

Ordered Solvents

Liquid-Crystalline Ionic Liquids as Ordered Reaction Media for the Diels–Alder Reaction

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Abstract: Liquid-crystalline ionic liquids (LCILs) are ordered materials that have untapped potential to be used as reaction media for synthetic chemistry. This paper investigates the potential for the ordered structures of LCILs to influence the stereochemical outcome of the Diels–Alder reaction between cyclopentadiene and methyl acrylate. The ratio of *endo-* to *exo-*product from this reaction was monitored for a range of ionic liquids (ILs) and LCILs. Comparison of the *endo:exo* ratios in these reactions as a function of cation, anion and liquid crystallinity of the reaction media, allowed

Introduction

Solvents play a crucial role in most chemical reactions, from the small scale of the laboratory to large-scale, industrial applications. The properties of a solvent (e.g. dielectric constant, boiling point, vapour pressure) can have a profound influence on reactions taking place within it, for example, by affecting the solubility of reagents or products, promoting desired reaction pathways by preferential stabilisation of certain transition states, or simply by allowing control over the reaction temperature. Solvents can also have a significant impact on the sustainability of a chemical process, and there is a great deal of current interest in alternative solvent systems that may allow for greener processes. As such, choice of solvent is an important part of the optimisation of many reactions.

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for the effects of liquid crystallinity to be distinguished from anion effects or cation alkyl chain length effects. These data strongly suggest that the proportion of *exo*-product increases as the reaction media is changed from an isotropic IL to a LCIL. A detailed molecular dynamics (MD) study suggests that this effect is related to different hydrogen bonding interactions between the reaction media and the *exo-* and *endo-*transition states in solvents with layered, smectic ordering compared to those that are isotropic.

In recent years, ionic liquids (ILs) have emerged as a novel class of solvent with properties that are often rather different to conventional reaction media (e.g. their ability to dissolve solutes with a range of different polarities, negligible vapour pressures, and high chemical and thermal stability). Significant efforts have been made to understand the role that ILs can play as tuneable, neoteric solvents for organic synthesis, catalysis, the synthesis of nanomaterials and many more.^[1] However, most conventional solvents and ILs have one property in common, that they are isotropic fluids, that is, they exhibit no long-range ordering in their liquid state. There exists significant untapped potential in reaction media that are anisotropic fluids, which are structured and exhibit long-range ordering that is resistant to perturbation. The order inherent in these phases could place steric or electronic constraints on reactants, transition states or products so provide a directing influence on a chemical reaction and thus increasing the chemist or engineer's toolkit for controlling reaction outcomes. Liquid crystals (LCs) are anisotropic fluids that form a wide range of phase types with different structures and as such have significant potential to be used as ordered reaction media, which may allow control over the rate and/or stereochemical outcome of reactions taking place within them. Other systems that structurally confine reactants, for example, micelles or coordination cages, have previously been shown to influence reaction outcomes.^[2] The long-range ordering and chemical and structural versatility of LCs gives them additional opportunities for chemical control compared to these systems.

Thermotropic LCs were investigated for their potential to influence the outcome of chemical reactions in a range of systems in the 1980s.^[3] Many interesting results were obtained, but two main issues are likely to have held back developments

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in this area. Firstly, neutral thermotropic LCs are not particularly versatile solvents, tending to dissolve only those substrates with relatively similar polarity, functional groups and structure to the LC phase itself. Secondly, and perhaps more importantly, the addition of solutes to LC phases tends to destabilise them, leading to loss of their ordered structures. ILs that display liquid-crystalline mesophases, liquid-crystalline ILs (LCILs), have the potential to overcome both of these problems. The ability of ILs to solubilise a range of substrates of differing polarities is well known and so LCILs are likely to be much more versatile solvents than neutral LCs. The ability to influence reaction chemistry occurring within the LCIL by chemical modification of the anion or cation also gives significant potential to 'tune' the properties of a LCIL to suit a reaction of interest. In addition to their favourable solvent properties compared to neutral LCs, LCILs often form mesophases that are stable over a wide temperature range (over 200°C in some cases).^[4] This means that LCILs are significantly more tolerant to the addition of non-LC compounds and any depression of the clearing point that occurs on adding solutes will still leave a very large LC range within which to work. As such, LCILs represent extremely attractive targets as LC solvents.

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Although there have been many reports of ILs being used as reaction media, there are few reports of the use of LCILs as reaction media. Lee et al., used the LCIL 1-dodecylimidazolium chloride ([C₁₂mim]Cl·H₂O_n), formed as its hydrated salt by protonation of 1-dodecylimidazole with aqueous HCl, as a reaction medium for the Diels-Alder (DA) reaction between cyclopentadiene and diethylmaleate.^[5] The stereochemical outcome of this reaction (i.e. the ratio of endo- to exo-product) was significantly different to that found when EtOH was used as a solvent (0.85 vs. 7.3, respectively) and it was proposed that this may indicate a liquid-crystalline effect on the stereochemistry of the reaction. However, later studies by Welton and Dyson, which investigated the endo:exo ratio for the DA reaction between cyclopentadiene and methyl acrylate in a range of ILs,^[6] found that there is a significant difference in endo:exo ratio between different ILs and between ILs and some conventional solvents. These observations have been attributed to hydrogen bonding between the solvents and the carbonyl oxygen of the dienophile, which favours the endo transition state to varying degrees depending on hydrogen bonding ability.^[6a] Hence, because only two solvent systems were considered in the study by Lee et al., it is not clear whether their observations are evidence of a liquid-crystal effect on this reaction or simply a consequence of changing between the very different solvent systems of EtOH and the LCIL. In addition, the potential for HCI and/or significant H₂O impurities in the LCIL used by Lee et al. may complicate the analysis of these data.

A recent study by Do and Schmitzer showed that LCILs with layered smectic T (SmT) phases can promote an intramolecular over an intermolecular DA reaction, when compared to a conventional isotropic IL ($[C_4 mim][Tf_2N]$).^[7] This is suggested to occur because the substrate conformation that leads to intramolecular reactivity is favoured in the LCIL and because substrate molecules are well-dispersed so that bimolecular reactivity is disfavoured. Although potentially compelling, this study only compared reactivity in one LCIL with one conventional IL, the chemical structures of which are somewhat different and so there is still some potential for the chemical differences between the salts to play a role in the observed results, in addition to changes in ordering.

To shed more light on the possibility for ordered LCIL solvents to influence the outcome of a chemical reaction, we have re-investigated the DA reaction between cyclopentadiene and methyl acrylate in a range of ILs and LCILs. In particular, combinations of these solvents were chosen in order to allow the best possibility of distinguishing between anion effects, alkyl chain length effects and true liquid-crystalline effects on the stereochemical outcome of this reaction. This reaction was chosen because benchmark data from the Welton^[6a] and Dyson^[6d] groups were available for some of the ILs used, which allowed us to gain confidence in the results, by comparison with previous established reactions.

Results and Discussion

The DA reaction between cyclopentadiene and methyl acrylate proceeds via a highly ordered transition state, which can have either an *endo* or *exo* geometry, leading to two different stereochemical outcomes (Figure 1). It was anticipated that such ordered transition states would interact in different ways with the ordered structure provided by a LCIL solvent, leading to differences in the stereochemical outcome of the reaction compared to isotropic reaction media.



Figure 1. The *endo* and *exo* transition-state structures and their products for the DA reaction between cyclopentadiene and methyl acrylate.

DA reactions such as this have been studied in detail in conventional solvents and the *endo:exo* product ratio is known to be sensitive to the solvent used.^[8] However, there tends to be a preference for the *endo* product in many of these reactions (the so-called '*endo* rule'). The origin of this effect has been the subject of much debate and factors such as secondary orbital interactions and unfavourable steric interactions between oxygen atoms on the dienophile and the methylene protons on cyclopentadiene in the *exo* transition state are likely to play a role.^[9] A number of studies have explored DA reactions involving cyclopentadiene in ILs.^[6,10] As with conventional solvents, there is a general preference for the *endo* product when ILs are used as reaction media, but the observed *endo:exo*

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ratios are strongly dependent on the nature of the IL used (see Table 1 for examples). Welton et al. have suggested that hydrogen bonding between the acidic C-2 proton of imidazoliumbased ILs and the carbonyl oxygen of methyl acrylate particularly stabilises the *endo* transition state in these solvents.^[6a]

The ILs and LCILs for this study were chosen to investigate the effects of different anions, increasing alkyl chain length, LC effects and the effects of different LC mesophase structures on the *endo:exo* ratio. Figure 2 shows the structures and abbreviated names used for each of the ILs and LCILs used. The LC phases observed and their temperature ranges for the LCILs are shown in Table 1 (entries 11–15).

We used a similar experimental procedure to that described by Welton et al. and Dyson et al. to study the DA reaction between cyclopentadiene and methyl acrylate in IL and LCIL solvents (see the Supporting Information for details).^[6a,d] It was hoped that by using comparable reaction conditions and repeating some of the measurements made previously, we could validate our methodology and ensure that the endo:exo product ratios were not being biased by potential impurities present in the ILs. All ILs and LCILs in this study were synthesised and dried to minimise potential impurities such as halide salts and water (see the Supporting Information for details). A comparison of the endo:exo ratios between this study and those of Welton and Dyson (Table 1, entries 1-4) showed that for ILs based on the bis(trifluoromethylsulfonyl)imide ([Tf₂N]⁻) anion there is a very good agreement between the three studies, with a maximum deviation of 0.1 in the endo:exo ratios. How-



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Figure 2. The IL and LCILs, and their abbreviated names, used in this study.

ever, although there is good agreement between the present study and that of Welton for $[C_4mim][BF_4]$ and $[C_4mim][PF_6]$, the data from Dyson's study find lower *endo:exo* ratios for these two ILs. This has been discussed previously in terms of the concentration-dependence of the *endo:exo* ratio in these reactions and the different concentrations used in the two studies.^[6d] In any case, the good agreement between the pres-

Table 1. Phase-transition temperatures and *endo:exo* ratios for the DA reaction between cyclopentadiene and methyl acrylate observed here and in selected related studies. For LCIL materials POM measurements were used to check that the LCIL+substrate mixtures displayed the desired LC mesophase at 25 °C.

Entry	IL/LCIL	Transition ¹	Temp. [°C]	endo:exo (literature)	endo:exo (this work) ^[c]
1	[C₄mim][PF ₆]			4.8 ^[a] , 3.8 ^[b]	4.7
2	[C₄mim][BF₄]			4.6 ^[a] , 3.5 ^[b]	4.4
3	[C₄mim][Tf₂N]			4.3 ^[a] , 4.2 ^[b]	4.2
4	[C ₈ mim][Tf ₂ N]			3.9 ^(b)	4.0
5	[C ₈ mim][Br]				4.0
6	[C ₈ mim][BF₄]				4.0
7	[C ₁₂ mim][Tf ₂ N]				3.8
8	[C ₈ mim][PF ₆]				3.8
9	[fan-c8-im][Tf ₂ N] ^[d]	Cr–lso	9.0		3.8
10	[gemini-848][Tf ₂ N] ^[d]	Cr–lso	42.5		3.7
11	[fan-c8-im][PF ₆] ^[e]	Cr–Col _h	-38.0		3.6
		Col _h –Iso	73.0		
12	[C ₁₂ mim][Br] ^[f]	Cr–SmA	45.8		3.5
		SmA–Iso	126.0		
13	[fan-c8-im][BF ₄] ^[d]	g–Col _h	-35.1		3.4
		Col _h –lso	132.7		
14	[C ₁₂ mim][BF ₄] ^[g]	Cr–SmA	7.4		3.3
		SmA–Iso	37.0		
15	[gemini-848][BF₄] ^[d]	Cr–Col _h	34.4		3.3
		Col _b –lso	237.5		
16	methanol			6.7 ^[h]	
17	ethanol			5.2 ^[h]	
18	acetone			4.2 ^[h]	
19	diethylether			2.9 ^[h]	

[a] From ref. [6a]: 72 h at 25 °C. [b] From ref. [6d]: 24 h at room temp. [c] This work: one week at 25 °C. [d] Phase change data (on 1st cooling) from ref. [4b]. [e] Phase change data (on 1st cooling) from ref. [4e]. [f] Phase change data from ref. [11]. [g] Phase-change data (on 1st cooling) from ref. [12]. [h] From ref. [8a].

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ent study and Welton's data, which were collected using similar conditions, gave us confidence in both the ILs and the methodology used for the DA reaction.

Figure 3 shows a plot of the *endo:exo* ratios seen in this study for each of the ILs and LCILs used as reaction media. In general, it was seen that increasing the volume fraction of alkyl chains compared to polar groups (defined as the imidazo-lium ring, including the α -carbons of the alkyl groups at the



Figure 3. Chart showing the *endo:exo* ratios in each IL for the DA reaction studied here. Error bars are set at +/-0.05, as the median deviation seen between the *endo:exo* ratio in this study and previous studies was 0.1. The insert shows selected *endo:exo* ratios for four ILs, which allow anion and LC effects to be disentangled.

ring, and the anion) in the ILs resulted in a decrease in the endo:exo ratio. For example, increasing the alkyl chain length on $[C_n mim][Tf_2N]$ salts from C₄, to C₈, to C₁₂ gave endo:exo ratios of 4.2, 4.0 and 3.8, respectively. Increasing the number of alkyl chains on a cation, albeit in a system with a slightly different chemical structure, from [C₈mim][Tf₂N] to [fan-C8-IM][Tf₂N] also decreases the endo:exo ratio from 4.0 to 3.8. These are small effects, but we believe that they are significant based on the close agreement (endo:exo ratio within 0.1) between this study and previous work for [Tf₂N]-based ILs, where one might expect the data to be most scattered because the ILs used were synthesised completely independently and DA reactions were performed in different laboratories. The fact that the endo:exo ratio decreases as the volume fraction of the IL occupied by non-polar alkyl chains increases is consistent with observations in conventional solvents, whereby this ratio decreases with decreasing solvent polarity. Entries 16-19 in Table 1 show how the endo:exo ratio for this reaction decreases markedly from methanol ($\varepsilon = 6.7$) to diethylether ($\varepsilon = 2.9$). Molecular dynamics (MD) studies (vide infra) suggest that the DA products (and one can assume from this also the starting materials)

spend the majority of their time in the non-polar alkyl chain region of an IL such as [C12mim][Tf2N]. As such, it makes sense that the endo:exo ratio will move towards that seen in nonpolar solvents as the IL volume is increasingly filled by nonpolar domains. However, the MD simulations also suggest that although the reactants/products may be located predominantly in the alkyl chain regions, they do make contact with the polar domains from time to time, which allows for crucial interactions (such as imidazolium C-H-O hydrogen bonding), which can influence the reaction, to take place. These observations are somewhat different to those in related DA reactions in micelles,^[13] for which little difference is seen between endo:exo ratios in pure water and in the presence of surfactant. The substrates appear to feel a much more polar environment in the micellar systems compared to ILs containing significant non-polar domains.

Changing the anion also affects the *endo:exo* ratio in this DA reaction. In ILs containing the $[C_4 \text{mim}]^+$ cation, moving from $[\text{Tf}_2\text{N}]^-$ to $[\text{BF}_4]^-$ to $[\text{PF}_6]^-$ increases the *endo:exo* ratio from 4.2 to 4.4 to 4.7 respectively. In previous studies, this has been discussed in terms of competition between the anion and the DA substrate/TS for hydrogen bonding to the relatively acidic imidazolium C-2 proton, which seems to favour formation of the *endo* product.^[6a]

An understanding of alkyl chain and anion effects on the *en-do:exo* ratio allows for the possibility of LC effects on the stereochemical outcome of this DA reaction to be explored, and crucially to be distinguished from competing effects due to changing the chemical structure of the IL/LCIL. In general, the LCIL solvents (entries 11–15 in Table 1) show lower *endo:exo* ratios compared to the isotropic ILs. One reason for this is that these systems have larger volume fractions of non-polar alkyl chain effect. However, the data also give a strong indication that the anisotropic ordering of the LCILs has an impact on the observed *endo:exo* ratio.

Examining in detail entries 2, 3, 7 and 14 in Table 1 (also highlighted as an insert in Figure 3), which show the stereochemical outcome of the reaction for [C₄mim][BF₄], [C₄mim] [Tf₂N], [C₁₂mim][Tf₂N] and [C₁₂mim][BF₄], allows alkyl chain, anion and LC effects to be disentangled. Moving from [C₄mim] [Tf₂N] to [C₄mim][BF₄] leads to a higher endo:exo ratio (4.2 to 4.4), thus the anion effect from $[\mathsf{BF}_4]^-$ to $[\mathsf{Tf}_2\mathsf{N}]^-$ increases the amount of endo product that is formed. Making the same anion substitution for the $[C_{12}mim]^+$ cation, from $[C_{12}mim]$ [Tf₂N] (which is an isotropic liquid) to [C₁₂mim][BF₄] (which is a LCIL that displays a layered smectic A (SmA) phase at 25 °C) would be expected to result in the same type of anion effect, that is, that the amount of endo product would increase relative to the exo product. In fact, moving from [C₁₂mim][Tf₂N] to [C12mim][BF4] leads to the opposite effect and a marked decrease in the endo:exo ratio, from 3.8 to 3.3, is seen. The anion effect is therefore not driving this change in the stereochemical outcome of the reaction. Although there is a small increase in the volume fraction of the liquid that is taken up by the alkyl chains on moving between these salts, the magnitude of the observed change in endo:exo ratio is much larger than

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would be consistent with a simple alkyl chain effect. As such, it seems there is a strong suggestion that in these systems the anisotropic ordering of the LCIL $[C_{12}mim][BF_4]$ has an impact on the stereochemical outcome of this reaction, increasing the proportion of *exo* product that is formed. This would be consistent with the sterically less demanding nature of the *exo* transition state being slightly better accommodated by the ordered fluid that is the LCIL. To test this assumption, detailed MD studies were conducted and are now described.

Molecular dynamics studies

To gain a deeper insight into the experimental observations and to provide a molecular basis upon which to understand the LC effects described above, a detailed MD study of selected IL, LCILs and solutions containing the *endo* or *exo* product of these materials was undertaken. The reaction products were used as proxies for the transition states (TS) in the DA reaction, as their structures are quite similar to the TSs, but being ground-state species, are significantly simpler to parameterize for the MD simulations.

1. Ionic liquids as crystalline, liquid-crystal (LC), and isotropicliquid media

Figure 4 shows three MD simulation snapshots of 1-dodecyl-3methylimidazolium tetrafluoroborate, $[C_{12}mim][BF_4]$, as a crystalline phase, as a liquid crystal, and as an isotropic liquid (panels a-c, respectively). Each panel is supplemented by a set of three radial distribution functions between selected atoms belonging to the charged parts of the cation (the carbon between the two nitrogen atoms in the imidazolium ring) and the anion (the boron atom). The three possible combinations (cation–anion, cation–cation and anion–anion) are depicted as green, blue and red lines, respectively.

The simulations in the crystalline phase of $[C_{12}mim][BF_4]$ were started from initial configurations based on crystallographic information for $[C_{12}mim][PF_6]$ deposited at the CCDC (ref: HIWNOQ).^[14] The crystals exhibit layered structures, in



Figure 4. (left panels) Radial distribution functions, RDFs, between interaction-centre pairs representative of the charged parts of the $[C_{12}mim](BF_4]$ ions. Green lines = cation(imidazolium ring C2 atom)-anion(boron atom) RDFs; red = anion-anion RDFs; blue = cation-cation RDFs. (right panels) simulation snapshots of the corresponding IL phases. a) $[C_{12}mim](BF_4]$ crystal; b) $[C_{12}mim](BF_4]$ SmA liquid crystal; c) $[C_{12}mim](BF_4]$ isotropic liquid.

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which the anions and the polar moiety of the cations (red and blue, respectively) form different tiers separated by non-polar regions composed of the dodecyl chains. The distance between the polar planes in [C₁₂mim][PF₆] is 1.63 nm (minimal distance between boron atoms belonging to two polar planes mediated by the non-polar strata), whereas in [C₁₂mim][BF₄] the distance obtained after equilibration of the MD runs is 1.75 nm. The larger distance observed between the polar planes in the $[BF_4]^-$ salt, despite the fact that both systems contain C_{12} chains, can be rationalised in terms of the smaller area occupied by the [BF₄]⁻ ions in the polar planes and the smaller tilt of the dodecyl chains relative to the polar planes (31° in [C₁₂mim][BF₄] against 34° in [C₁₂mim][PF₆]) that is necessary to accommodate this (see the Supporting Information for an illustration of this). The multitude of peaks in the corresponding q(r) functions (Figure 4, top-left panel) reflect the ordering of the ions within each plane. The liquid-crystalline phase of [C₁₂mim][BF₄] was obtained by partially melting the corresponding crystalline phase using a series of temperatureannealing runs. The snapshots show a smectic phase in which the layered structure of the crystal remains; order is still maintained in the direction normal to the planes/strata but disrupted in the two in-plane directions. This can be seen by the 'fusing' of the peaks in the corresponding q(r) functions. Nevertheless it must be stressed that the same degree of charge ordering is maintained within each polar plane as attested by the out-of-phase character of the three functions depicted. The distance between polar planes increases to a value of 1.90 nm (and the tilt from the normal decreases to 18°). Some ordering is also maintained within the non-polar strata: dodecyl chains originating from two different polar layers adopt interdigitated configurations relative to each other (cf. Figure 5).

Finally, some simulations were performed in the isotropicliquid region of [C₁₂mim][BF₄]. These were obtained starting from expanded and random configurations containing both ions. Here, the layered structure is lost but the segregation of the system into polar and non-polar domains is retained. On one hand, charge ordering within the polar domains is very similar to that observed for the liquid-crystal phase (cf. middleleft and bottom-left panels of Figure 4). On the other hand, Xray diffraction studies predict (by extrapolation) that in this case the non-polar domains should have characteristic thicknesses of 3.10 nm.^[15] This very large increase in the bulk of the non-polar domains can be understood if one recognises that the non-polar domains are no longer constrained to strata (they can also form more globular structures) and that, whereas the chains are interdigitated in the crystal or liquid-crystalline structure, the dodecyl chains can adopt head-to-head and/ or side-by-side configurations in the isotropic liquid, for example as seen in Figure 5.

2. endo/exo molecules in the IL media

The different characteristics of the ILs can now be used to rationalise their behaviour as reaction media, namely their effect on the ratio of *endo/exo* products obtained in the DA reaction between cyclopentadiene and methyl acrylate. Figure 6 a shows the *endo*-to-*exo* ratio as a function of the alkyl side chain obtained in six different IL media that were also mod-



Figure 5. Radial distribution functions, RDFs, between interaction-centres in the alkyl side chains of the imidazolium rings in $[C_{12}mim][BF_4]$. The colour coding refers to pairs of carbon atoms occupying the same position in the dodecyl chain (e.g. a C7–C7 RDF is depicted in red). a) [C12 mim][BF_4] isotropic liquid.; b) [C12 mim][BF_4] SmA liquid crystal. The change in height of the first RDF peak along the two series — monotonous in a), with a maximum in b)—reflect the parallel (head-to-head) or interdigitated arrangements of the alkyl side chains in the two cases, as depicted by the two inserts.

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Figure 6. a) Experimental *endo/exo* ratio of DA products in six different ionic liquids as a function of the alkyl side chain length, $n_{c'}$ in the IL cation. The heights of the symbols correspond to the estimated uncertainty of the experimental data (ca. 0.05). b) Volume fraction occupied by the polar network of the ILs, x_v polar, as a function of n_c . The inset correlates directly x_v polar with the experimental *endo/exo* ratio. c) The number of contacts, OC–HCR/W, between the carbonyl oxygen atom of the *endo* or *exo* compound (OC) and one of the aromatic hydrogen atoms of the imidazolium ring (HCR, HCW₁ or HCW₂). The inset correlates directly OC–HCR/W with the experimental *endo/exo* ratio. The red circles indicate bis(triflamide)-based ILs ([C₄mim][Tf₂N]); the blue squares represent tetrafluoroborate-based ILs ([C₄mim][BF₄], [C₈mim][BF₄]) and [C₁₂mim][BF₄]). The thinner blue square in c) corresponds to [C₁₂mim][BF₄] simulated as an isotropic liquid phase.

elled using MD simulations. One of the ionic liquids under discussion, $[C_{12}mim][BF_4]$, can exhibit a SmA phase.

The *endo*-to-*exo* ratio always decreases with increasing alkyl chain length in the ILs. It is a known fact that the polarity of the reaction media strongly influences the *endo*-to-*exo* ratio of a DA reaction:^[8] strongly dipolar media favour the *endo* product (e.g. in methanol the *endo*-to-*exo* ratio of 6.7, Table 1), whereas more apolar solvents reduce such tendency (e.g. in toluene or in ethers, the *endo*-to-*exo* ratio is around 3). Although there is still some controversy regarding the origin of such solvent effects—theories range from hindrance and deformation of the transition state to stabilisation of π -orbitals involved in the cycloaddition reaction^[8–9]—one can certainly transpose these facts to the media under discussion.

Given the fact that ILs are segregated at a nanoscopic level (a polar network permeated by non-polar domains), the most obvious way to rationalise this behaviour is to calculate the volume fraction occupied by the polar network for each type of ionic liquid. Figure 6b shows the polar volume fractions, x_{y} as a function of the alkyl side chains for the six ILs under discussion. The x_v polar results were estimated taking into account the volume of each ion and non-polar moiety, calculated by a group-contribution scheme based on the additive volumetric behaviour of ionic liquids.^[16] The results show that the volume fraction occupied by the polar network decreases with the increasing length of the alkyl side chains in a way similar to the trends observed for the endo-to-exo ratios. In other words, as the alkyl chains of the ionic liquid grow longer, the DA reactants find themselves more often than not in a more non-polar alkane-like environment, which decreases the endo-to-exo ratio. In other words, the ionic liquids are amphiphilic solvents for which the amount of each part (polar and non-polar regions) can be inferred by the corresponding polar volume fraction. Nevertheless, when one compares the two IL series based on the bistriflamide and tetrafluoroborate anions, respectively, one can notice that the steeper endo-enrichment trend observed for the latter series relative to the former one is not totally reflected by the corresponding polar volume fraction shifts. Moreover, the liquid-crystalline nature of the $[C_{12}mim]$ [BF₄] system is not a factor in a simple calculation of polar volume fraction.

To analyse the types of interaction present in the different systems in more detail, it was decided to compute the number of interactions between the *endo* and *exo* products and the polar network of the ionic liquid. In this case the *endo* and *exo* products are acting as proxies for the two DA reactants arranged in the corresponding transition states. We performed several MD runs with either the *endo* or *exo* isomers present. In most cases we did not observe any difference in the results within statistical uncertainty. Thus, unless otherwise stated explicitly, the following discussion will be based on results that are the data average from both types (*endo* and *exo*) of run.

Figure 7 shows the pair radial distribution functions (RDFs) between the oxygen atom (OC) in the carbonyl group of the *endo/exo* product and the most acidic aromatic hydrogen atom (HCR) of the imidazolium cation (hydrogen in the 2-position—see Table 2 inset) in [C_n mim][Tf₂N] (n = 4, 8, 12) solutions. We have chosen these two interaction centres as the most representative of the possible specific interactions taking place between the DA products (or reactants in the transition state) and the polar parts of the ionic liquid. RDFs between interaction centres in the anions and in the *exo* and *endo* products show no specific interactions.

Integration of the RDFs up to a cut-off distance of 2 nm allowed us to calculate the number of *endo/exo* compounds (OCs) and IL cations (HCRs) within the cut-off radius and the total number of possible (HCR–OC) pairs. These numbers (depicted in Figure 7a–c) were combined with the values (also depicted between parentheses in Figures 7a–c) obtained from the total number of species within the simulation box and the volume ratio between the cubic boxes and the cut-off spheres. The conformity of the numbers reflects the fact that at the cut-off distance of 2 nm, the anisotropy of the IL has been averaged-out relative to the centre of the cut-off sphere. This

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Figure 7. Radial distribution functions, RDFs, between interaction centres in the *endo* or *exo* DA products (oxygen atom, OC, of the carbonyl group) and in the IL cation imidazolium ring (aromatic hydrogen atom, HCR, connected to the C2 (=CR) carbon atom). a) [C₄mim][Tf₂N]; b) [C₈mim][Tf₂N]; c) [C₁₂mim][Tf₂N]. The light shaded areas beneath the RDFs correspond to integrations up to cut-off radii of 2 nm, yielding the number of DA products found within the cut-off sphere and the total number of possible DA products-IL cation pairs. The dark shaded areas correspond to contact in DA compound-IL cation pairs.

allowed us to estimate with some confidence the number of contact (HCR-OC) pairs by integration under the first RDF peaks (up to a distance of ca. 0.4 nm).

The number of HCR–OC contact pairs decreases as the alkyl side chain along the $[C_nmim][Tf_2N]$ increases. If the number of HCR–OC contacts per *endo/exo* compound present in the box are calculated (cf. column 6 in Table 2), the values also decrease along the series, confirming the 'dilution' of the charged part along the IL series, the more 'non-polar' environment felt by the *endo/exo* products and, consequently, their tendency to

yield smaller *endo*-to-*exo* product ratios. This is apparent if data for $[C_n mim][Tf_2N]$ in Figure 6a–c are compared: the *endo*-to-*exo* ratio versus alkyl side chain length (Figure 6a) is reflected both in the trends found for the volume fraction occupied by the polar network (Figure 6b) and for the total number of contacts between the OC oxygen of the *endo/exo* products and the aromatic hydrogen atoms of the imidazolium rings (Figure 6c). It must be stressed that Figure 7 shows only the contact pairs involving the HCR hydrogen atom of the imidazolium ring. Table 2 includes the partial (columns 6–8) and total (column 5) number of contacts for each type of OC–HCR/W contact per number of *exo/endo* molecules present in the cut-off sphere (inset to Table 2 gives a key).

Similar RDF integration procedures were performed for the $[C_n mim][BF_4]$ series. In this case we have modelled the $[C_4 mim][BF_4]$, $[C_8 mim][BF_4]$ and $[C_{12} mim][BF_4]$ systems not only as isotropic fluid media but also, in the case of $[C_{12} mim][BF_4]$, as a SmA phase.

The RDF integration results (also included in Table 2) show that the number of OC–HCR/W contacts decreases faster in the [BF₄]-based IL series than in the [Tf₂N]-based one—a trend that is not captured fully in the polar volume fraction analysis (cf. Figure 6b), probably because the specificity of the interactions between ions within the polar network is not taken into account. A more pronounced segregation between polar and apolar domains in the isotropic [C₁₂mim][BF₄] relative to all other isotropic ILs (for which the volume fraction occupied by the non-polar domains is smaller and the tendency to form LC structures is suppressed) can explain the relatively low values for the contacts between the DA product and the charged parts of the IL. These facts can also be appreciated by the correlations between the two types of analysis and the observed *endo*-to*-exo* ratios (cf. insets in Figure 6 b and 6 c).

Table 2 and Figure 6c also show that there is a difference between the results obtained for the endo/exo compounds included in [C₁₂mim][BF₄] modelled as an isotropic liquid or as a SmA liquid crystal. The experimental endo-to-exo ratios correlate very well with the contact numbers obtained in the (real) [C₁₂mim][BF₄] liquid crystal phase, but deviate from those obtained in the (hypothetical) [C₁₂mim][BF₄] isotropic liquid, (cf. Figure 6 c). In fact it is quite easy to unveil the reason behind the lower number of OC-HCR/W contacts (and lower observed endo-to-exo ratios) in the SmA phase: the layered nature of the polar network of the smectic ionic liquid crystal (cf. Figure 4b) means that one of the HCW hydrogen atoms of the imidazolium ring (labelled in our simulations as HCW₂) is embedded within the polar layer. Since the DA reactants spend very little time within the polar network (they are located preferentially within the alkyl chain regions of the LCIL) they are therefore not able to interact with HCW₂. This fact is endorsed by the MD simulation results, which show that the decrease in the number of OC-HCR/W contacts from the [C12mim][BF4] liquid to the [C₁₂mim][BF₄] liquid crystal is due to the large decrease in the number of OC-HCW₂ contacts (cf. final column of Table 2). In other words, the observed endo-to-exo ratio is even

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Table 2. Summary of experimental, correlation, and molecular dynamics simulation data calculated for the seven (IL plus DA) products under discussion. The experimental results (EXP) refer to *endo*-to-*exo* ratios of DA products; the correlation (CORR) results refer to estimations of the volume fraction of the system occupied by the polar network of the ionic liquid; the MD results tally the number of contacts between the DA products and the charged part of the IL cations per DA product found in the simulation box.

IL/Media	<i>n</i> _c	endo/exo EXP	x _v polar CORR	ΣOC-HCR/W MD	OC-HCR MD	OC-HCW ₁ MD	OC-HCW ₂ MD		
[C₄mim][BF₄]/ISO	4	4.35	0.73	1.03	0.30	0.35	0.38		
[C ₈ mim][BF₄]/ISO	8	3.95	0.53	0.84	0.25	0.29	0.30		
[C ₁₂ mim][BF ₄]/ISO	12	NA ^[a]	0.42	0.54	0.20	0.17	0.17		
[C ₁₂ mim][BF ₄]/LC	12	3.30	0.42	0.40	0.20	0.17	0.03		
[C₄mim][Tf₂N]/ISO	4	4.20	0.83	1.00	0.30	0.35	0.35		
[C ₈ mim][Tf ₂ N]/ISO	8	4.00	0.67	0.85	0.27	0.27	0.30		
[C ₁₂ mim][Tf ₂ N]/ISO	12	3.80	0.56	0.73	0.22	0.27	0.24		
[a] DA reaction not attempted in the isotropic phase of $[C_{12}mim][BF_a]$, by heating above the clearing point, due to the volatility of the cyclopentadiene									

(b.p. = 41 °C).

lower than expected in the LC-based systems because one potential C–H hydrogen bond donor site is hidden from the Diels–Alder reactants because of the layered ordering of the SmA phase. This effect is not seen in the isotropic liquids, for although they display nanoscale segregation of the polar and non-polar parts of their constituent ions, the cationic head groups are orientated randomly in the polar domains and so all parts of the cation are accessible to solutes residing in the non-polar regions. Thus, there is an LCIL effect in this system (at least for $[C_{12}mim][BF_4]$) where the order in the system causes the LC phase to appear less polar than the isotropic phase. This results in an increased proportion of *exo* product, as expected from the shift in apparent polarity.

The MD simulation runs have also unveiled other interesting structural issues. Thus, during the course of the simulation runs we have witnessed several (unexpected) events where one of the endo or exo compounds would leave the non-polar strata where it usually resides for periods of some nanoseconds, partially disrupt a polar layer, get embedded in it for some tenths of nanoseconds (in the mid-region of the doubleplane polar layer), and eventually migrate to a neighbouring (or return to the original) non-polar stratum (Figure 8). During the whole process the polar network contained in the polar planes was always able to accommodate the (bulky) DA compound without any disruption of the layered structure of the smectic ionic liquid (a movie of this process is given in the Supporting Information). Such permeability and resilience of the polar layers is another proof of the flexibility and adaptability of the strong electrostatic interactions that exist among the IL ions.

Although the simulations were performed with very few solute molecules (1–6 *endo* or *exo* compounds in systems with a few hundred ion pairs) and the corresponding statistics are poor for the estimation of cross interactions—the main conclusions concerning the *endo*-to-*exo* ratio drawn from the previous analyses of results from the MD runs with *endo* and *exo* results combined—the runs in the smectic $[C_{12}mim][BF_4]$ system seemed to suggest some sort of differentiation between the two types of molecules. It can be seen from Figure 9a that the *exo* product appears to form a more significant interaction



Figure 8. Three simulation snapshots showing the DA products in the SmA liquid crystal phase of $[C_{12}mim][BF_a]$. (bottom) DA product in a non-polar, alkane-like layer; (middle) DA product embedded in a polar layer; (top) DA product exiting to another non-polar layer. The three snapshots occurred during the same simulation run and were registered a few ns apart.

with HCR than the *endo* form. One can speculate that the more structured nature of the SmA LCIL promotes better interactions between the polar layer and the more exposed carbonyl group of the *exo* product. If this is so (and assuming again that the DA product can be used as a proxy for the reactants arranged in the corresponding transition state) the *exo* product would also react more efficiently and the outcome would also contribute to the observed lower *endo*-to-*exo* ratio in liquidcrystalline ILs.

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Figure 9. Radial distribution functions, RDFs, between interaction centres in the *endo* or *exo* DA products (oxygen atom, OC, of the carbonyl group) and in the IL cation imidazolium ring (aromatic hydrogen atoms, a) HCR, b) HCW_1 and c) HCW_2) in the $[C_{12}mim][BF_4]$ smectic liquid crystal phase system. Red lines: *exo* DA product system; blue lines: *endo* DA product system.

Conclusion

As outlined briefly in the introduction, one of the attractions of using liquid crystals as reaction solvents is the inherent order that characterises the mesophase, which it is postulated can affect some combination of rate of reaction and regio-/stereochemical outcome. This can be exemplified by the work of Leigh and co-workers who showed, for example, how the trans/cis isomerisation of 1,2-di(4-cyanophenyl)-1,2-diphenylethylene was slowed in LC solvents compared to isotropic solvents^[17] or how the regiochemistry of the Diels-Alder addition of *N*-biphenylmaleimide to cholesta-5,7-dien-3 β -yl acetate was influenced by carrying out the reaction in the LC mesophase.^[18] Curiously, however, in studying the Diels-Alder reaction between 2,5-dimethyl-3,4-diphenylcyclopentadienone and a variety of dienophiles, no effect of LC solvent was observed, which was tentatively attributed both to lack of discrimination in solvating the two transition states and also the high tendency for the diene to destabilise the LC phase of the solvents used.^[19] Therefore, the nature of the effect being observed is not necessarily a generalised phenomenon.

One of the reasons for choosing to investigate LCILs as solvents is the fact that the wide LC range means that it is unlikely that solutes will effect too strong a destabilisation of the LC phase and so it was envisaged that specific effects of this nature would not come into play. As such, it was reasonable, as a first assumption, that the LC effect observed in the present system arose from a combination of solvent order and anisotropy. However, the results from the atomistic simulations painted a subtly different picture.

MD simulations of the SmA phase of $[C_{12}mim][BF_4]$ suggest that the layered structure of this LCIL restricts the accessibility of C–H hydrogen bond donor groups on the IL cation to both DA products (as proxies for the *exo* and *endo* transition states) when compared to the isotropic phase. This reduces hydrogen bonding interactions between the solutes and the IL, and thus lowers the effective polarity of the solvent, which correlates well with the reduction in *endo/exo* ratio seen experimentally. This effect is not seen in simulations of the isotropic phase of $[C_{12}mim][BF_4]$ or other isotropic ILs, where all C–H bonds on the imidazolium cation are accessible to solutes. In addition, there are hints in the results of the MD simulations (Figure 9) that there is preferential hydrogen bonding to the *exo*-product (as proxy for the *exo*-transition state) in the polar region of the segregated bilayer of the SmA phase of the LCILs, which is both the more polar region (which would favour the *exo* product) and also the region in which the order of the phase is greatest (much less motional/conformational freedom owing to the electrostatic interactions locating the imidazolium cations.

Therefore, the LC effect in this system, which favours the *exo* product, is attributed to a combination of two factors: A change in apparent solvent polarity, due to the ordering present in the SmA mesophase, and better shape complementarity between the *exo* transition state and the LCIL, which leads to preferential hydrogen bonding. Both of these effects support each other to promote the formation of more *exo* product. Such a result is exciting because the detailed mechanism for the observed effect was not predicted a priori, which shows the benefit of a combined experimental and computational approach, and also because it shows that specific intermolecular interactions can be used in conjunction with the LC solvent to exert influence on the product distribution. As such, this opens up more exciting design possibilities for exploitation in other solvent/solute combinations.

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FULL PAPER

Ordered Solvents

D. W. Bruce,* Y. Gao, J. N. Canongia Lopes,* K. Shimizu, J. M. Slattery*

Liquid-Crystalline Ionic Liquids as Ordered Reaction Media for the Diels-Alder Reaction

Stereochemistry by order: Liquid-crystalline ionic liquids are used as reaction media and their ordered structures are

favoured

shown to influence the stereochemical outcome of a Diels-Alder reaction (see figure).

promoted

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