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Probing the importance of ionic liquid structure: a general ionic liquid effect on an S_NAr process†

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The effect of a range of ionic liquids, with systematic variations in the cation and anion, on the rate constant of an aromatic substitution process was investigated. Temperature-dependent kinetic data allowed calculation of activation parameters for the process in each solvent. These data demonstrate a generalised ionic liquid effect, with an increase in rate constant observed in each ionic solvent, though the microscopic origins of the rate constant enhancement differ with the nature of the ionic liquid.

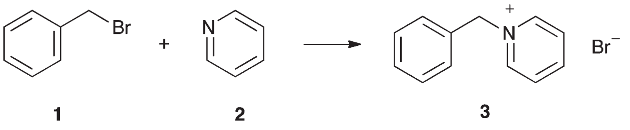
Introduction

Ionic liquids, which are salts consisting of bulky organic cations and charge-diffuse anions[1] with melting points below 100 °C,[2] have garnered a great deal of attention as potential replacements for traditional molecular solvents in well-studied organic reactions.[3] This attention can be attributed to favourable properties such as negligible vapour pressure,[4] potential recyclability,[5] and, most importantly, the ability to modify the charged components, which may result in drastic changes in the physicochemical properties of the solution.[6,7] However, their widespread usage is currently limited by the lack of understanding related to the origin of the changes frequently observed in the outcome of organic processes when ionic liquids replace molecular solvents.[8,9]

Several groups, including those of Welton,[10–18] Chiappe[19–27] and D'Anna,[28–35] have considered the microscopic origins of changes in the reaction outcome of organic processes in ionic liquids. We have previously examined substitution,[36–42] cycloaddition[43,44] and catalysed processes,[45,46] particularly focussing on cases where activation parameter data could be determined. Such data indicate that interactions between the components of a given ionic liquid and either the starting materials or the incipient charges in the transition state result in significant changes to the entropy and enthalpy of activation for the process. In cases where the key solvent interactions were shown to be those with reagents,[38–40] identification of the primary site of interaction on the starting material was carried out using molecular dynamics simulations and/or experimentally by modifying the reagents. Whilst the site of interaction on the starting material was determined, this work did not indicate the site of interaction on the ionic liquid.

We have recently considered experimentally what is required of the cation of an ionic liquid to enhance the rate of the reaction of the bromide **1** with pyridine **2** to give the salt **3** (Scheme 1). Initial studies using the ionic liquid 1-butyl-3-methylimidazolium ($[\mathrm{Bmim}]^+$) bis(trifluoromethanesulfonyl)imide ($[\mathrm{N(CF_3SO_2)_2}]^-$) **4** showed a rate enhancement due to an entropic effect,[39] which was attributed to coordination of the cation of the species to the nitrogen centre of the nucleophile **2**. Through modification of the cation of the ionic liquid, it was demonstrated that general electrostatic interactions between the nucleophile and the positively charged centres on the cation (rather than specific hydrogen bonding) are particularly important and that access of the nucleophile to the charged centre was necessary to observe a rate enhancement relative to a molecular solvent.[42]

In contrast to the Menschutkin reaction described above, whilst there is also an entropy-driven increase in the rate constant of the reaction outlined in Scheme 2 on moving from a molecular solvent to the ionic solvent **4**, the principal interaction is an anion-π interaction between the substrate **5** and the anion of the ionic liquid **4**; this interaction was inferred, from molecular dynamics simulations, to decrease on moving to the



Scheme 1 The Menschutkin reaction between the bromide **1** and pyridine **2** to give the corresponding salt **3**, which proceeds *via* an S_N2 mechanism.

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† Electronic supplementary information (ESI) available: Preparation of the ionic liquids **8–15**, general kinetic procedures, rate data for the Eyring plots shown in Fig. 1 and 2. See DOI: 10.1039/c3ob41634h

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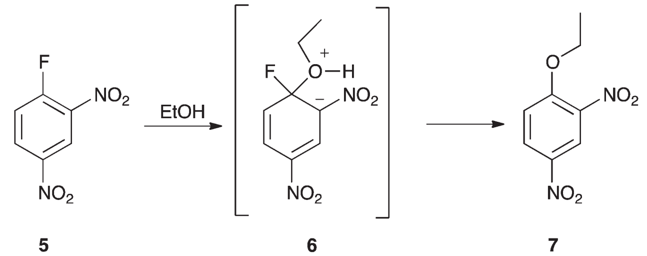


Scheme 2 Ethanolysis of the fluorinated nitrobenzene **5**, through the Meisenheimer complex **6**, to give the ether **7**.

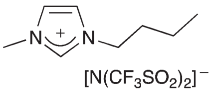
intermediate **6**.[39]§¶ Once again, while the site of interaction on the substrate **5** is understood, it was not clear what features of the solvent anion are important in influencing reaction outcomes. Further, since the initial organisation of the solvent around the substrate also indicates close association of the cation with both the anion and the substrate **5**, it was unknown how changing that component of the solvent might affect reaction outcome.

The work described herein seeks to clarify the above by systematically altering the nature of either the anion or the cation of the ionic liquid and observing the effect on the activation parameters of the reaction shown in Scheme 2. Initially a series of ionic liquids (**4**, **8–11**) containing anions with increasing charge localisation was considered to determine whether the degree of interaction of the anion with the substrate is a factor in the observed rate enhancement and, therefore, if charge localisation can be manipulated to optimise reaction outcome.[47] Subsequently, a series of ionic liquids (**4**, **12–15**) containing cations of different structure was investigated. These structural alterations vary access to the positively charged centres[42] and it was of interest to see whether this change affects reaction outcome, be it through direct interaction with the starting material **5** or by varying the cation–anion interaction and hence the anion-substrate **5** interaction.

Experimental

Ethanol and triethylamine were both purified and dried according to literature methods,[48] whilst the fluorodinitrobenzene **5** was used as received without further purification. The ionic liquids **8–10** were prepared from the chloride **11** through anion metathesis.[49] The ionic liquids **12–15** were prepared from the corresponding chloride,[49,50] whilst ionic liquid **9** was prepared from the corresponding bromide (see ESI†).[51] All ionic liquids were dried to constant weight at 70 °C under reduced pressure (1 mbar) before use.

^{19}F NMR spectra were recorded either on a Bruker Avance 400 spectrometer (400 MHz) or a Bruker Avance 600 spectrometer (600 MHz) using *ca.* 0.6 mL of reaction mixture in a 5 mm NMR tube. In the case of ionic liquids **8–9** and **12–16**, kinetic analyses were carried out in solutions containing ethanol (*ca.* 2.1 mol), triethylamine (*ca.* 0.42 mol) and dinitrofluorobenzene **5** (*ca.* 0.06 mol) over a range of temperatures between 304 K and 344 K. In the case of ionic liquids **10** and **11**, the ionic liquid component was diluted by ionic liquid **4** (mole fraction of ionic liquids **10** and **11** are 0.53 and 0.42, respectively) to ensure miscibility with the reagents, then used as described above. In each case, the reaction was followed using ^{19}F NMR spectroscopy until more than 95% of the starting material **5** was consumed. Spectra were taken at regular intervals during the reaction and at least twenty spectra were obtained for each kinetic run. The extent of reaction was deduced by integration of the signal corresponding to the fluorine in the starting material (*δ ca.* −109). From this information, the pseudo-first order rate constants for the reaction of the benzene **5** under these conditions, and subsequently the second-order rate constants, at each temperature were calculated. The activation parameters were then determined using the bimolecular Eyring equation.[52]



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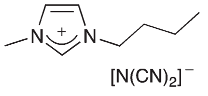

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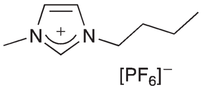

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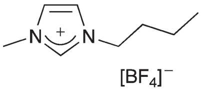

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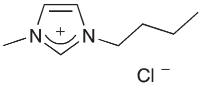

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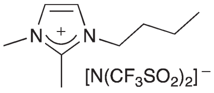

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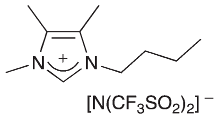

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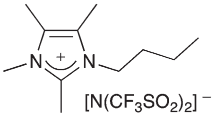

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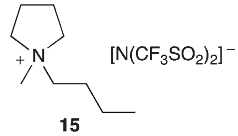

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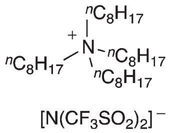

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Results and discussion

The reaction shown in Scheme 2 was initially carried out at a single temperature (324 K) in ethanol and ionic liquids **8–16** to establish the relative values of the rate constants in all of the solvents and to allow comparison with literature data in ionic

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§The interactions are also different to the cases where a charged nucleophile is used,[35] as the principal interactions are between the nucleophile and the cation.

¶While some theoretical studies have shown that S_NAr reactions proceed by a concerted mechanism, the stepwise mechanism through the Meisenheimer intermediate **6** would be expected for reaction of the fluoride **5**.[53]

liquid **4**.[39] At this temperature, the second-order rate constant for the ethanolysis of the benzene derivative **5** is similar in all of the ionic solvents **4** and **8–16** and, at a minimum, ten times greater than that in the molecular solvent under the same conditions. Given this general rate constant increase, temperature-dependent kinetics were undertaken to better understand if the origin of this increase varies across the ionic liquids studied, which may be indicative of changes in the solvent–solute interactions. Kinetic experiments allowed the construction of Eyring plots and from these activation parameters were obtained, which provide information on the interactions occurring at a microscopic level in the solution.

Initially, ionic liquids containing different anionic components (**4**, **8–11**) were considered (Fig. 1, Table 1). Across the range of temperatures studied the rate constant for the reaction shown in Scheme 2 in the ionic liquids **4** and **8–11** was greater than in the molecular solvent. Within the range of ionic liquids, whilst there are some general trends (for example, the chloride case **11** has a greater rate constant than the other cases), the small differences relative to the uncertainties in the rate constants limit further discussion.

Of greater interest than the overall similar rates is the trend in the activation parameters for the process. If the ionic liquid **4** is considered the 'parent', the solvents with different anions can be separated into two groups based on the activation parameters observed. The first group, consisting of ionic liquids **8** and **9**, show significant increases in both activation enthalpy and entropy when compared with both the molecular solvent and the parent system **4**. In these cases, the large increase in activation enthalpy, which can be attributed to increased interactions between the anion and the starting material **5**, is offset by the corresponding increase in activation entropy that facilitates the observed rate enhancement. The changes relative to when the ethanolysis of the benzene derivative **5** is carried out in the ionic liquid **4** suggest that a greater degree of charge localisation in the anion, compared to the bis(trifluoromethanesulfonyl)imide anion considered originally, facilitate stronger anion-π interactions.

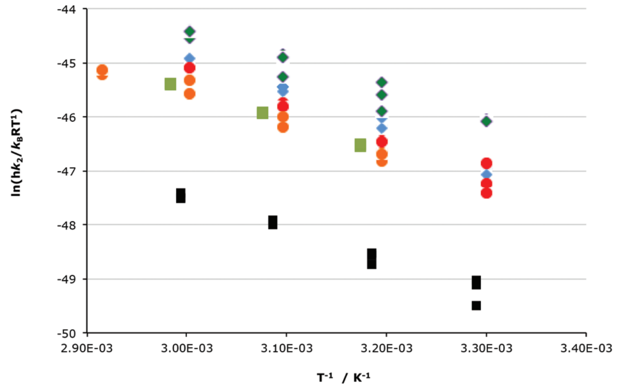

Fig. 1 Eyring plot for the second-order rate constants for the reaction outlined in Scheme 2 carried out in either ethanol (■) or one of the ionic liquids **4** (🟩),[39] **8** (●), **9** (◆), **10** in **4** (●) or **11** in **4** (◆). In all cases, the ionic liquid was only diluted by reagents (benzene **5**, ethanol and triethylamine; mole fractions outlined in Table 1), except ionic liquids **10** and **11**, as outlined below.

Table 1 Activation parameters for the reaction described in Scheme 2 in the solvent specified, with the mole fraction given for the ionic liquid cases

Solvent	χ_{IL}	$\Delta H^{\ddagger}$/kJ mol^{-1} [a]	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1} [a]
Ethanol	—	48.1 ± 1.7	−250 ± 5
4[b]	0.54	49.6 ± 0.5	−229 ± 2
8	0.63	58.0 ± 3.1	−201 ± 10
9	0.62	57.4 ± 1.9	−201 ± 6
10 in **4**	0.53 (0.59)[c]	47.2 ± 2.7	−238 ± 8
11 in **4**	0.43 (0.60)[c]	45.6 ± 3.7	−233 ± 12

[a] Uncertainties quoted are standard deviations. [b] Data reproduced from Jones *et al.*[39] [c] Number in parentheses is the total mole fraction of ionic liquid, including dilution by ionic liquid **4**.

The second pairing consists of the ionic liquids **10** and **11**.‖ These are not practical as solvents alone for the process as the tetrafluoroborate **10** does not dissolve the reagent **5**, whilst the chloride **11** is a solid over the range of temperatures studies. As such, they were diluted with the ionic liquid **4** prior to use, though they still constituted the majority of the ionic component of solution (Table 1). When the reaction was carried out in these solvent systems, the ethanolysis of the fluoride **5** proceeded with activation parameters that matched those observed by the parent ionic liquid **4**. The anions of the ionic liquids **10** and **11** are considered more coordinating than all of the other ionic solvents discussed previously, so it was anticipated that both the activation enthalpy and entropy would be more positive as a result; this was not the case, suggesting that the interactions between the anionic component of the solvent and reagent **5** had not changed. This could be because the tetrafluoroborate and chloride anions interact with the starting material **5** to the same degree as the bis(trifluoromethanesulfonyl)imide anion. However, given the former are much more coordinating, this seems unlikely. A more probable explanation would be that the charge-dense anions interact with the cations to a greater extent than in the simple ionic liquids (as there is a larger cation-interacting anion ratio than in the binary

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‖ It is worth noting that in molecular solvents chloride is more nucleophilic than ethanol,[54] so reaction with the ionic liquid **11** must be considered. Initial experiments to follow reaction of the fluoride **5** showed that the signal due to the starting material **5** in the ^{19}F NMR spectrum decreased in size and a signal due to the fluoride anion each appeared at a rate qualitatively similar to previous cases. At *ca.* one half-life, both the starting material **5** and the product **7** were observed using ^{1}H NMR spectroscopy; the presence of the latter was confirmed through addition of an authentic sample. There was no evidence of 1-chloro-2,4-dinitrobenzene, the result of the chloride ion reacting with the starting material. Given the reactivity of aryl chloride species with ethanol are known to be lower than the reactivity of the corresponding fluoride species,[55] if it were an intermediate its conversion to the ether **7** would be the rate determining step of this process (given the rate of fluoride ion formation has already been determined and is comparable to reaction of ethanol with aromatic **5**). In such a case, the chloride intermediate would build up and be observable in the ^{1}H NMR spectrum. As it is not, this indicates the chloride anion does not act as a nucleophile in this reaction. While this is interesting in that the nucleophilicity of the two competing species is inverted in ionic liquids relative to molecular solvents this was not further considered here. Changes in the relative nucleophilicity of halide anions have been shown previously,[15,16] including in reference to nucleophilic aromatic substitution processes.[23,24]

systems considered previously). As a result, the bis(trifluoromethanesulfonyl)imide anion is free to interact with the starting material **5**, resulting in identical activation parameters to those observed when ionic liquid **4** is used alone.**

In combination, the rate and activation parameter data for the process outlined in Scheme 2 in the ionic liquids **4** and **8–11** suggest the increase in rate constant observed relative to the molecular solvent[39] is not dependent on the charge localisation in the anion; however, the activation parameters indicate differences at the microscopic level. That is, a change in one activation parameter is balanced by a proportionate, but inverse, change in the other. Irrespective of this, an increase in the rate constant for the ethanolysis of the fluoride **5** is seen for all ionic liquids considered. Further, the small differences between reaction outcomes on using mixtures of ionic liquids compared to the parent **4** indicate that the presence of small amounts of halide impurities in the ionic solvent – a frequent concern for ionic liquids synthesised through salt metathesis – would not be expected to significantly affect reaction outcome provided that the interactions between the halide and the ionic liquid cation are much stronger than those between the halide and the reagent **5**.††

Given the importance of the anion–cation interactions in determining reaction outcome demonstrated above, it is of interest to consider what impact structural alterations on the cation of the ionic liquid have on the relationship with the anion and the substrate **5** and, consequently, the rate constant. As such, the rate constant of the reaction outlined in Scheme 2 was measured over a range of temperatures in the ionic liquids **4** and **12–16** and the activation parameters determined (Fig. 2, Table 2). As was observed in the series of ionic liquids with varying anions, across the range of temperatures studied the rate constant of the reaction in the ionic liquids **4** and **12–16** is greater than in the molecular solvents. The differences in observed rate constants are smaller than those observed for the series of ionic liquids with different anions and will not be further discussed.

Once again, of more interest are the activation parameters for the process in the various solvents. Initially it is useful to consider the imidazolium series of ionic liquids used (**4** and **12–14**). Previously, methyl substitution at the C-2 position has been shown to not affect the ability of the cation to interact with electron-rich reagents, whilst methyl substitution at the C-4 and C-5 positions does decrease the extent of interaction.[42] As shown in Table 2, the activation parameters for the process outlined in Scheme 2 in the ionic liquids **4** and **12–14** are very similar where no clear trend can be seen. This suggests that substitution of the imidazolium framework does not affect the cation–anion or cation-reagent **5** interactions substantially to impact the entropy-driven rate enhancement observed when using ionic solvent **4**, or that any effects cancel each other out.

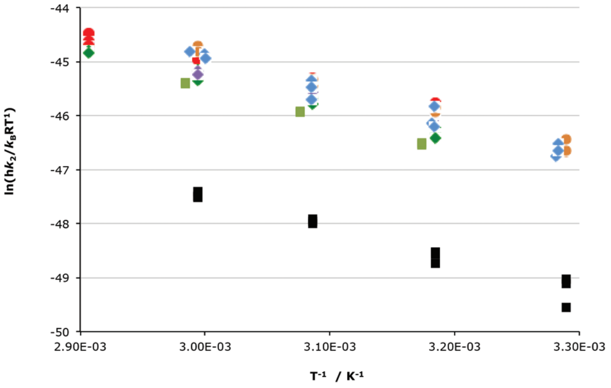

Fig. 2 Eyring plot for the second-order rate constants for the reaction outlined in Scheme 2 carried out in either ethanol (■) or one of the ionic liquids 4 (🟩),[39] **12** (●), **13** (◆), **14** (●), **15** (◆) or **16** (◆). In all cases, the ionic liquid was only diluted by reagents (benzene **5**, ethanol and triethylamine; mole fractions outlined in Table 2).

Table 2 Activation parameters for the reaction described in Scheme 2 in the solvent specified, with the mole fraction given for the ionic liquid cases

Solvent	χ_{IL}	$\Delta H^{\ddagger}$/kJ mol^{-1} [a]	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1} [a]
Ethanol	—	48.1 ± 1.7	−250 ± 5
4[b]	0.54	49.6 ± 0.5	−229 ± 2
12	0.52	49.0 ± 3.9	−223 ± 12
13	0.50	51.5 ± 3.2	−211 ± 10
14	0.51	50.5 ± 1.7	−221 ± 5
15	0.51	45.7 ± 1.9	−240 ± 6
16	0.32[c]	41.0 ± 2.6	−252 ± 8

[a] Uncertainties quoted are standard deviations. [b] Data reproduced from Yau *et al.*[38] [c] Lower value due to the cation being larger than in the other cases. Volume fraction remains the same.

In the case of pyrrolidinium-based ionic liquid **15**, the activation parameters determined are the same within uncertainty as in the molecular solvent, ethanol, and differ from the previously considered ionic liquids **4** and **12–14**. While from these data the microscopic origin of the rate enhancement observed in the salt **15** cannot be determined, two points are clear from the data presented; (i) that the origin of the enhancement in the rate constant is different from that of all of the previous ionic liquids considered (**4**, **8–14**) and (ii) even dramatic structural changes do not affect the capacity for the ionic liquid to facilitate rate enhancement in this class of reaction.

The final ionic liquid considered, the tetraalkylammonium salt **16**, represents a case where access to the charged centre of the cation is extremely restricted. The use of an ionic liquid with such a bulky cation also results in changes to the activation parameters for the process outlined in Scheme 2 when compared with both the molecular solvent and the parent ionic liquid **4**. Rather than the entropic benefit observed in the ionic solvent **4**, the rate constant enhancement relative to ethanol observed in solvent **16** is due to a decrease in the enthalpy of activation. This decrease suggests that the

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This argument is consistent with the decreased reactivity of chloride observed in these systems and detailed in the footnote above. It should be noted that the anion ($[N(CF_3SO_2)_2]^-$) is present in excess relative to the reagent **5.

††This is reasonable given the relative interaction energies shown previously between components of an ionic liquid and between each component and an aromatic solute.[56]

organisation of the components of the solvent about the starting material **5** seen for solvent **4** is not present; given the decreased access to the charged centre of the cation, this is unlikely to be due to increased interactions between the cation and anion. Rather, it is probably the result of the steric bulk of the cation preventing the organisation seen earlier.[39] Irrespective, the observed rate data indicate that, while large structural changes to the cation do affect microscopic interactions, the rate constant of the reaction remains effectively unchanged irrespective of the ionic liquid used.

Finally, it is worth considering that, generally, an increase in one activation parameter on moving to any of the ionic liquids considered is paired with an increase in the other parameter. This enthalpy–entropy compensation is consistent with what has been observed previously by us in this[39] and other systems.[37,38,40–42,44] In the case shown here, it is rationalised by organisation of the components of the ionic solvent about the electrophile **4** and the rate enhancement is the result of the entropic benefit outweighing the enthalpic cost. Whilst it may be of interest to consider what this indicates in terms of the organisation of components of solution (how bulk solvent ordering changes about species along the reaction coordinate) further discussion is limited given that mole fraction dependent data, reported for other examples,[9,36,37,41] is not available here.

Conclusions

This comprehensive study of an aromatic substitution process in various ionic solvents demonstrates the presence of a generalised ionic liquid effect that results in a rate enhancement regardless of changes to the individual components of the ionic solvents used. The microscopic origins of the observed second-order rate enhancements are ionic liquid-dependent. In the case of the cation, structural changes do result in changes in activation parameters if the bulky nature of the cation disrupts organisation in solution. In the cases where the nature of the anion changes, a higher level of coordinating ability does result in a greater degree of ordering about the starting materials, enhancing the entropic benefit; although this only occurs provided that the more coordinating anion is not diluted with a less coordinating one. Irrespective, in all cases changing the nature of the ionic liquid does not affect the overall enhancement of rate, as any change in one of the activation parameters is compensated by an equivalent but opposite change in the other. This is significant as it enables solvents from the range examined (and likely the wider range available also) to be used interchangeably, allowing selection of solvent to be made on more pragmatic points, such as cost or viscosity. This study also suggests that contamination of an ionic liquid with halide impurities would not be expected to affect the reaction outcome in reactions of this type, which reduces the need for potentially time-consuming and expensive purification procedures prior to use.

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