The effects of ionic liquids on azide-alkyne cycloaddition reactions†

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The effect of a series of ionic liquids on the regioselectivity of the azide-alkyne cycloaddition process was investigated, demonstrating an increased selectivity for the least hindered triazole. The effects of an ionic liquid on the activation parameters for the process were determined and found to be intermediate between coordinating and non-coordinating salts. The importance of knowing the water content of the system is demonstrated by marked changes in the activation parameters in the presence of small concentrations of water.

Introduction

Ionic liquids are arbitrarily defined as salts which are liquid below 100 °C.[1] The typically bulky and charge diffuse ions[2–4] on which they are based frustrate crystallisation, while the electrostatic forces present result in very low vapour pressures.[5] This, along with the ability to 'tune' the properties of the solvent through variation of the constituent ions,[3,4,6] has seen these systems proposed as alternatives to environmentally damaging organic solvents.[7,‡]

A current limitation to the application of ionic liquids is that the outcomes of reactions in terms of rates and selectivities often differ between ionic liquids and molecular solvents and there has been limited investigation of the origin of these changes.[8,§] To increase their application, an understanding of their effects on reactions similar to that available for molecular solvents is required.[9]

Our group has focussed on considering the key difference between molecular and ionic solvents, that being the electrostatic interactions between the components of the latter. This has involved kinetic studies of a range of substitution mechanisms,[10,11] which have demonstrated the importance of considering both the interactions of the ions with incipient charges in the transition state and with the starting materials. Particularly, the entropic change due to differences in solvent ordering has been shown to be crucial in determining the effect of ionic liquids on reaction outcome.

Of particular interest are recent results investigating the effect of a range of ionic liquids on the outcome of nitrile oxide cycloadditions.[12] Related Diels–Alder cycloadditions have been extensively studied in ionic liquids[13] and rate enhancements and selectivity changes[14] observed have been attributed to various solvent parameters,[15,16] particularly hydrogen bonding to the Lewis acidic cation.[15] In contrast, the rate enhancements observed for the nitrile oxide case[12] cannot be explained by interaction with the cation of the ionic liquid (which would, in fact, decrease the rate[17]), nor can the increase in preference for the more sterically hindered dihydroisoxazole product.[12] Rather, the results were rationalised in terms of the electrostatic interactions between the ions resulting in compression of, and hence increased steric demand in, the transition state.

The work described herein considers the effects of an ionic liquid on cycloaddition reactions between an alkyne and an azide.[18] Whilst a previous report[19] has considered such effects of ionic liquids on an azide-alkyne cycloaddition, the ionic liquid was significantly diluted by reagents ($\chi < 0.5$), only one example of effect on regioselectivity is reported and rate changes are reported qualitatively in terms of isolated yields after a given time. This report seeks to test the generality of the effects of ionic liquids on heterocycle-forming cycloaddition processes by considering at high dilution changes in regioselectivity and rates compared to molecular solvents. The origin of such effects has been probed through determination of activation parameters for the process. This overcomes a limitation present in our previous work,[12] where such kinetic interpretation was impossible due to dimerisation of the nitrile oxide starting material.

Experimental

The alkynes **1a,b** were commercially available and used without further preparation. The azides **2a–d** were prepared using literature methods, from the corresponding bromides in the case of azides **2a,b**,[20] the corresponding amine using a diazo transfer reagent[21] for compound **2c**[22] and the corresponding alcohol for the *t*-butyl case **2d**.[23] 1-Butyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide was prepared from the corresponding chloride[4] and dried to constant weight over phosphorus pentoxide. ^{1}H NMR spectra were recorded either on a Bruker Avance 500 spectrometer (500 MHz), a Bruker Avance 400 spectrometer (400 MHz) or on a Bruker DPX 300 spectrometer (300 MHz).

Mixtures of the regioisomeric pairs **3** and **4** were prepared by taking the appropriate azide **2** (*ca.* 5 mmol) in the appropriately substituted alkyne **1** (*ca.* 20 mmol) and heating at reflux for either

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† Electronic supplementary information (ESI) available: Spectral data for mixtures of the regioisomers **3** and **4**. Regioselectivity data for reaction of compounds **1a** and **2c** in various molecular solvents. Comparison of observed activation parameters to those for individual processes in parallel reactions. Activation parameters for the formation of each of the isomers **3i** and **4i** in reaction of compounds **1c** and **2a**. Rate data, activation parameters and Eyring plots for the reaction of compounds **1c** and **2a** in various solvent systems. See DOI: 10.1039/c0ob00306a

‡ It is worth highlighting that these species are not entirely innocuous (for some toxicology studies see the work of Scammells,[33] and others[34]). However, the ability to retain the solvent remains a significant advantage.

§ There are specific cases where the reactivity of the components of an ionic liquid,[35] particularly through the use of protic cations[36] and basic anions[37] alters the reaction outcome. These cases do not rely on fundamental properties of the ionic liquid and will not be referred to further here.

48 h (reactions of azides **2a–c**) or 7 days (reaction of azide **2d**). The reaction mixture was concentrated *in vacuo* to remove excess alkyne and the residue was purified using column chromatography (pentane followed by ethyl acetate) to give a mixture of the desired triazoles **3** and **4**. The connectivity of the systems was determined through comparison with literature[24] examples which either allowed for direct determination of signals due to the 4-substituted isomers **3** (and by elimination, the 5-substituted isomer **4**) or for similar core structures to be compared and the connected signals determined using COSY 2D NMR spectroscopy. This assignment allowed determination of regioselectivity by analysis of the crude reaction mixtures using ^{1}H NMR spectroscopy in these and subsequent cases.

To examine the solvent effects on regioselectivity, the appropriately substituted azide **2** (*ca.* 20 mg) and alkyne **1** (*ca.* 3 equiv.) were dissolved in the desired solvent (600 μL). The mixtures were then heated to 60 °C for two weeks. Where molecular solvents were used, the solvent was removed *in vacuo* and the crude product mixture analysed using ^{1}H NMR spectroscopy. In the case of the ionic liquids, a small sample of the reaction mixture was dissolved in deuteriochloroform and then analysed using ^{1}H NMR spectroscopy.

Kinetic analyses in solvents containing molecular solvents were carried out by preparing solutions containing the azide **2a** (*ca.* 2.5 mg) in the appropriate molecular solvent (600 μL). The molecular solvent was either d_3-acetonitrile, d_3-acetonitrile containing lithium *bis*(trifluoromethanesulfonyl)imide (5.0 g in 2.0 mL) or d_3-acetonitrile containing tetrabutylammonium tetrafluoroborate (4.0 g in 2.0 mL). The azide solution was then added to the alkyne **1c** (*ca.* 25 mg) in an NMR tube, the vessel sealed and the reaction followed at either 325, 335 or 345 K to >50% completion by considering the integration of the signal due to methyl group on the alkyne **1c** in the ^{1}H NMR spectrum. Kinetic analyses for the ionic liquid cases were carried out similarly, except that samples of the alkyne **1c** (*ca.* 2.5 mg) dissolved in the 1-butyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide/d_3-acetonitrile mixture (600 μL, 7% d_3-acetonitrile v/v) were added to the azide **2a** (*ca.* 25 mg). From this information, the pseudo first-order rate constants for the reactions under these conditions were calculated and, consequently, the second-order rate constants at each temperature were also calculated. The activation parameters were then determined using the bimolecular form of the Eyring equation.[25]

Results and Discussion

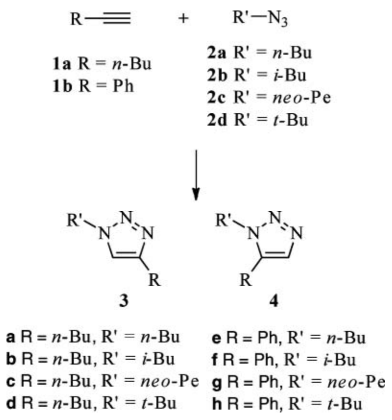
The cycloaddition reactions between each of the alkynes **1a,b** and each of the azides **2a–d** (Scheme 1) were examined to determine the steric effects of substituents on the stereoselectivity of the reaction, without significantly altering any electronic contributions. The azides **2a–d** were chosen as, along with being readily prepared, the substituents cover a large range of steric bulk as measured using Taft–Hancock constants.[26] Similarly, the commercially available alkynes **1a,b** present contrasting extremes.

After initial preparation and characterisation of the regioisomeric mixtures **3** and **4**, the regioselectivity of the process was determined through comparison of the integrations of the signals unique to each isomer due to either the 4-substiuent, the 5-substiuent or the resulting aromatic system. Relaxation time studies demonstrated insignificant differences between the signals being compared, indicating this method as reliable for determining the regioisomeric composition of these mixture. The results for reactions carried out in an excess of alkyne **1** as solvent are summarised in Table 1.

Table 1 The ratios of the triazoles **3** and **4** formed in the reaction between one of the azides **2a–d** in an excess of one of the alkynes **1a,b** at reflux. The results are the averages of triplicate experiments

Azide	**3** : **4** on reaction with alkyne **1a**[a]	**3** : **4** on reaction with alkyne **1b**[a]
2a	1.2 ± 0.1 : 1	1.00 ± 0.05 : 1
2b	1.20 ± 0.07 : 1	1.00 ± 0.05 : 1
2c	3.1 ± 0.2 : 1	1.2 ± 0.1 : 1
2d	>10 : 1[b]	3.6 ± 0.4 : 1

[a] Uncertainties quoted are 95% confidence intervals.
[b] Only one isomer was observed.



Scheme 1 The Huisgen reaction between each of the alkynes **1a,b** and each of the azides **2a–d**, carried out to determine the steric requirements of the cycloaddition process.

Reaction of each of the azides **2a,b** with each of the alkynes **1a,b** gave mixtures of the corresponding isomers **3** and **4** in approximately equal amounts indicating that there are no significant steric interactions in these cases favouring one isomer over the other. The slight decrease in regioselectivity upon using phenylacetylene **1b** highlighted a possible secondary effect when such a substituent is present (which will be discussed further below) though the effect is small when compared to subsequent changes.

Formation of the triazoles **3c** and **4c** occurred with notable regioselectivity, indicating the the neopentyl substituent introduces significant steric interactions. Whilst reaction of the alkyne **1a** with the azide **2d** did not proceed readily, only the isomer **3d** could be detected in the reaction mixture.

Perhaps surprisingly, the selectivities observed on reaction of each of the azides **2c,d** with phenylacetylene **1b** were not as marked as in the hexyne **1a** case. This was shown to not be a function of temperature¶ and replacing the phenyl group with a cyclohexene substituent did not have a significant effect.‖ This suggests that

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¶ Reactions between compounds **1b** and **2c** carried out at 50 °C rather than 90 °C result in a measured ratio of 1.02 ± 0.06 : 1 from triplicate experiments.

‖ Reactions between the azide **2c** and cyclohexenyl acetylene gave the triazoles **3** and **4** in a ratio of 1.1 : 1 from a single experiment.

Table 2 The ratios of the triazoles **3h** and **4h** formed in the reaction between reagents **1b** and **2d** in the solvent specified. The results are the averages of triplicate experiments

Solvent system	**3h** : **4h**[a]
heptane	3.2 ± 0.2 : 1
acetonitrile	5.3 ± 0.4 : 1
ethanol	3.8 ± 0.2 : 1
[Bmim][$N(SO_2CF_3)_2$] ($\chi = 0.68$)	7.3 ± 0.9 : 1
[Bmim][PF_6] ($\chi = 0.74$)	6.3 ± 0.4 : 1
[Bmim][$N(CN)_2$] ($\chi = 0.76$)	6.7 ± 0.6 : 1

[a] Uncertainties quoted are 95% confidence intervals.

the conformationally restrained nature of the substituent reduces steric effects in the transition state in these cases.

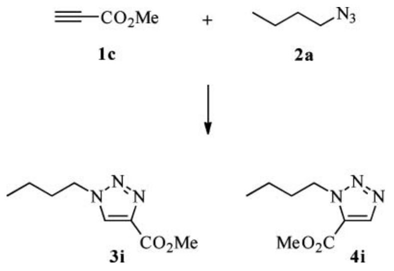
Based on the above, the reactions between the alkyne **1a** and the azide **2c** and between the alkyne **1b** and the azide **2c** were considered to examine the effects of ionic liquids on the regioselectivity of azide-alkyne cycloadditions. However, carrying out the former set of reactions in molecular solvents showed the selectivity of the process to be markedly dependent on the molecular solvent chosen (see Table S1, ESI†). The observed greater selectivity in polar solvents may be due to coiling of the butyl group on the alkyne **1a**, as has been observed for squalene,[27] increasing the steric bulk of the substituent. Irrespective, given the non-homogeneous nature of ionic liquids[28] (which contributes to the reason that use of dipole and dielectric descriptors to describe ionic liquids remains fraught[29]) the reaction site and its nature would be poorly defined in these systems. Therefore, it was considered unsuitable to examine the reaction between compounds **1a** and **2c** in ionic liquids as it would be difficult to deconvolute any data garnered, with any generic effects of the ionic liquid being impossible to separate from polarity induced effects.

The reactions producing the regioisomers **3h** and **4h** were analysed in a range of molecular solvents and ionic liquids (Table 2). The molecular solvents were chosen as they represent a range of polarity and hydrogen-bonding ability. The ionic liquids chosen are based on the 1-butyl-3-methylimidazolium ($[Bmim]^+$) cation with the charge balanced by one of three anions *bis*(trifluoromethanesulfonyl)imide ($[N(SO_2CF_3)_2]^-$), hexafluorophosphate ($[PF_6]^-$) and dicyanimide ($[N(CN)_2]^-$). Along with being representative ionic liquids from literature, being readily prepared and purified, representing a range of observed miscibility behaviour,[30] they were also considered in the nitrile oxide case previously.[12]

The effect of changing the nature of the molecular solvent on the reaction outcome in this case is not as significant as in the previous case. On changing the solvent from molecular to ionic, there was an increase in the observed regioselectivity with more of the sterically less hindered isomer **3h** formed in each of the ionic liquids. Based on the observations in molecular solvents, this change cannot be accounted for in terms of apparent solvent polarity. The observations indicate that steric interactions in the transition state are more significant in the ionic liquid cases than for molecular solvents; this is consisent with what has been observed previously for nitrile oxide cycloadditions in ionic liquids.[12] The results may, once again, be rationalised by considering a compression of the transition state resulting from the increased internal pressure of the solvent.

In the one previously reported case[19] where an ionic liquid was found to affect the regioselectivity of an azide-alkyne cycloaddition, the effect was in the opposite direction. That is, an increase in preference for the more sterically hindered isomer was observed. However, given the smaller nature of the substituents on the resultant triazole in this case and the requirement for significant steric bulk in order for regioselectivity to be observed it is unlikely that steric factors dominate in this case; interaction of the components of solution with the frontier molecular orbitals of the reagents may account for the outcome. Whilst such interactions cannot be ruled out in the examples reported here, the argument presented remains the simplest one to account for the effects of the ionic liquids and is consistent with previous findings.[12]

In order to further examine the effects of the ionic liquid on the outcome of azide/alkyne cycloaddition processes, temperature dependent kinetic studies were undertaken to garner enthalpic and entropic information. Rather than use the systems described above, which proceeded impractically slowly for kinetic studies, the reaction between the azide **2a** and methyl propiolate **1c** to give the regioisomers **3i** and **4i** was examined (Scheme 2). The polarisation of the alkyne **1c** not only increases the rate of reaction by *ca.* fifty times, but also increases the selectivity of the process to *ca.* 8 : 1 in favour of the less hindered regioisomer **3i**. The reaction was followed by observing consumption of the alkyne **1c**. As such, the activation parameters calculated clearly have contributions from each of the triazole formation pathways, however the high regioselectivity of the process means that the contribution from the major product dominates (see ESI†). Further, due to the small proportion of the minor product and the resulting uncertainties, calculated values in the acetonitrile case for each isomer were the same and so such analysis was not considered for the other systems (see Table S2, ESI†).



Scheme 2 The Huisgen reaction between the alkyne **1c** and the azide **2a** to produce the triazoles **3i** and **4i**, used for kinetic studies.

It is worth noting that in the ionic liquid case, decomposition of the alkyne **1c** was observed in concentrated solutions. Hence, an excess of the azide **2a** was used in this case and, under the conditions of the experiment (which included d_3-acetonitrile to facilitate NMR spectroscopy), the alkyne **1c** was found to be stable.

The kinetic data (see Table S3, ESI†) gathered allowed generation of an Eyring plot (see ESI†), which in turn allowed generation of the activation parameters for each system (Table 3). The activation parameters for the reaction in acetonitrile indicate two major energetic costs on going to the transition state; both entropic and enthalpic. Considering the extent of bond breakage and formation required to form the transition state, the significant

Table 3 Activation parameters for the reaction between the alkyne **1c** and the azide **2a** in the solvent system specified

Solvent system	$\Delta H^{\ddagger}$/kJ mol$^{-1\,a}$	$\Delta S^{\ddagger}$/J K^{-1} mol$^{-1\,a}$
acetonitrile	69.8 ± 2.2	−178 ± 6
acetonitrile containing lithium *bis*(trifluoromethanesulfonyl)imide ($\chi = 0.31$)	79.0 ± 3.3	−138 ± 10
acetonitrile containing tetrabutylammonium tetrafluoroborate ($\chi = 0.24$)	63.1 ± 2.3	−194 ± 7
[Bmim][N(SO_2CF_3)$_2$] ($\chi = 0.50$)	71.8 ± 3.8	−166 ± 11

[a] Uncertainties quoted are 95% confidence intervals.

enthalpy of activation is expected for the system. The negative entropy change is consistent with the two starting materials coming together in the transition state; that is, an increase in the ordering of the system occurs upon transition state formation and thus an entropic cost is incurred.

Upon the addition of lithium *bis*(trifluoromethanesulfonyl) imide to acetonitrile both the enthalpy and entropy of activation are seen to increase. The rate increases observed on moving to this system can therefore be put down to an entropic benefit offsetting an enthalpic cost. In the case of the addition of this lithium salt, the key point observed previously from regioselectivity studies of nitrile oxide cycloadditions and kinetic studies of Menschutkin reactions[31] was coordination of the starting material by the lithium cation. In the reaction being examined here, coordination of the starting materials might be expected to be greater than the transition state. This is borne out in the observed increase in both the activation parameters.

In contrast, addition of the non-coordinating salt tetrabutylammonium tetrafluoroborate to acetonitrile results in a decrease in both the activation parameters; in this case, the observed rate increases can be put down to an enthalpic benefit. The origin of this enthalpic benefit is not immediately apparent but can be considered as due to properties of the system other than coordination. The results imply either both a destabilisation and an increase in degrees of freedom of the starting materials, or a stabilisation and a decrease in the degrees of freedom of the transition state as compared to when the solvent is acetonitrile. As any interaction of the starting materials with the salt solution would likely stabilise and order the system, the above results are most likely due to a decrease in the enthalpy and entropy of the transition state. This effect may be caused by either an increase of ordering around the transition state, a compression of the transition state (likely, lowering the energy required to react and lowering the degrees of freedom) or both factors simultaneously.

The addition of >90% v/v ionic liquid [Bmim][N(SO_2CF_3)$_2$] does give a rate increase when compared to the acetonitrile case, however the differences in activation parameters between the two cases are alone insufficient to determine the origin of the effect. Consideration of the differences between the two other salts used and the ionic liquid allows some information to be garnered, as does the earlier regioselectivity studies. The latter suggest a compression of the transition state but any decrease in the activation parameters associated with such is offset by coordination of the cation to the starting materials. The former demonstrate that the ionic liquid might be considered to lie intermediate in terms of coordinating ability in this system, between the two extremes of the other salts used.

It is worth noting that some caution is required in the use of the ionic liquid [Bmim][N(SO_2CF_3)$_2$] in studying these reactions. Unless the ionic liquid is rigorously dried (reaction mixture $\chi_{H_2O} < 0.01$, corresponding to to < 0.03% v/v), the reproducibility of the rate data is typically very poor with very large changes in observed rates with small changes in the amount of water present. Further, the results for activation parameters are markedly different. For example, at χ_{H_2O} *ca.* 0.05 in the reaction mixture, corresponding to 0.15% v/v, the activation parameters are (43.2 ± 3.5) kJ mol^{-1} and (−256 ± 10) J K^{-1} mol^{-1}. Whilst it is of interest that both are much less than in acetonitrile, it is difficult (and likely not particularly useful) to discuss the origin of the change except to say that the addition of water to the ionic liquid clearly introduces greater stabilisation of, and organisation about, the starting materials. Further, it serves as a warning to highlight the importance of knowing the makeup of any ionic liquids used and confirms that the physical changes observed for small concentrations of impurities in ionic liquids[32] also translate to kinetic studies.

Conclusions

The effects of a series of ionic liquids based on the [Bmim]$^+$ cation on the addition of an azide to an alkyne showed an increase in the proportion of the less sterically hindered triazole. This is consistent, though the change not as dramatic, as that observed with nitrile oxide cycloaddition processes.[12] The rate of an azide-alkyne cycloaddition was shown to be faster in an ionic liquid than acetonitrile, though the effect was smaller than might have been expected based on the nitrile oxide case. The origin of this effect could not be attributed to either an entropic or enthalpic origin, however the effects on the activation parameters were intermediate between those of a coordinating and those of a non-coordinating salt.

Finally, this work demonstrates the importance of knowing the composition of the reaction medium. While we have shown previously the marked effects of changing the mole fraction of ionic liquid on reaction rates,[10] the small changes in composition here result in significant changes in activation parameters and rate of reaction. This needs to be borne in mind by anyone using ionic liquid reaction media.

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