been observed i.e. the longer is the DA chain, the greater is the RMSD value which provides a measure of the difference between experimental and reference crystal structures. This trend can partially explain inability of long-acid systems to crystallise.
- A previously undetermined low-temperature form I (β -form) of C13 acid has been isolated and analysed by SXRD.
- Solubility of LID, when prepared as LID:C6 and LID:C8 salts, has been determined to be 73.41 ± 0.10 mg/ml and 82.36 ± 0.61 mg/ml, respectively. Equimolar ILs of LID:C5, LID:C7 and LID:C9 appeared to be completely miscible in water.
- IDRs of the equimolar LID:DA systems were observed to be significantly faster compared to the IDR of LID base.
- Thermal stability of the LID:DA systems was shown to be comparable with thermal stability of LID base.
- DVS analysis has revealed that the LID:DA are hygroscopic with moisture being mainly adsorbed to the surface of the material. Unlike other properties studied in this work, moisture sorption propensity does not follow the even-odd trend. Instead, hygroscopicity decreases with increasing acid chain length.

6.3. Future research directions

- It was hypothesised that a 2:1 LID:C8 cocrystal might exist, however a single crystal structure has not been obtained as a proof. Additional crystallisation experiments might be performed as an attempt to crystallise this system.
- DSC analysis of LID:C6 system in Chapter 2 suggests the eutectic phase formation stems from the interactions between C6 and LID:C6 salt. It can be further investigated by mixing pure recrystallised LID:C6 salt and C6 acid as mixture components at various molar fractions and analysing them by DSC. Hence, plotting the data to construct a new binary phase diagram.
- Ionisation of components within the systems in the liquid state can be further investigated by ^1H and ^{14}N NMR spectroscopy. It has been suggested that ^1H and ^{14}N NMR can be used to estimate the strength of H-bonding¹⁰⁴ and to quantify the percentage of proton transfer species in a sample.¹⁰⁷
- The IDR method employed had inherent flaws due to the semi-liquid nature of the sample. An alternative sample holder should be evaluated in order to obtain results that would not be influenced by sample viscosity.
- A different buffer system with a greater buffer capacity should be considered for PAMPA assay to prevent self-buffering effects. For example, Britton-Robinson buffer is commonly used in skin-PAMPA assays.²⁴⁶
- Toxicity is another important pharmaceutical attribute that needs to be investigated. *In vitro* cytotoxicity test using HaCaT cells has previously been described for studies involving ILs intended for transdermal applications.²⁵⁰
- Formulation studies have not been attempted in this work and could be addressed in future research. Possible directions include design of transdermal formulations, investigation of multicomponent phase:excipient compatibility, *in vivo* permeability studies, etc.
- The applicability of the structure-property correlation investigated in this work could be trialled using other model drugs. For example, mepivacaine, which is a structurally-close local anaesthetic could be used as a cation instead of LID.

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Appendices

Appendix I

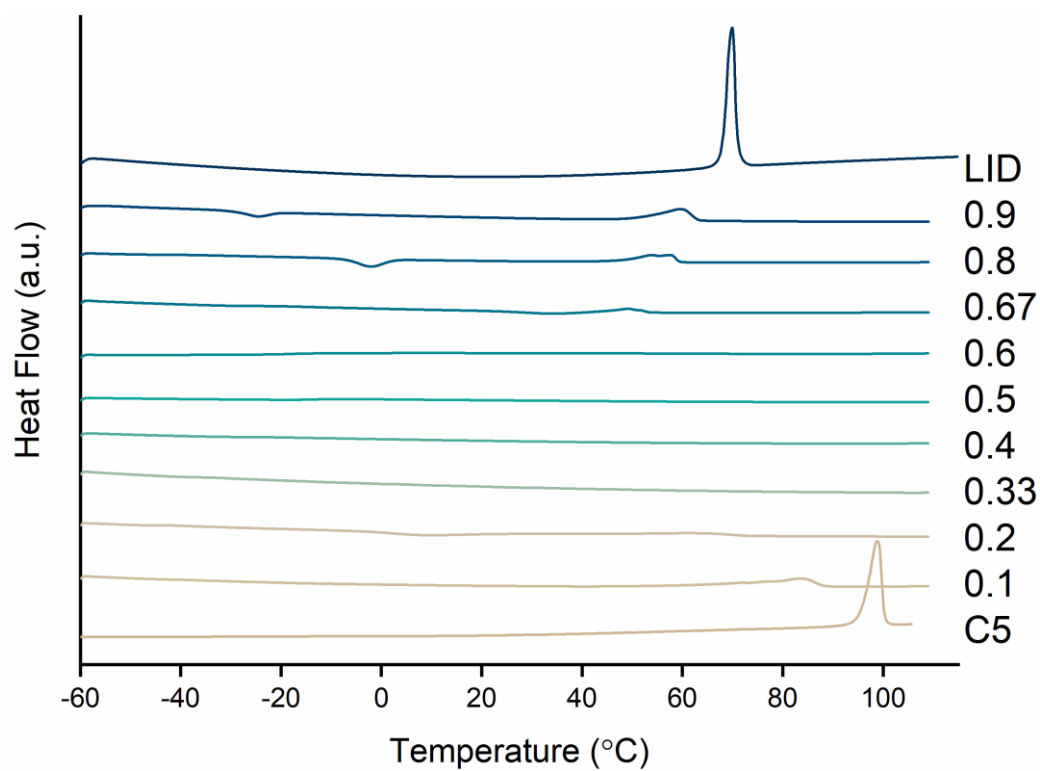


Figure AI.1. A stack of DSC traces of LID:C5 samples at various molar compositions.

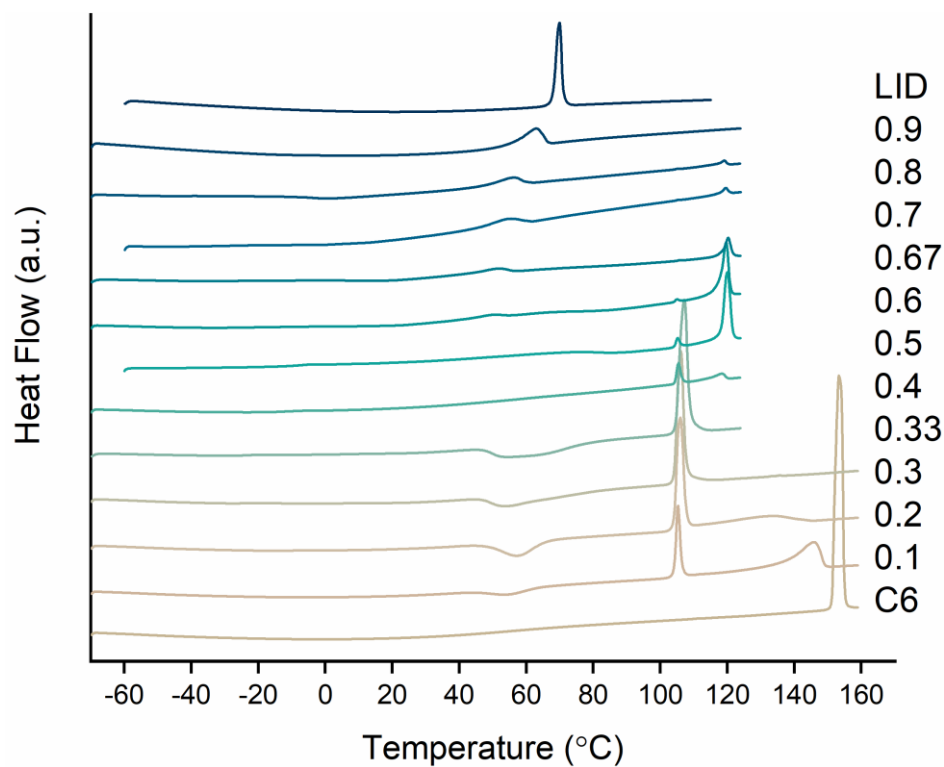


Figure AI.2. A stack of DSC traces of LID:C6 samples at various molar compositions.

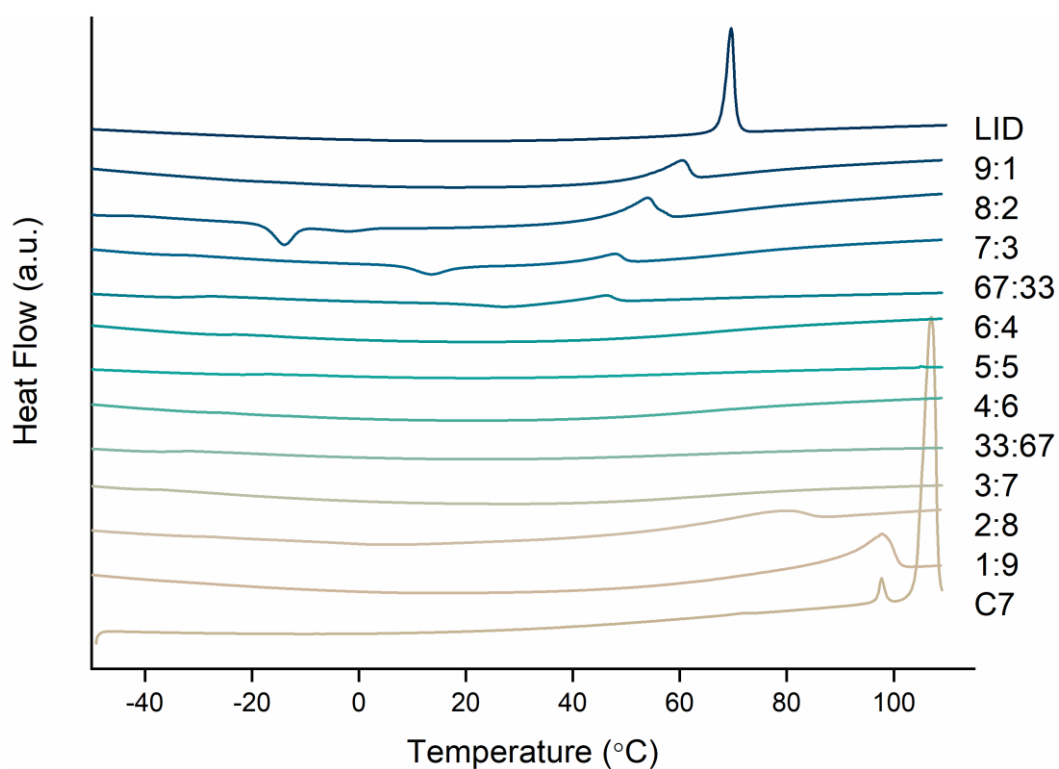


Figure AI.3. A stack of DSC traces of LID:C7 samples at various molar compositions.

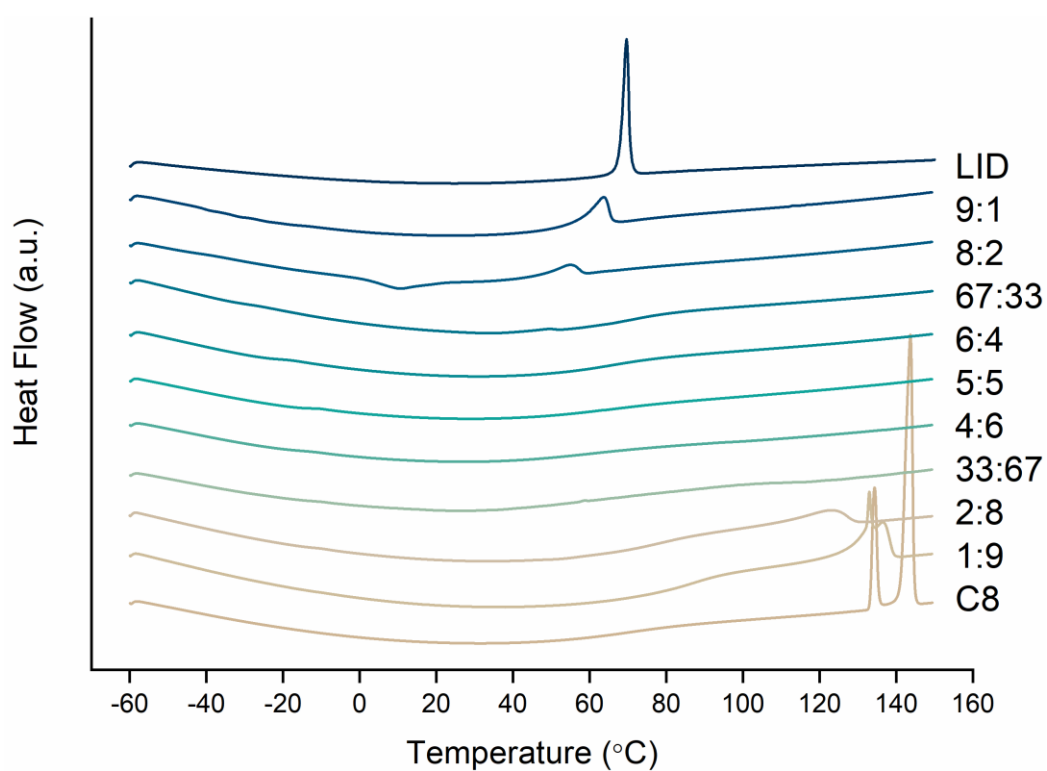
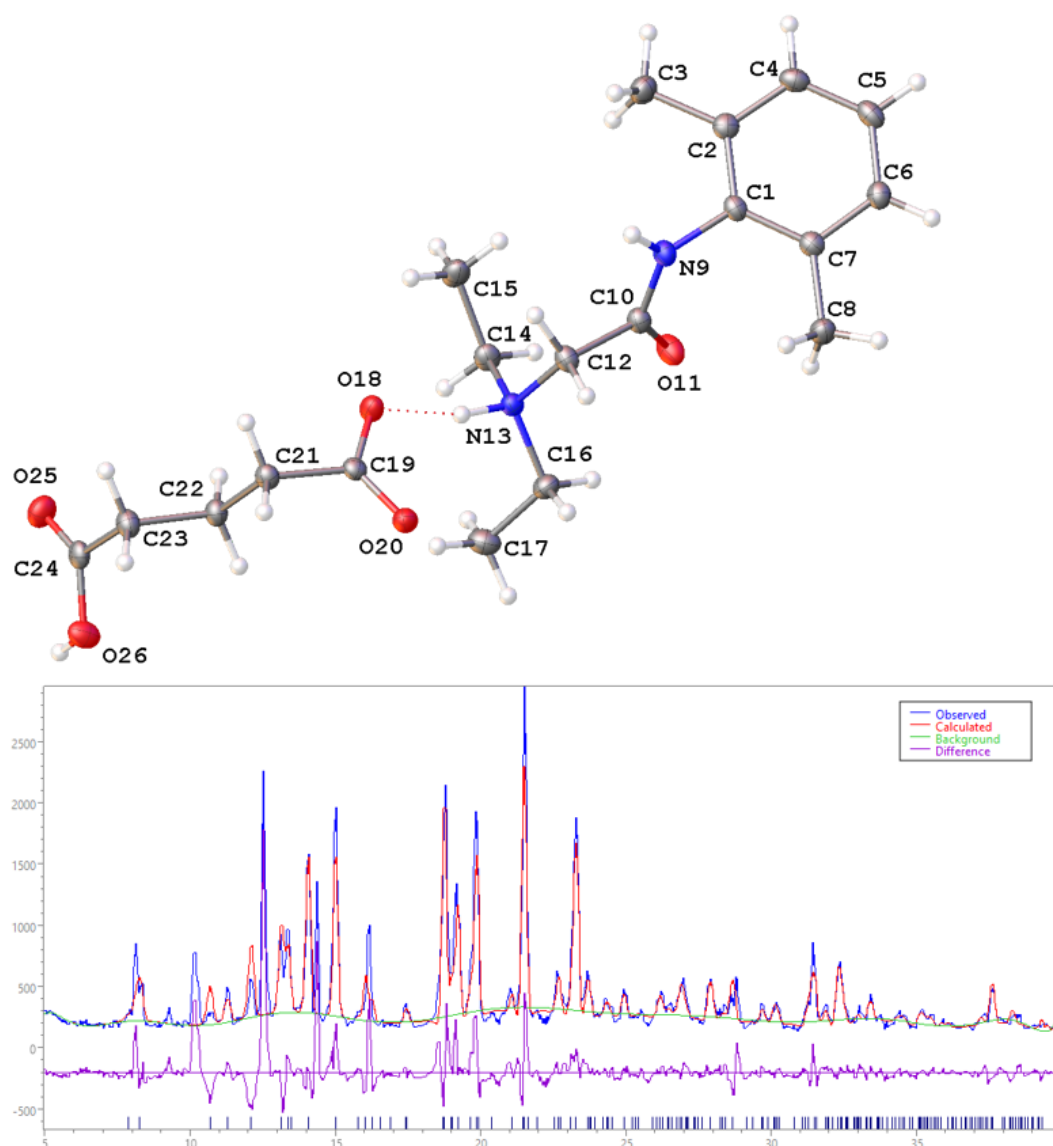


Figure AI.4. A stack of DSC traces of LID:C8 samples at various molar compositions.

Table AI.1.. Crystal details and structure refinement for **LID:C5**, **LID:C6**, **LID:C7** and **LID:C8**.

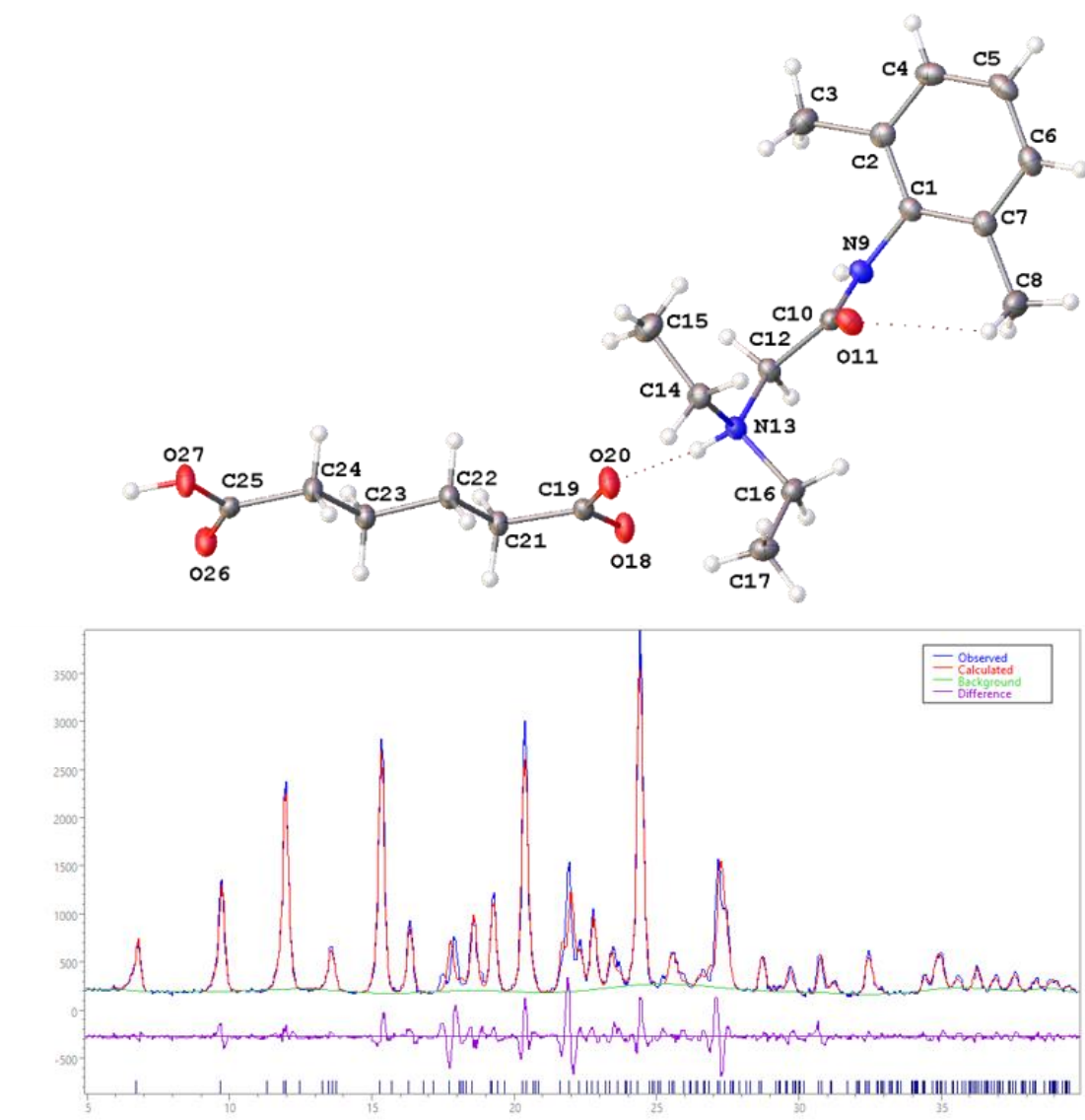
Identification code	LID:C5	LID:C6	LID:C7	LID:C8
CCDC No.	2031291	2031292	2031293	2031294
Empirical formula	C ₁₉ H ₃₀ N ₂ O ₅	C ₂₀ H ₃₂ N ₂ O ₅	C ₂₁ H ₃₄ N ₂ O ₅	C ₂₂ H ₃₆ N ₂ O ₅
Formula weight	366.45	380.47	394.50	408.53
Temperature (K)	100(2)	100(2)	100(2)	100(2)
Crystal system	monoclinic	monoclinic	triclinic	triclinic
Space group	P2 ₁ /c	P2 ₁ /n	P-1	P-1
a (Å)	11.2621(9)	8.2001(3)	8.1851(5)	8.2330(3)
b (Å)	8.3941(6)	25.9622(10)	11.6842(7)	12.0082(4)
c (Å)	21.2049(17)	10.3163(4)	12.1672(7)	12.0670(4)
α (°)	90	90	87.438(2)	97.1399(15)
β (°)	97.647(2)	110.4620(10)	71.468(2)	103.8615(16)
γ (°)	90	90	79.691(2)	101.6113(16)
Volume (Å ³)	1986.8(3)	2057.69(14)	1085.39(11)	1115.72(7)
Z	4	4	2	2
ρ _{calc} (g/cm ³)	1.225	1.228	1.207	1.216
μ (mm ⁻¹)	0.088	0.716	0.086	0.693
F(000)	792.0	824.0	428.0	444.0
Crystal size (mm ³)	0.288 × 0.235 × 0.187	0.36 × 0.22 × 0.13	0.3 × 0.28 × 0.013	0.38 × 0.1 × 0.09
Radiation	Mo Kα	Cu Kα	Mo Kα	Cu Kα
2θ range (°)	5.668 to 54.552	6.81 to 139.99	5.33 to 55.378	7.642 to 137.09
Reflections collected	33932	26857	15670	25892
Independent reflections	4447	3854	5034	4086
	R _{int} = 0.0612, R _{sigma} = 0.0355	R _{int} = 0.0357, R _{sigma} = 0.0219	R _{int} = 0.0364, R _{sigma} = 0.0390	R _{int} = 0.0508, R _{sigma} = 0.0327
Data/restraints/parameters	4447/3/251	3854/3/260	5034/3/269	4086/3/276
S	1.040	1.013	1.027	1.058
Final R* indexes [I ≥ 2σ (I)]	R ₁ = 0.0460, wR ₂ = 0.1264	R ₁ = 0.0362, wR ₂ = 0.0911	R ₁ = 0.0446, wR ₂ = 0.1070	R ₁ = 0.0469, wR ₂ = 0.1314
Final R indexes [all data]	R ₁ = 0.0606, wR ₂ = 0.1392	R ₁ = 0.0369, wR ₂ = 0.0918	R ₁ = 0.0651, wR ₂ = 0.1177	R ₁ = 0.0521, wR ₂ = 0.1363
Largest diff. peak/hole (e Å ⁻³)	0.35/-0.38	0.17/-0.28	0.42/-0.28	0.25/-0.24

$$^*R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|, wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$$



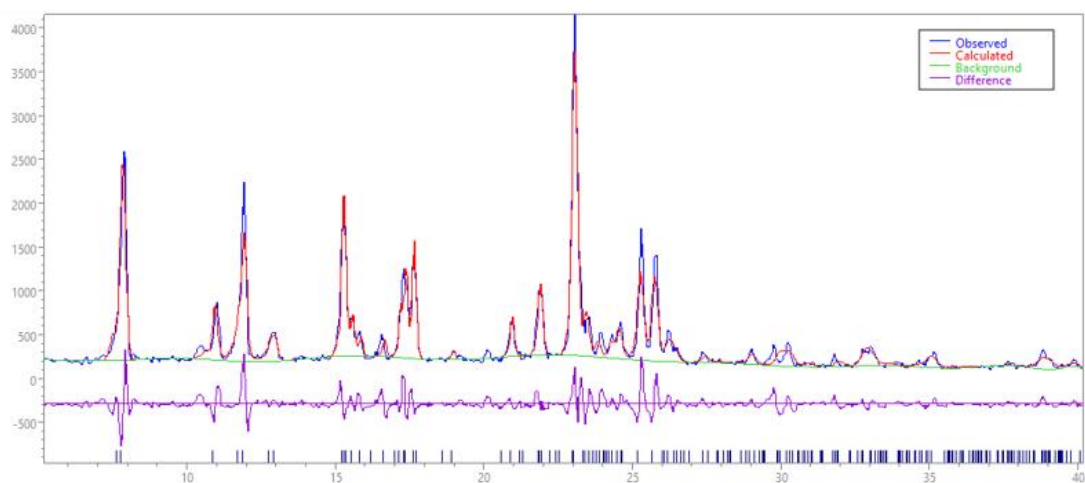
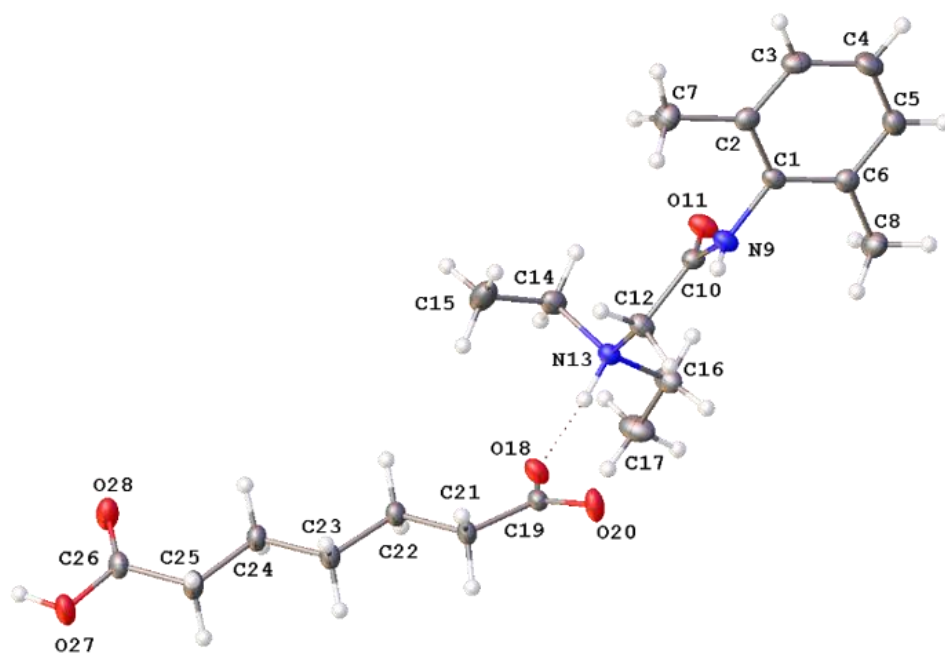
$R_p = 17.578$
 $R_{wp} = 25.563$
 $R_e = 5.073$
 $\chi^2 = 25.389$

Figure AI.5. Fully labelled molecular structure of **LID:C5** with the corresponding powder XRD fit and difference patterns with associated R values (EXPO2014¹). The fit for LID:C5 is poor as the sample is not phase pure and is contaminated with mainly LID.



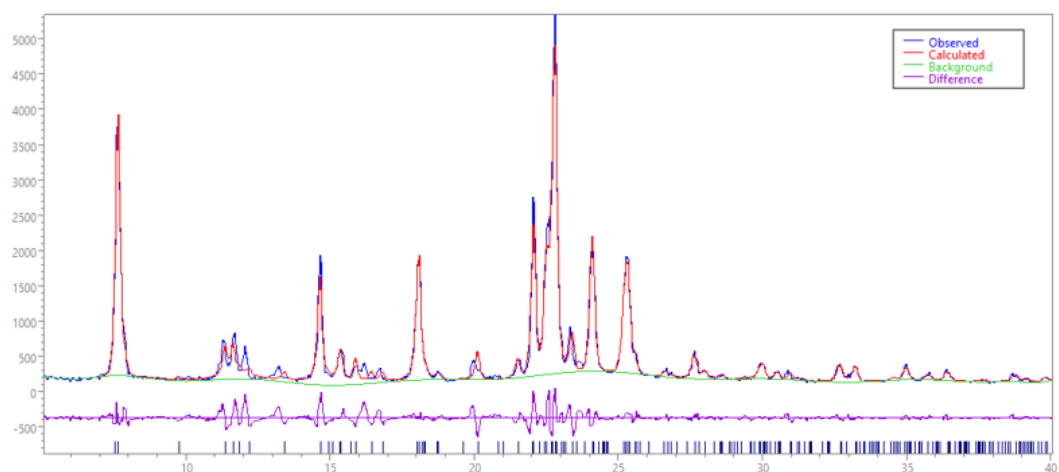
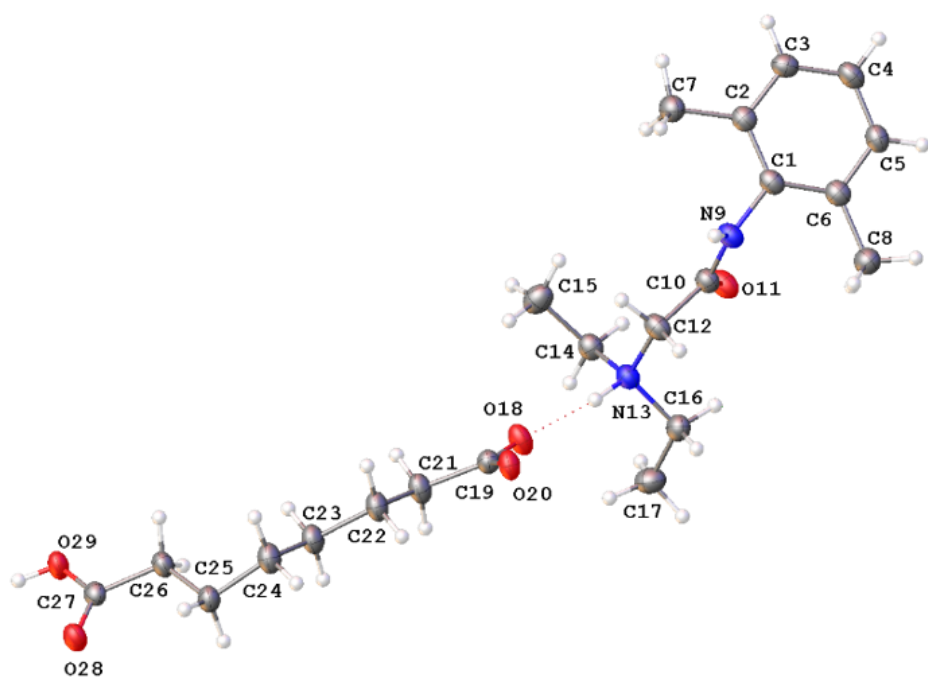
$R_p = 9.812$
 $R_{wp} = 14.103$
 $R_e = 4.792$
 $\chi^2 = 8.663$

Figure AI.6. Fully labelled molecular structures of **LID:C6** with the corresponding powder XRD fit and difference patterns with associated R values (EXPO2014).



$R_p = 12.569$
 $R_{wp} = 16.355$
 $R_e = 5.194$
 $\chi^2 = 9.916$

Figure AI.7. Fully labelled molecular structures of **LID:C7** with the corresponding powder XRD fit and difference patterns with associated R values (EXPO2014).



$R_p = 10.03$
 $R_{wp} = 14.624$
 $R_e = 5.056$
 $\chi^2 = 8.366$

Figure AI.8. Fully labelled molecular structures of **LID:C8** with the corresponding powder XRD fit and difference patterns with associated R values (EXPO2014).

Hydrogen bonding motifs

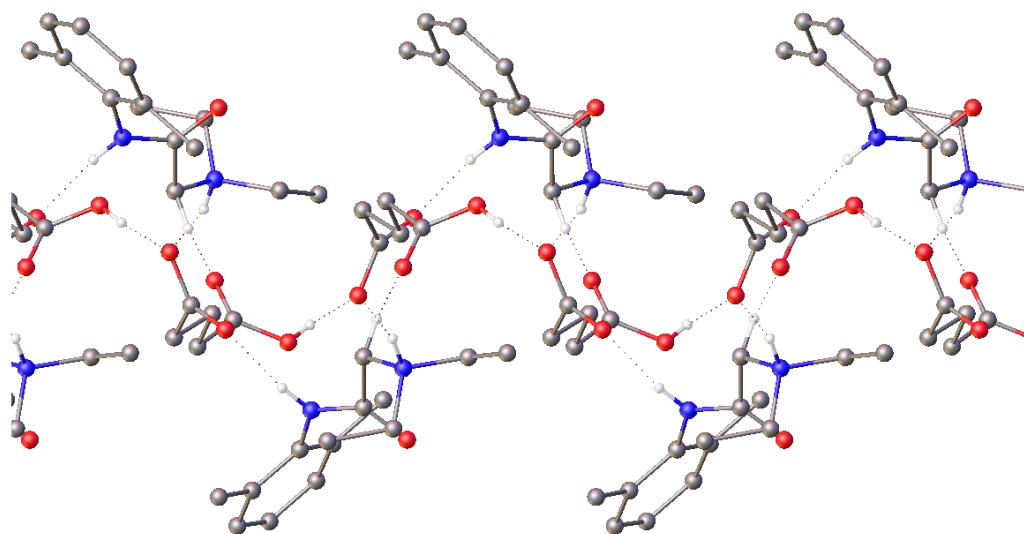


Figure AI.9. Major H bonding arrangement (dotted lines) in LID:C5 in the DA homosynthon side to side stack with only hydrogen atoms involved in intermolecular hydrogen bonding shown.

Table AI.2. Main hydrogen bonds for LID:C5 [$\text{\AA}$ and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
O26-H26...O18 [†]	0.856(10)	1.717(10)	2.5708(15)	175(2)
N9-H9...O20 [‡]	0.883(9)	1.949(10)	2.8257(16)	172(2)
C12-H12A...O25 [#]	0.99	2.36	3.2549(18)	149.4
C12-H12B...O20 [‡]	0.99	2.41	3.2059(18)	137.0
N13-H13...O18	0.990(9)	1.709(10)	2.6841(16)	167.3(19)
C15-H15B...O11 ^{\$}	0.98	2.58	3.2192(19)	122.5

Symmetry transformations used to generate equivalent atoms:

[†] = $-x+2, y-1/2, -z+1/2$; [‡] = $-x+1, y+1/2, -z+1/2$; [#] = $x-1, y, z$; ^{\$} = $-x+1, -y+1, -z+1$

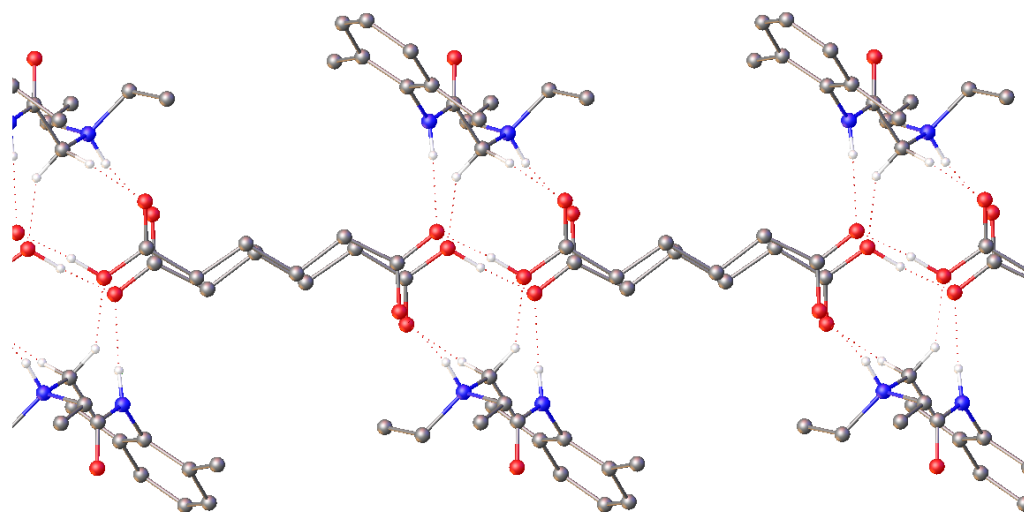


Figure AI.10. Head to tail DA homosynthon arrangement in LID:C6, where the homosynthon is bridged by the cationic LIDH⁺ and via NH and weak CH..O hydrogen bonding interactions.

Table AI.3. Main hydrogen bonds for LID:C6 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C8-H8B...O11	0.98	2.49	3.1551(14)	125
C12-H12B...O27 [†]	0.99	2.35	3.1528(13)	138
N9-H9...O18 [‡]	0.892(9)	1.950(9)	2.8349(12)	171.5(14)
N13-H13...O20	0.914(9)	1.796(9)	2.6968(11)	168.3(14)
O27-H27...O18 [#]	0.980(9)	1.538(10)	2.5145(11)	173.9(19)

Symmetry transformations used to generate equivalent atoms:

[†] = x+1,y,z+1; [‡] = -x+1,-y+1,-z+2; [#] = x-1,y,z-1

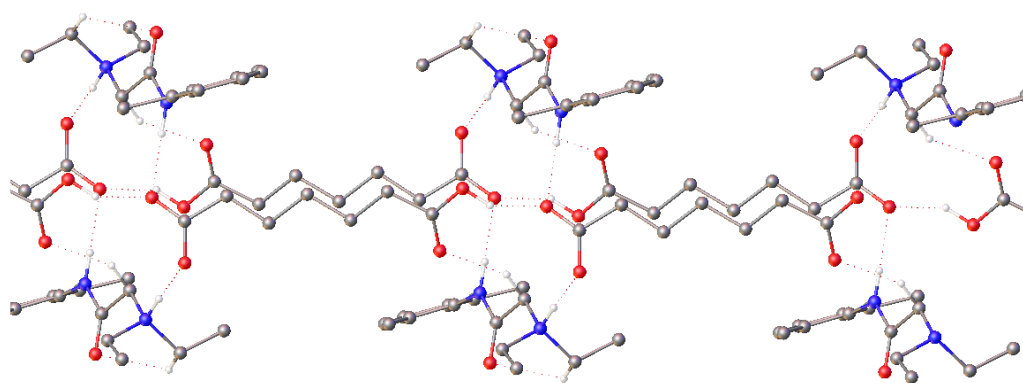


Figure AI.11. Head to tail DA homosynthon arrangement in LID:C7, where the homosynthon is bridged by the cationic LIDH⁺ and via NH and weak CH...O hydrogen bonding interactions.

Table AI.4. Main hydrogen bonds for LID:C7 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N9-H9...O20 [†]	0.945(9)	1.923(9)	2.8663(16)	175.9(17)
N13-H13...O18	0.971(9)	1.644(10)	2.6118(15)	174.6(18)
C12-H12A...O28 [‡]	0.99	2.25	3.1378(18)	148
C14-H14B...O11	0.99	2.46	3.0960(18)	122
C15-H15B...O18	0.98	2.66	3.355(2)	128
O27-H27...O20 [#]	0.966(10)	1.693(15)	2.5720(14)	149(2)

Symmetry transformations used to generate equivalent atoms:

[†] = -x+1,-y+1,-z+1; [‡] = x,y,z-1; [#] = x,y,z+1

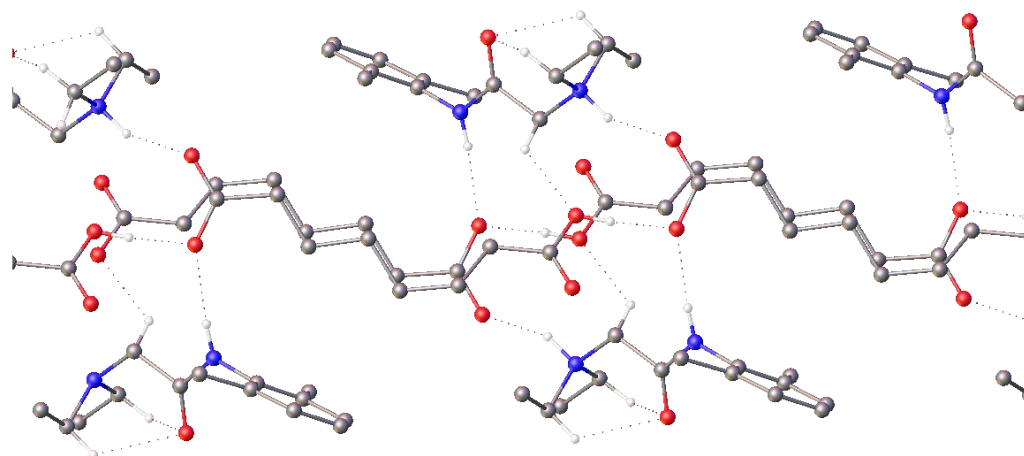


Figure AI.12. Sinusoidal head to tail SA homosynthon arrangement in LID:C8 where the homosynthon is bridged by the cationic LIDH⁺ and via NH and weak CH...O hydrogen bonding interactions.

Table AI.5. Main hydrogen bonds for LID:C8 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C12-H12A...O29 [†]	0.99	2.37	3.0483(17)	125
N13-H13...O18	1.00	1.72	2.6682(15)	157
C14-H14A...O11	0.99	2.38	3.0063(18)	120
C15-H15C...O18	0.98	2.59	3.2722(19)	127
C16-H16B...O11	0.99	2.47	3.0966(19)	121
O29-H29...O20 [‡]	0.84	1.71	2.5396(13)	169

Symmetry transformations used to generate equivalent atoms:

[†] = x,y,z+1; [‡] = x,y,z-1

Table AI.6. ΔD_{C-O} (Å) values for carboxylic acid groups participating in proton transfer with LID. Bond length values was obtained from SXRD data.

Compound	C-O bonds measured	D_{C-O} (Å)	ΔD_{C-O} (Å)	ΔpK_a *
LID_{0.5}:C5_{0.5}	C(19)-O(18)	1.2800	0.0394	3.56
	C(19)-O(20)	1.2406		
LID_{0.5}:C6_{0.5}	C(20)-O(18)	1.2764	0.0316	3.49
	C(20)-O(19)	1.2448		
LID_{0.5}:C7_{0.5}	C(19)-O(18)	1.2505	0.0111	3.40
	C(19)-O(20)	1.2616		
LID_{0.5}:C8_{0.5}	C(19)-O(18)	1.2487	0.0205	3.37
	C(19)-O(20)	1.2692		

* The most acidic pK_a values of the DAs were used for calculations.

References:

1. Altomare, A.; Cuocci, C.; Giacovazzo, C.; Moliterni, A.; Rizzi, R.; Corriero, N.; Falcicchio, A. EXPO2013: A Kit of Tools for Phasing Crystal Structures from Powder Data. *J. Appl. Crystallogr.* **2013**, 46 (4), 1231–1235.

Appendix II

Table AII.1. Crystal Data and Structure Refinement details for LID:C9.

Identification code	LID:C9 co-crystal	LID:C9 salt
CCDC number		
Empirical formula	C ₃₇ H ₆₀ N ₄ O ₆	C ₅₅ H ₉₂ N ₄ O ₁₄
<i>M</i> (g/mol)	656.89	1033.32
<i>T</i> (K)	100(2)	100(2)
Crystal System	monoclinic	Triclinic
SG	P2 ₁	P $\bar{1}$
<i>a</i> (Å)	8.6179(4)	8.4182(5)
<i>b</i> (Å)	21.0877(10)	12.0466(7)
<i>c</i> (Å)	10.4030(5)	30.401(2)
α (°)	90	84.902(5)
β (°)	93.494(2)	85.418(5)
γ (°)	90	77.698(5)
<i>V</i> (Å ³)	1887.04(15)	2994.4(3)
<i>Z</i>	2	2
<i>D</i> _{calc} (g/cm ³)	1.156	1.146
μ (mm ⁻¹)	0.623	0.665
<i>F</i> (000)	716.0	1124
Radiation	Cu K α (λ = 1.54178)	Cu K α (λ = 1.54178)
Reflections collected	20984	26023
Independent reflections	6930 R _{int} = 0.0519 R _{sigma} = 0.0500	10722 R _{int} = 0.1405 R _{sigma} = 0.1844
Data/restraints/parameters	6930/5/449	10722/0/670
Goodness-of-fit on <i>F</i> ² (<i>S</i>)	1.009	1.006
Final R indexes [<i>I</i> ≥ 2σ (<i>I</i>)]*	R ₁ = 0.0448, wR ₂ = 0.1150	R ₁ = 0.0992, wR ₂ = 0.2351
Final R indexes [all data]	R ₁ = 0.0477, wR ₂ = 0.1175	R ₁ = 0.2025, wR ₂ = 0.3003
Largest diff. peak/hole / e Å ⁻³	0.26/-0.30	0.46/-0.37
Flack parameter	0.3(2)	-

$$*R_1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}, wR_2 = [\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2}]^{1/2}.$$

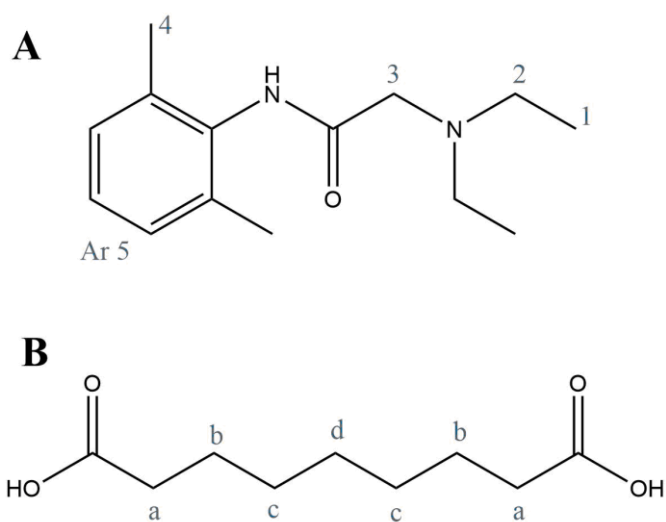


Figure AII.1. ^1H -NMR peak assignment. ^1H atom labels for A: LID and B: C9.

2:1 LID:C9 cocrystal (400 MHz, DMSO- d_6 , 30 °C): δ = 1.08 (t, J = 7.1 Hz, 6H, H_1), 1.26 (broad s, 6H, H_c and H_d), 1.48 (m, 4H, H_b), 2.14 (s, 6H, H_4), 2.19 (t, J = 7.4 Hz, 4H, H_a), 2.62 (q, J = 7.1 Hz, 4H, H_2), 3.14 (s, 2H, H_3), 7.07 (s, 3H, H_5), 9.16 (s, 1H, NH), 11.95 ppm (broad s, 1H, LIDH+).

1:1 LID:C9 salt (400 MHz, DMSO- d_6 , 30 °C): δ = 1.08 (t, J = 7.1 Hz, 6H, H_1), 1.26 (broad s, 6H, H_c and H_d), 1.48 (m, 4H, H_b), 2.14 (s, 6H, H_4), 2.19 (t, J = 7.4 Hz, 4H, H_a), 2.62 (q, J = 7.1 Hz, 4H, H_2), 3.14 (s, 2H, H_3), 7.07 (s, 3H, H_5), 9.16 (s, 1H, NH), 11.95 ppm (broad s, 1H, LIDH+).

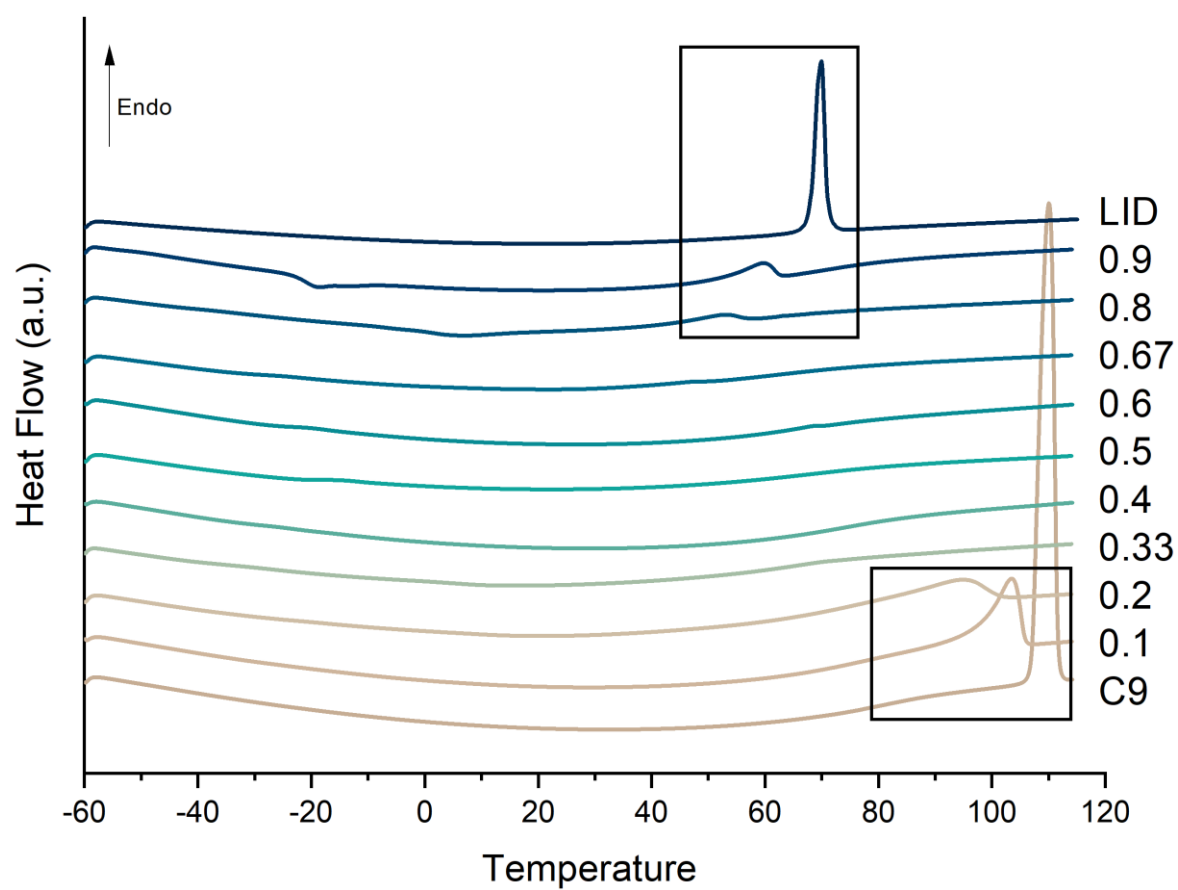


Figure AII.2. A stack of second heating DSC thermograms of the supercooled LID, C9 and LID:C9 at a range of LID molar fractions.

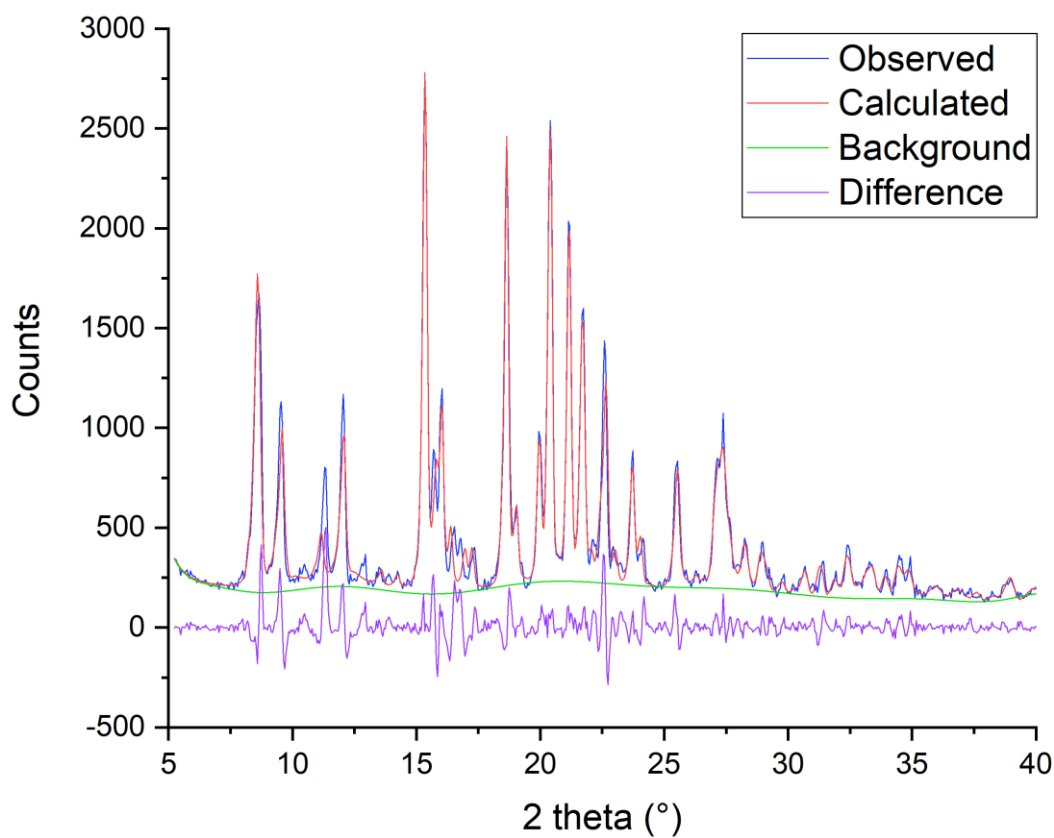


Figure AII.3. LeBail fit of powder XRD data to single crystal data for 2:1 LID:C9 using EXPO2014¹ with a weighting scheme of $w=1.0/\text{count}$ and the Pearson VII function for final peak profile refinement. $R_p = 10.017$, $R_{wp} = 14.60$. Final agreement factors: $R_p = 10.017$, $R_{wp} = 14.605$, $R_e = 4.926$ and $\chi^2 = 8.791$.

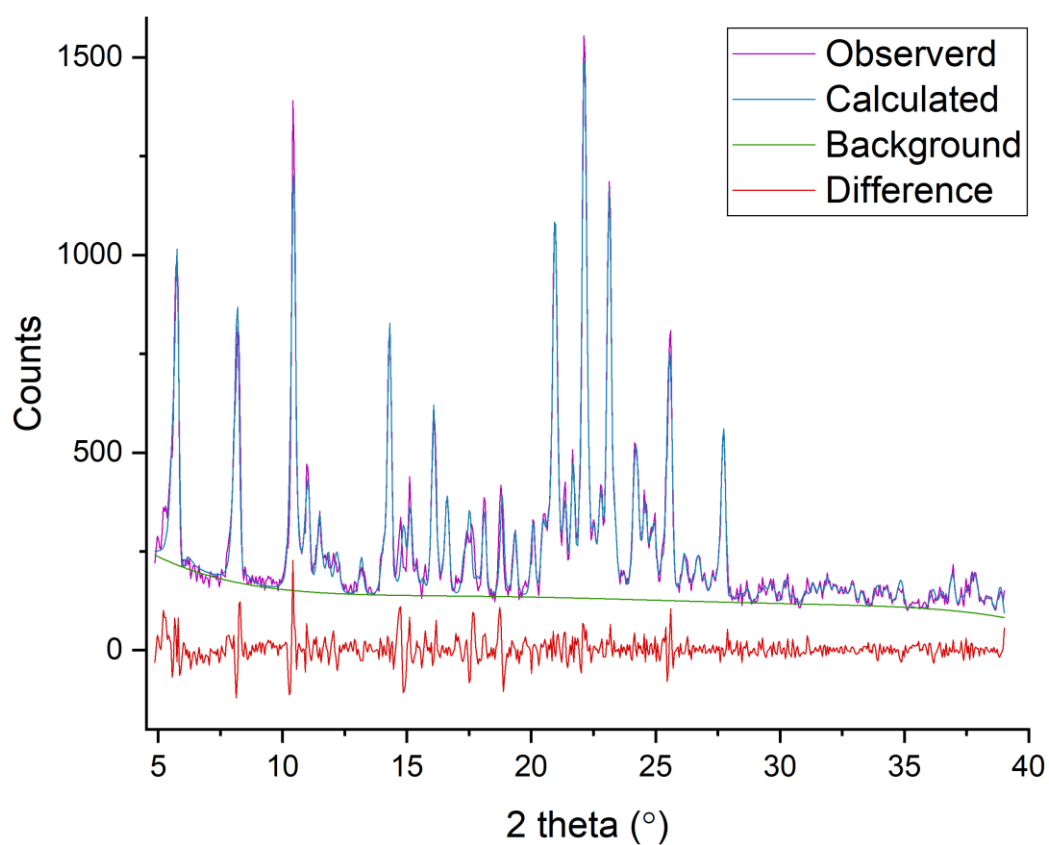


Figure AII.4. LeBail fit of powder XRD data to single crystal data for 2:3 LID:C9 using EXPO2014¹ with a weighting scheme of $w=1.0/\text{count}$ and the Pearson VII function for final peak profile refinement. Final agreement factors: $R_p = 7.525$, $R_{wp} = 10.284$, $R_e = 6.203$, $\chi^2 = 2.748$.

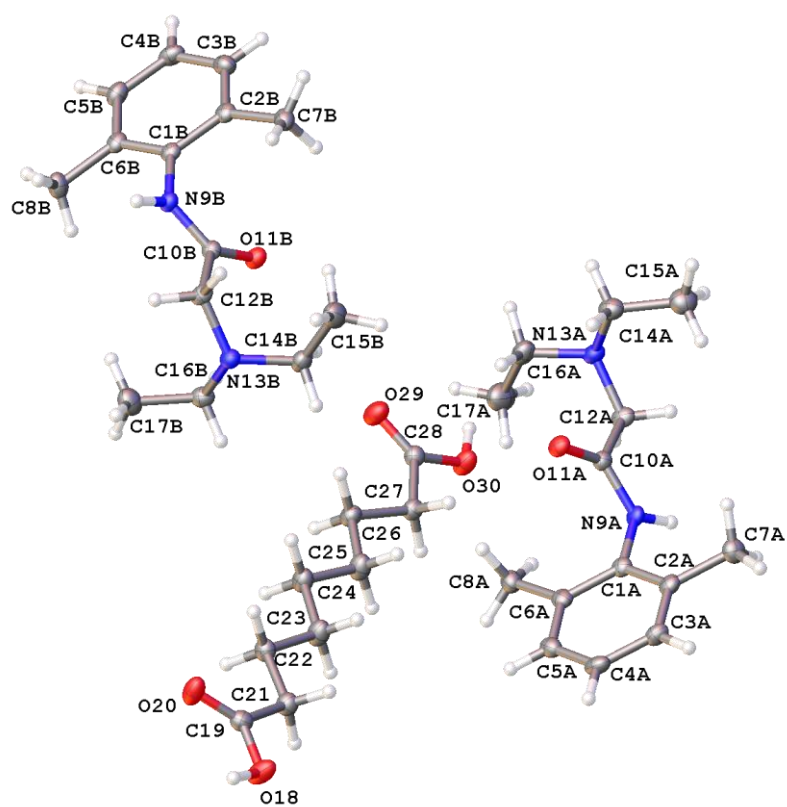


Figure AII.5. Molecular structure of 2:1 LID:C9 with atomic displacement shown at 50% probability.

Table AII.2 Hydrogen bonds for 2:1 LID:C9 [$\text{\AA}$ and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(9A)-H(9A)...O(11B)#1	0.880(14)	2.06(2)	2.900(3)	158(4)
C(3A)-H(3A)...O(20)#2	0.95	2.46	3.385(4)	164
C(12A)-H(12A)...O(11B)#1	0.99	2.56	3.243(3)	126
C(15A)-H(15A)...O(29)#1	0.98	2.50	3.312(4)	140
N(9B)-H(9B)...O(11A)#3	0.877(14)	2.105(19)	2.932(3)	157(3)
C(8B)-H(8BC)...O(11A)#3	0.98	2.51	3.289(3)	136
O(18)-H(18)...N(13A)#4	0.974(15)	1.63(2)	2.583(3)	165(6)
O(30)-H(30)...N(13B)#5	0.977(14)	1.638(18)	2.603(3)	169(5)

Symmetry transformations used to generate equivalent atoms:

#1 $-x+1, y+1/2, -z+1$ #2 $-x+2, y+1/2, -z$ #3 $-x+2, y-1/2, -z+1$

#4 $x+1, y, z-1$ #5 $x-1, y, z$

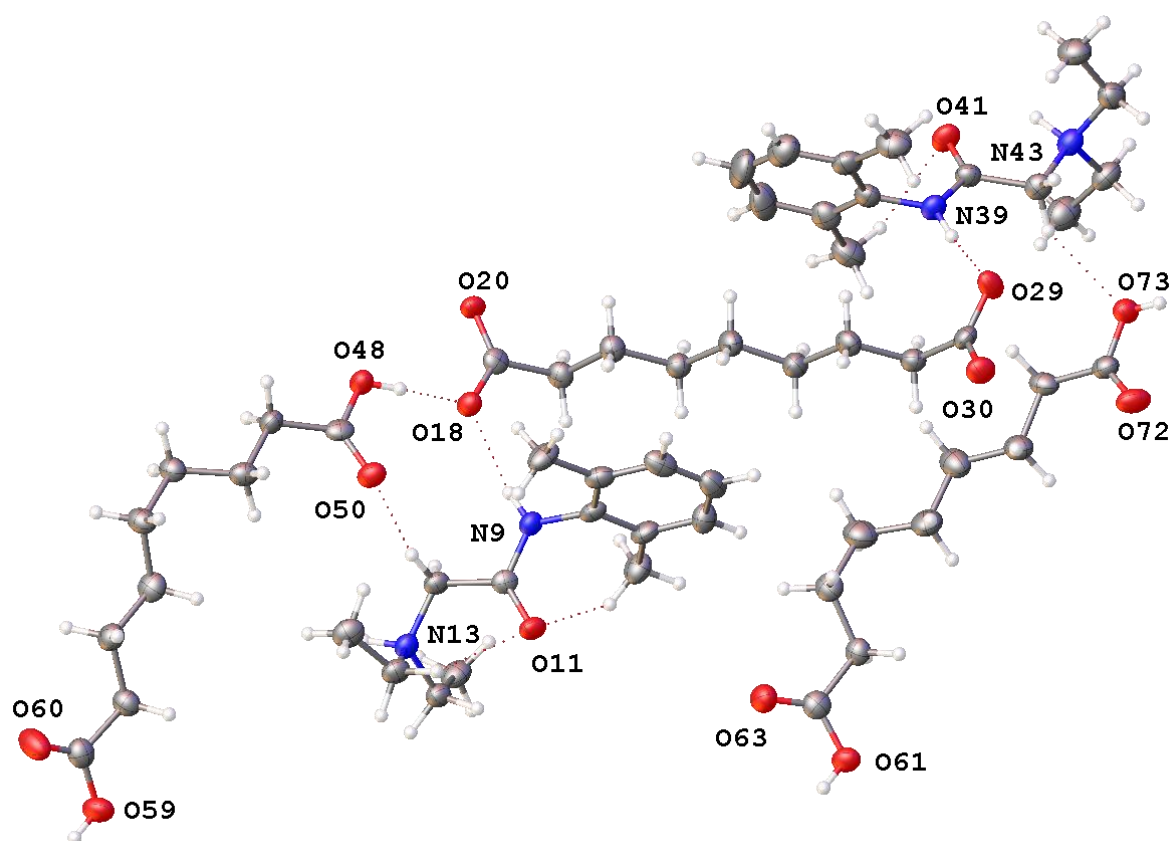


Figure AII.6. Molecular structure of 2:3 LID:C9 with atomic displacement shown at 50% probability.

Table AII.3. Hydrogen bonds for 2:3 LID:C9 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(8)-H(8B)...O(11)	0.98	2.57	3.293(8)	131
N(9)-H(9)...O(18)	0.88	2.08	2.916(6)	159
C(12)-H(12A)...O(50)	0.99	2.30	3.273(7)	168
C(12)-H(12B)...O(48)#1	0.99	2.28	3.243(7)	164
N(13)-H(13)...O(20)#1	1.00	1.87	2.837(6)	162
C(14)-H(14A)...O(63)#2	0.99	2.46	3.245(7)	136
C(16)-H(16B)...O(11)	0.99	2.47	3.094(7)	121
C(38)-H(38A)...O(41)	0.98	2.51	3.214(8)	129
N(39)-H(39)...O(29)	0.88	1.95	2.811(6)	167
C(42)-H(42A)...O(72)#3	0.99	2.20	3.189(8)	174
C(42)-H(42B)...O(73)	0.99	2.38	3.242(7)	146
N(43)-H(43)...O(41)#4	1.00	1.94	2.814(7)	144
C(44)-H(44B)...O(30)#3	0.99	2.48	3.263(8)	136
C(46)-H(46B)...O(30)#3	0.99	2.47	3.261(8)	136
O(61)-H(61)...O(20)#5	0.84	1.79	2.633(6)	177
O(73)-H(73)...O(29)#3	0.84	1.73	2.559(6)	171
O(48)-H(48)...O(18)	0.84	1.75	2.566(5)	162
O(59)-H(59)...O(30)#6	0.84	1.78	2.603(6)	166

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1 #2 -x+2,-y,-z+1 #3 -x+1,-y,-z+2
 #4 -x+1,-y+1,-z+2 #5 x+1,y-1,z #6 -x+1,-y,-z+1

References:

- Altomare, A.; Cuocci, C.; Giacovazzo, C.; Moliterni, A.; Rizzi, R.; Corriero, N.; Falcicchio, A. EXPO2013: A Kit of Tools for Phasing Crystal Structures from Powder Data. *J. Appl. Crystallogr.* **2013**, *46* (4), 1231–1235.

Appendix III

Table AIII.1. Crystal details and structure refinement for **C13 Form I**.

CCDC No.	2168827
Empirical formula	C ₁₃ H ₂₄ O ₄
<i>M</i> (g/mol)	244.32
<i>T</i> (K)	99.99
Crystal System	monoclinic
SG	C2/c
<i>a</i> (Å)	29.942(18)
<i>b</i> (Å)	4.691(2)
<i>c</i> (Å)	9.597(6)
α (°)	90
β (°)	99.839(18)
γ (°)	90
<i>V</i> (Å ³)	1328.1(13)
<i>Z</i>	4
<i>D</i> _{calc} (g/cm ³)	1.222
μ (mm ⁻¹)	0.723
<i>F</i> (000)	536.0
Crystal size (mm ³)	0.20 × 0.15 × 0.05
Radiation	Cu K α (λ = 1.54178)
Reflections collected	5630
Independent reflections	1241
	<i>R</i> _{int} = 0.0376, <i>R</i> _{sigma} = 0.0338
Data/restraints/parameters	1241/0/82
Goodness-of-fit on <i>F</i> ² (<i>S</i>)	1.141
Final <i>R</i> indexes [<i>I</i> ≥ 2σ (<i>I</i>)]*	<i>R</i> ₁ = 0.0397, <i>wR</i> ₂ = 0.1194
Final <i>R</i> indexes [all data]	<i>R</i> ₁ = 0.0422, <i>wR</i> ₂ = 0.1224
Largest diff. peak/hole / e Å ⁻³	0.18/-0.22

$$*R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|, \quad wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}.$$

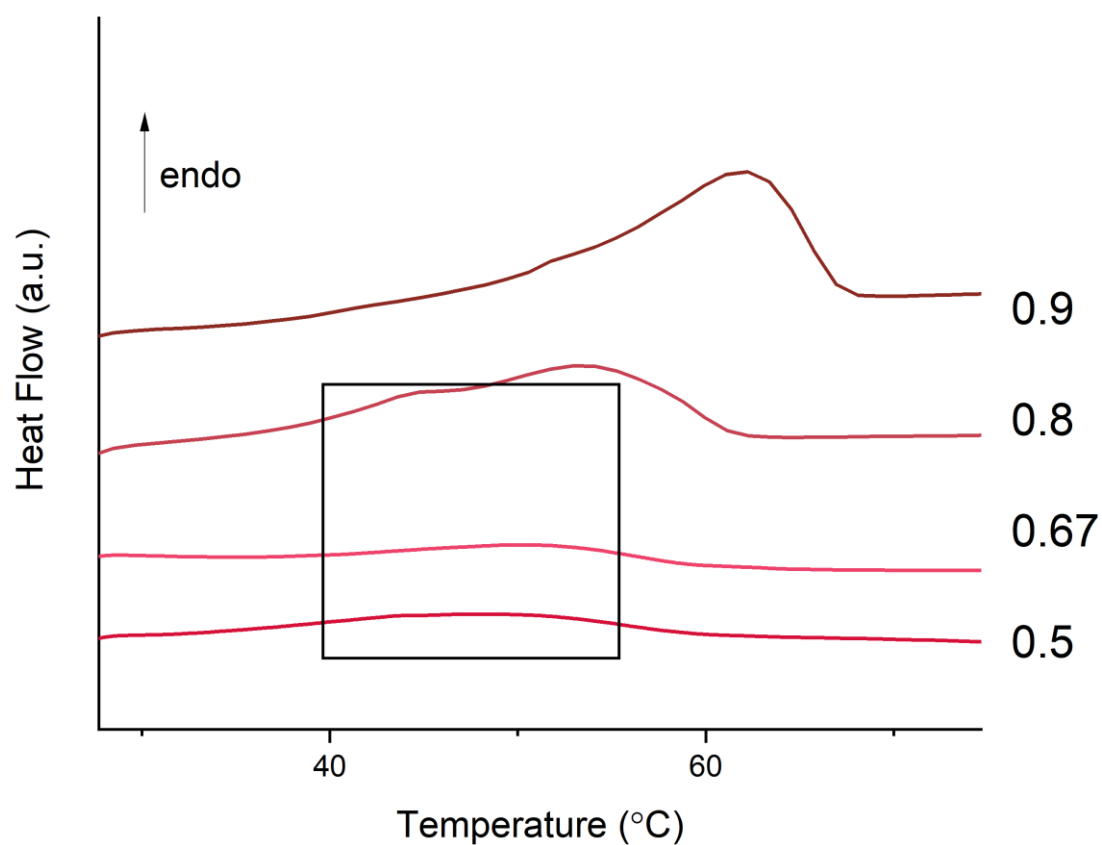
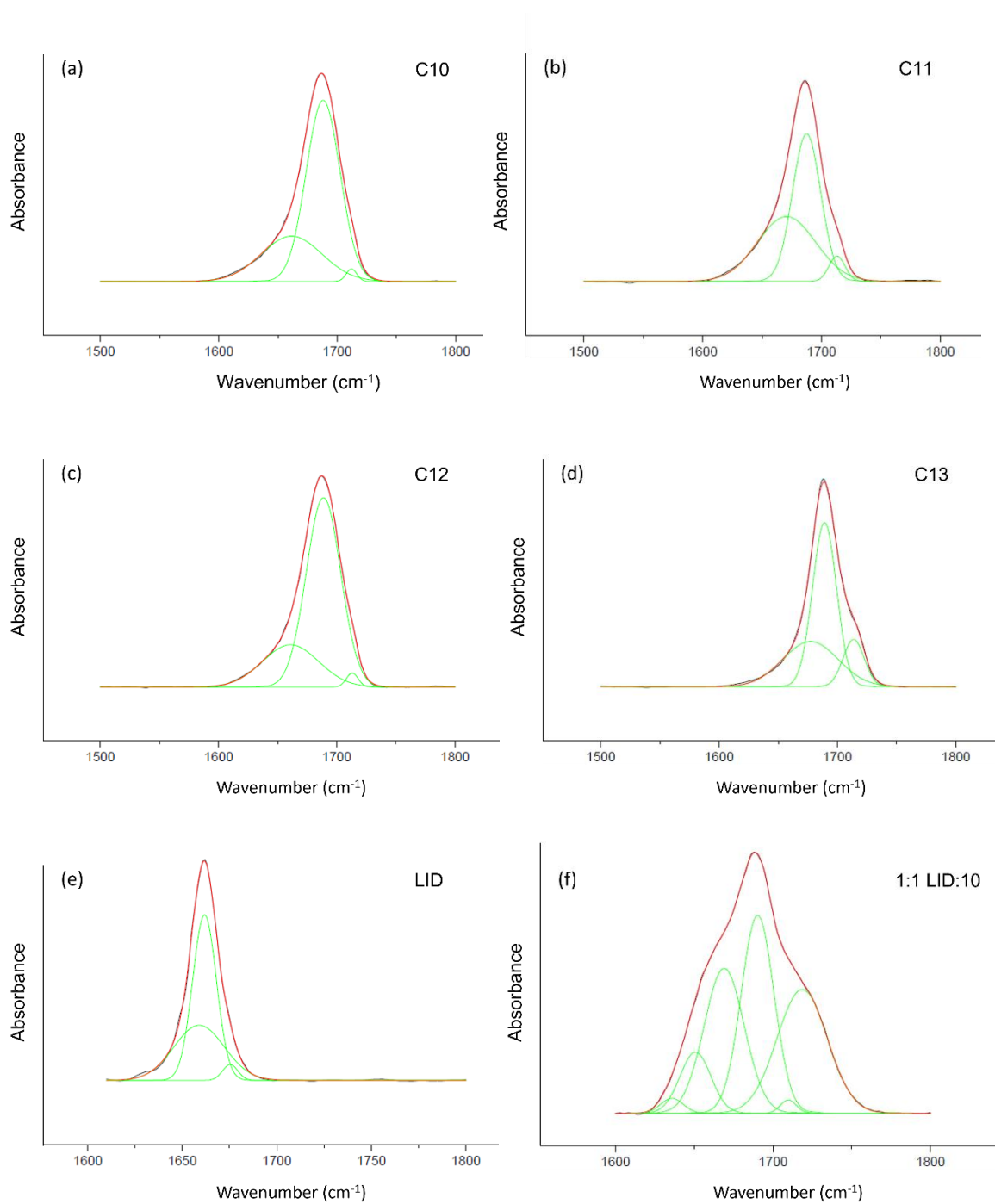


Figure AIII.1. A stack of DSC thermograms for the LID:C11 samples at the range of $\chi_{\text{LID}} = 0.9 - 0.5$ molar fractions with the 40 – 60 °C temperature region magnified to show broad endothermic peaks attributed to eutectic melting transitions.



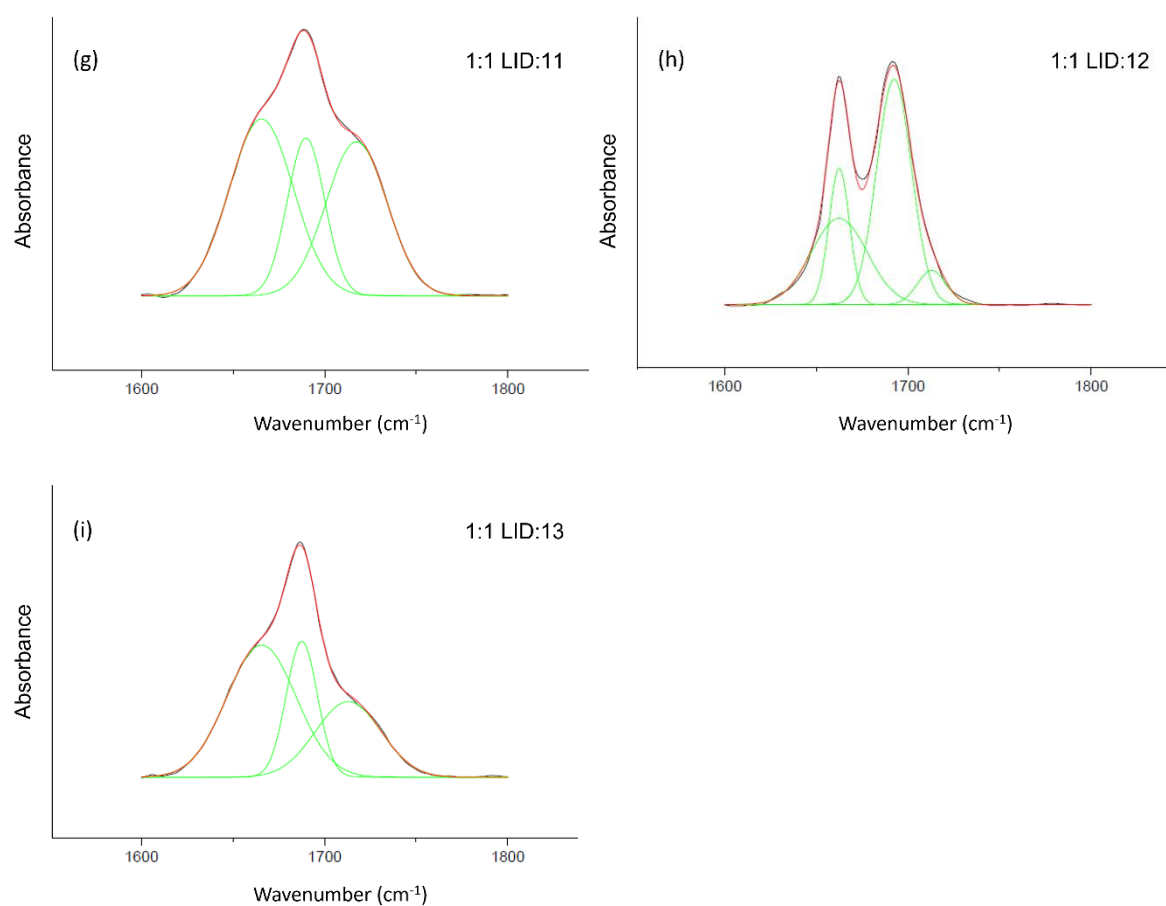


Figure AIII.2. FTIR peak deconvolution of (a) C10, (b) C11, (c) C12, (d) C13, (e) LID, (f) 1:1 LID:C10, (g) 1:1 LID:C11, (h) 1:1 LID:C12 and (i) 1:1 LID:C13. Black line: recorded spectrum; green lines: deconvoluted individual Gauss peaks; and red line: sum of the component peaks.