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Friedel–Crafts Benzoylation of Anisole in Ionic Liquids: Catalysis, Separation, and Recycle Studies

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Abstract:

The comparison of three ionic liquid-mediated catalytic processes for the benzoylation of anisole with benzoic anhydride is presented. A detailed understanding of the mechanism by which the zeolite and metal triflate reactions in bis{trifluoromethanesulfonyl}imide-based ionic liquids has been reported previously, and these routes are considered together with an indium chloride-based ionic liquid system. Solvent extraction and vacuum/steam distillation have been assessed as possible workup procedures, and an overall preliminary economic evaluation of each overall process is reported. Although the predominant activity is associated with the in situ formation of a homogeneous acid catalyst, the low cost and facile separation of the zeolite-catalysed process leads to this route being the most economically viable overall option. The results of a continuous flow miniplant based on the zeolite catalyst are also presented and compared with the reaction using a small plug flow reactor.

Introduction

The industrial manufacture of aryl ketones is conventionally carried out by the aluminium trichloride-mediated Friedel–Crafts acylation of aromatic substrates. The products of such reactions are intermediates or final products in many important processes such as the formation of pharmaceuticals Ibuprofen and (*S*)-naproxen and in pesticides and fragrances; however, due to the formation of a complex with the ketone product a stoichiometric excess of aluminium trichloride is used which, following hydrolysis required for product isolation, generates large quantities of metal salt waste. Alternatively, the reaction can be catalysed by HF; however, its toxicity and corrosive nature causes difficulties in the construction and operation of any plant. In addition, current industrial acylation processes require the use of large quantities of volatile organic compounds (VOCs) as solvents, which are detrimental to the environment. Therefore, much research is being conducted to develop a truly catalytic reaction, where the catalyst does not form a complex with the product, making it recyclable, while also minimising the use of VOCs. Ionic liquids have been successfully used as alternative reaction media for a wide variety of reactions including Friedel–Crafts,[1–3] and their negligible volatility gives them an environmental advantage over traditional molecular solvents.

Friedel–Crafts alkylations and acylations were some of the first synthetic reactions carried out in ionic liquids[4] with the acylation of benzene, toluene, and chlorobenzene in a chloroaluminate system, where the ionic liquid behaves both as a solvent and a catalyst. These reactions are catalysed by Lewis acids, such as BF_3 or $AlCl_3$, and various properties of ionic liquids make them attractive from a reaction and process engineering perspective. For example, their ability to dissolve both metal catalysts and organic reagents allows improved contact of substrates and catalysts, whilst their negligible vapour pressure can aid the separation of products.[5] However, in the case of ionic liquid-mediated acylation reactions, the chloroaluminate-based systems also complex with the ketone product, as found with the conventional $AlCl_3$ process, and these reactions offer no advantages for scale-up.

The issue of hydrolysis of the $AlCl_3$ may be overcome by replacing the aluminium with indium.[6] Recently, in our laboratory we reported an ionic liquid process for the benzoylation of anisole using a chloroindate melt[7] where the product isolation was performed using an aqueous extraction and the ionic liquid shown to be recyclable. Metal triflate and bis{trifluoromethanesulfonyl}imide ($[NTf_2]^-$) salts have also been shown to catalyse Friedel–Crafts acylations in both organic solvents[8–11] and in ionic liquids.[12,13] Importantly, recently it has been demonstrated that, in ionic liquids, the metal triflate salt may not be the catalyst but instead acts as a catalyst precursor which forms a Brønsted acid, such as HOTf.[14] Similar results were also found for solid acid-catalysed Friedel–Crafts processes in ionic liquids using heteropolyacids[15] and zeolites.[16] In this case, the acidic proton

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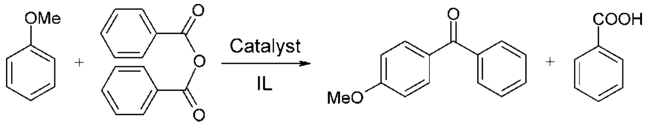
Scheme 1. **Formation of 4-methoxybenzophenone and benzoic acid from the benzoylation of anisole**



in the zeolite, for example, undergoes cation exchange with the ionic liquid 1-butyl-3-methyl imidazolium bis{trifluoromethanesulfonyl}imide ([C_4mim][NTf_2]) resulting in the formation of $HNTf_2$. In each system, the homogeneous acid formed acts as the main catalyst for the reaction.

While there are a number of ionic liquid-mediated catalytic routes, as discussed above, some facilitate product recovery and ionic liquid recycle better than others. In addition, for the purposes of process design the physical properties of the ionic liquids must be considered. For example their relatively high viscosities, when compared to typical organic solvents, will have implications on heat-, mass-, and momentum-transport processes.

Therefore, it is only through optimisation of the combined reaction and separation methods that the most effective overall combination of catalyst and ionic liquid can be determined. A range of separation methods are available for use with ionic liquids such as liquid−liquid extractants, including supercritical CO_2,[17−22] membrane separation,[23] crystallisation,[24] and distillation. The latter is an obvious choice for removing volatile components from the ionic liquid. However, the presence of ionic liquid can significantly reduce the vapour pressures of many components.[25,26] Together with the relatively high viscosities of ionic liquids[27] which reduces the mass transfer rate from the liquid to vapour phase, high energy costs and long workup times are required to achieve adequate separation. An additional problem is that many ionic liquids begin to decompose at around 300 °C.[28] It is, therefore, imperative that processing temperatures are kept well below the temperature at which decomposition is initiated in order to prevent product contamination and loss of the expensive ionic liquid. In such cases selective membrane separation may offer the advantages of a relatively lower energy input, and suitability for temperature-sensitive components. While recent studies have shown membrane technology to be a promising separation method for ionic liquid-based systems the technology still requires significant development work before it can be widely applied.[23] Supercritical carbon dioxide extraction is a promising method due to the ability to dramatically change the solubility of components in the supercritical fluid by varying the pressure and temperature whilst the ionic liquid is insoluble in the CO_2 phase.[21] However, a significant barrier to industrial uptake is the relatively high plant and equipment costs associated with supercritical fluids. If ionic liquids are to be used on a significant scale in industrial processes in the near future, there is a need to apply well-established separation technologies.

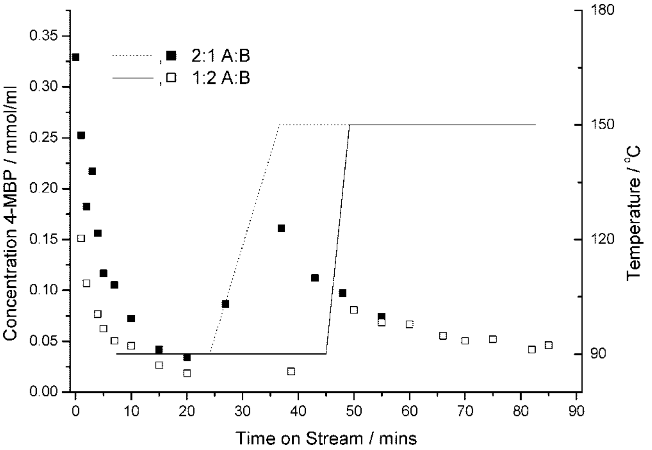


Figure 1. **Effect of increasing the temperature after the initial decrease in conversion on the zeolite-catalysed benzoylation of anisole (A) using benzoic anhydride (B) to produce 4-methoxybenzophenone (4-MBP). Reaction conditions: residence time 10 s, 1.5 mol dm^{-3} limiting reactant, 0.85 mol dm^{-3} [C_2mim]-[NTf_2], temperature 90 °C for first 20 min (2:1 A:B, dashed line) or 40 min (1:2 A:B solid line), followed by an increase to 150 °C.**

In this current study, the results of a relatively large-scale (500 cm^3 reactor volume) zeolite-catalysed Friedel−Crafts benzoylation of anisole to form 4-methoxybenzophenone, Scheme 1, in ionic liquids are reported. The zeolite-mediated process in the ionic liquids[16] is compared with the reactions catalysed by metal triflate salts[14] and indium chloride[7] as well as with molecular solvent-based reactions. In addition, a comparison of liquid−liquid extraction and steam distillation separation techniques for zeolite−ionic liquid, metal salt−ionic liquid, and chloroindate ionic liquid-catalysed systems is provided for the first time. This shows the importance of understanding the workup as well as the reaction in determining the best comparator from which to benchmark the process against molecular solvent processes.

Results and Discussion

Catalysis Studies. From the initial studies of ionic liquid-mediated zeolite-catalysed Friedel−Crafts acylation reactions, the predominant catalyst was shown to be a homogeneous acid formed by the cation exchange of the ionic liquid with the surface protons of the zeolite.[16] This effect is clearly illustrated by the rapid reduction in activity of the catalyst with time-on-stream at 90 °C, Figure 1, for both anisole-rich and benzoic anhydride-rich reaction mixtures using a plug flow reactor. On increasing the temperature to 150 °C, a significant increase in activity was observed which also showed a subsequent loss in conversion with reaction time albeit at a much slower rate than

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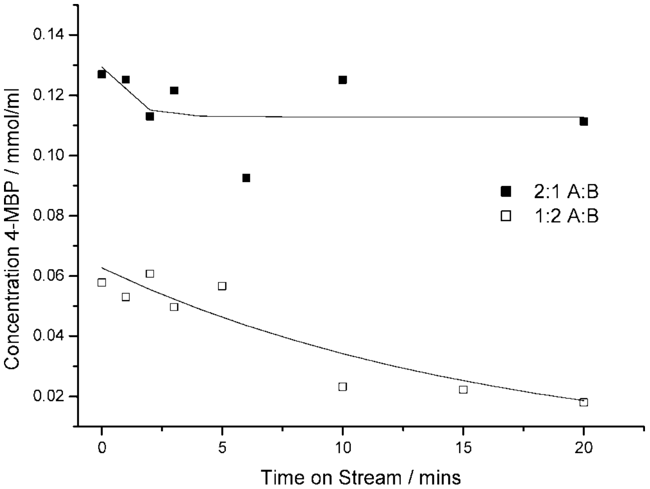

Figure 2. **Effect of the anisole (A) to benzoic anhydride (B) ratio on the outlet concentration of 4-methoxybenzophenone-(4-MBP) for the zeolite-catalysed benzoylation reaction. Reaction conditions: residence time 10 s, 1.5 mol dm^{-3} limiting reactant, solvent-free temperature 90 °C.**

that found at 90 °C. At the higher temperature, it is possible that the increase in activity may be due to further cation exchange at sites which become accessible on expansion of the zeolite framework. Previously we have reported that at 80 °C only 49% of the zeolite sites were found to be exchangeable.[16] However, since the activity levels off to a point above zero, it is likely that some heterogeneous catalytic activity of the zeolite also contributes, even though this is a minor component.

The similarity of the time-on-stream profile for both anisole-rich and benzoic anhydride-rich reaction mixtures in the ionic liquid is in contrast with the behaviour under solventless conditions, Figure 2. In the absence of solvent, lower initial activity was observed compared with the reaction in the presence of ionic liquid; however, neither a 2:1 or a 1:2 ratio of anisole:benzoic anhydride showed the rapid initial decrease in conversion observed with the ionic liquid system. Under the solventless conditions, the zeolite behaves predominantly as a heterogeneous catalyst with the slow decrease in activity observed associated with surface deactivation through poisoning of the catalyst. This effect is less pronounced for the anisole-rich reaction mixtures where not only are higher conversions obtained but also the activity remains approximately constant with time-on-stream. In contrast, an excess of benzoic anhydride results in a gradual decrease in 4-methoxybenzophenone yield. These results are consistent with those reported by Derouane et al.[29,30] where anisole acts as a solvent and maintains a clean surface, whereas at lower concentrations of anisole, there is a buildup of products on the surface of the catalyst which slowly deactivates the system.

Comparison of Workup Processes. Effective product separation from ionic liquids, in general, still remains one of the most significant drawbacks for their implementation within industrial processes and, therefore, must also be taken into consideration when developing an overall ionic liquid process. At temperatures below 70 °C, benzoic acid, a valuable byproduct with applications as an additive in food and pharmaceuticals, precipitated from the reaction mixture and could be removed by vacuum filtration. However, it carried with it an orange colour, thus making it undesirable for such industries. Recovery of 4-methoxybenzophenone using similar precipitation or crystallisation strategies was found to be more difficult due to its high affinity for the ionic liquid. Such effects have been reported by Blanchard and Brennecke for [C$_4$mim][PF$_6$][21] where compounds with high polarity and high aromaticity, in particular aromatic ketones, favour the ionic liquid phase. At high concentrations precipitation of the 4-methoxybenzophenone product from a pure ionic liquid was possible; however, this method was not successful when using typical reaction mixtures.

For each Friedel−Crafts system examined in detail previously, i.e. zeolite,[16] metal triflate salts,[14] and indium chloride[7]-mediated reactions, significant scale up issues associated with ionic liquid/catalyst recycle and workup needed to be addressed. The choice of workup is predominantly determined by the mechanism by which the catalysts operate. The efficiency of this process step significantly affects the viability of the ionic liquid processes over those under solventless or molecular solvent conditions, despite the fact that benchmarking the activity in each system indicates that the addition of ionic liquid increases the rate of reaction albeit with the reaction possibly occurring via a different catalytic mechanism. Due to little reaction in hydrophilic ionic liquids based on [BF$_4$]$^-$ and [OTf]$^-$ anions, reactions were carried out in [C$_4$mim][NTf$_2$] where high conversions were obtained for all catalyst systems. Detailed examination of both the zeolite and metal triflate routes indicates that the major catalytic species is the highly active HNTf$_2$ when reactions are performed in [NTf$_2$]$^-$-based ionic liquids. In the case of the chloroindate ionic liquids the catalytically active species has not been determined unequivocally as, when the ionic liquid is synthesised from combinations of [C$_4$mim]Cl and InCl$_3$, a high-density, viscous suspension is formed. Two main workup procedures have been evaluated for the acylation reaction studied herein, namely, solvent extraction and distillation.

Solvent Extraction. Solvent extraction is a common strategy employed for ionic liquids and is a mature separation technology; however, a number of characteristics must be considered when determining the most suitable solvent for an extraction process, such as cost, toxicity, flammability, and freezing and boiling points. Overall, the selectivity for the solute relative to the carrier is normally given the highest priority.[31] To determine the most selective agents, a large number of organic solvents were screened for use in the liquid−liquid extraction of 4-methoxybenzophenone from [C$_2$mim][NTf$_2$]. Table 1 shows the percentage extraction of 4-methoxybenzophenone from the ionic liquid into an equal volume of each solvent. All the solvents chosen have relatively low miscibility with the ionic liquids and are considered to be less harmful or polluting than halogenated solvents. Aromatic solvents showed the highest extraction ability compared with aliphatic solvents. In all cases except hexane and cyclohexane, a small amount of the extractant dissolved in the ionic liquid layer; however, in each case the

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***Table 1.* Comparison of various solvents for the extraction of 4-methoxybenzophenone from $[C_2mim][NTf_2]$**

solvent	% extraction[a]	boiling point (°C)	flammability	price[b] (relative to hexane)
hexane	21.3	68−69	high	1.00
mesitylene	79.8	163−165	medium	1.00
n-butylbenzene	73.4	182−183	medium	3.74
isobutylbenzene	73.7	172−173	medium	1.81
sec-butylbenzene	75.6	173−174	medium	2.34
tert-butylbenzene	70	167−168	medium	0.69
cyclohexane	27.2	80−81	high	0.75
o-xylene	32.3	143−145	medium	0.41
p-xylene	35.9	137−138	medium	0.48
tert-butyltoluene	48.5	189−192	medium	0.74
dibutylether	33.6	140−142	medium	0.35

[a] Indicates the percentage of 4-methoxybenzophenone extracted from a standard solution in $[C_2mim][NTf_2]$ into 5 mL of the solvent. [b] Prices taken from Sigma Aldrich for laboratory grade and used as an indication only.

ionic liquid content in the extractant layer was below the NMR detection limit.

Mesitylene was chosen for further study as it is resistant to Friedel−Crafts acylation preventing the formation of any unwanted side products on recycle. Although the boiling point is high, relative to those of other extractants such as hexane, the added energy costs for solvent recovery would be balanced by its superior product separation ability. Figure 3a shows the ternary phase diagram of the $[C_2mim][NTf_2]$/mesitylene/4-methoxybenzophenone system at 20 °C. It is notable that the points representing the extraction layer, i.e. mesitylene-rich, are all on the left axis, showing that over a range of compositions the contamination of this layer by ionic liquid is below detection limits. Points A and B represent the solubility of $[C_2mim][NTf_2]$ in mesitylene and mesitylene in $[C_2mim][NTf_2]$, respectively. With increasing concentration of 4-methoxybenzophenone the system remains biphasic until point C where the system becomes monophasic. Point C represents the limit of solubility of 4-methoxybenzophenone in mesitylene.

An examination of the $[C_2mim][NTf_2]$ layer, shows that in contrast with the extraction phase, the points lie away from the right axis, indicating that a significant amount of the mesitylene is dissolved in this layer. This phenomenon becomes clearer with increasing 4-methoxybenzophenone concentrations. From this data we can estimate that >97% recovery of 1 kg of product from ionic liquid (600 g) can be achieved using approximately 4.8 kg of solvent over 3 extractions (1.6 kg of solvent per extraction).

Diagrams b and c of Figure 3 show the ternary phase equilibria experiments at 50 and 80 °C, respectively. Although the temperature has very little effect on the shape or position of the equilibrium curve, temperature does have a small effect on the slope of the tie lines between equilibrium points. At 20 °C, the tie lines have a small positive gradient which becomes more negative as the temperature is raised, indicating increased extraction at higher temperatures. While this efficiency benefit is small and therefore unlikely to outweigh the increased energy costs associated with the higher operating temperatures if beginning at room temperature, it would be more beneficial during continuous operation where the reaction is already operating at these higher temperatures.

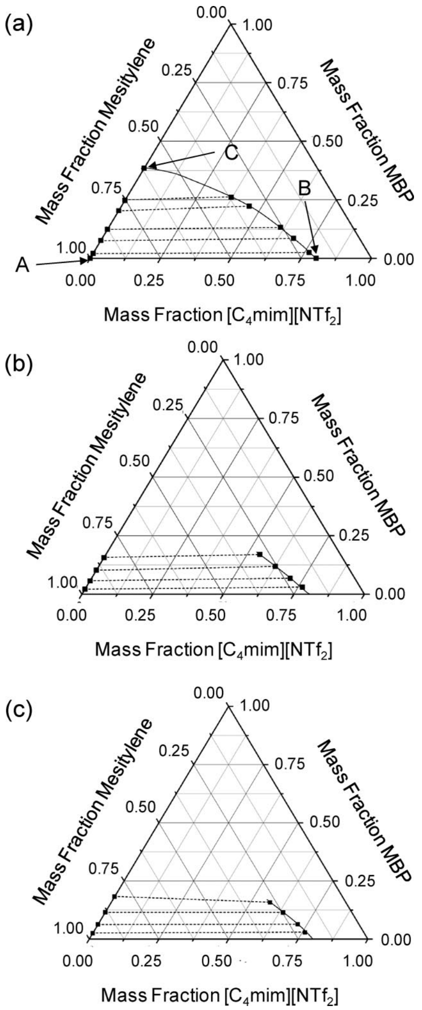

***Figure 3.* Ternary phase diagrams for the 4-methoxybenzophenone/$[C_2mim][NTf_2]$/mesitylene system at (a) 20 °C, (b) 50 °C, and (c) 80 °C.**

It should be noted that, while solvent extraction proved to be successful in recovering product from the ionic liquid reaction mixture with a purity of >98% as determined by NMR and HPLC, the product was coloured orange. It was observed that, during reaction in the ionic liquid using the zeolite or the metal triflates, the mixture became progressively more orange with the catalyst remaining white (in the case of the zeolite). In both cases this colour was transferred to the product during extraction. Therefore, solvent extraction may not be suitable when visual purity of the product is required. Interestingly, under solventless conditions and in molecular solvents, the zeolite becomes orange which has been attributed to formation of an acyl complex with the zeolite during the heterogeneously catalysed reaction.[29,30]

In the case of the chloroindate reactions, the ionic liquid can be extracted from the product mixture by the addition of water.[7] In order to facilitate the separation of the water layer from the organic, excess anisole, i.e. the reagent, was added to decrease the viscosity of the organic layer. After at least five washing procedures using an equal mass of water to ionic liquid, the aqueous extracts were combined and concentrated in vacuo to yield the original chloroindate ionic liquid. Recycling of the anisole−benzoic anhydride reaction system was carried out in this way, up to a total of 6 runs where the yield of 4-methoxy-

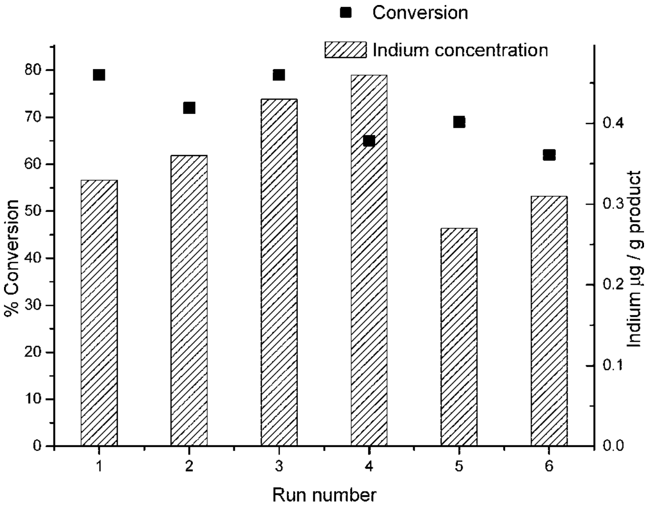

Figure 4. **Recycle studies on the 1-butyl-3-methyl imidazolium chloroindate, $[C_4mim]Cl-InCl_3$ ($X(InCl_3) = 0.67$), ionic liquid-catalysed benzoylation reaction of anisole using benzoic anhydride, showing the effect of the number of recycle runs on the conversion and indium concentration of the product. Reaction conditions: temperature 80 °C, anisole (9.95 g, 92.0 mmol), benzoic anhydride (23 g, 102 mmol), 5 mol % free $InCl_3$ with respect to anisole.**

benzophenone obtained in general showed a slight decrease over each recycle, Figure 4. As in the zeolite and metal triflate reactions the colour of the reaction mixture turned from colourless to deep orange. This disappeared almost completely during the washing/extraction procedure, and although the recovered ionic liquid was slightly coloured at the beginning of successive runs, no significant change was observed for the recycles. Despite the easier product extraction relative to the mesitylene extraction in the zeolite and metal triflate reactions, indium compounds are generally classified as toxic; therefore, any catalyst leaching would be problematic when considering scale up of this process. Samples of isolated product were tested using ICP analysis where it was found that the indium content was on average 0.36 ± 0.09 ppm per reaction over the 6 runs, Figure 4, thereby necessitating further purification steps to reduce the toxicity level.

Distillation. Since ionic liquids are considered nonvolatile unless operating under extreme conditions,[32] evaporation or distillation of the products is often considered to be an ideal method for product recovery. As distillation relies on the ability of the products to be volatilised rather than the solvent, this can cause problems when the boiling point of the product is high and therefore close to the thermal decomposition of the ionic liquid. Here thermogravimetric analysis of $[C_2mim][NTf_2]$ indicated that the ionic liquid was stable up to 350 °C; however, there was a significant loss of mass at 300 °C with almost 50% lost after heating for 15 h, thus negating direct distillation of the 4-methoxybenzophenone product (355 °C). In such cases this type of problem is often mitigated by using vacuum or steam distillation. Vacuum distillation was investigated as a possible method of removing reaction products while preserving the catalytic activity of the zeolite−acid−ionic liquid solution.

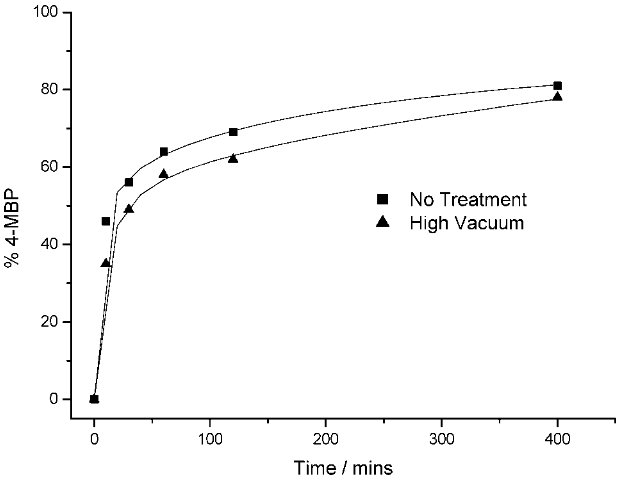

Figure 5. **Effect of high-vacuum treatment on the activity of $[C_2mim][NTf_2]$ doped with $HNTf_2$ as the catalyst system for the benzoylation of anisole using benzoic anhydride. Reaction conditions: temperature 90 °C, 1.5 mol dm^{-3} anisole, 3.1 mol dm^{-3} benzoic anhydride.**

To this end, a solution of $HNTf_2$ in $[C_2mim][NTf_2]$, which is known to be the major active catalyst in the zeolite reaction, was heated to 150 °C under high vacuum for 3 h and its activity re-examined. Figure 5 shows the comparison of the catalytic activity of the solution before and after vacuum treatment. A small decrease in the activity was observed, which was surprising, given that the boiling point of $HNTf_2$ is 90 °C under atmospheric pressure. While this indicates that vacuum distillation may be a useful method of separating the reaction products from the ionic liquid, this was not the case, as further studies showed that 4-methoxybenzophenone could not be easily recovered under such conditions.

Steam distillation, via superheated steam, is used in a variety of industries for the removal of organic material from wastewater, soil, and carbon adsorption columns. Organic reagents that are insoluble in water can be removed from the condensate by decantation or filtration whilst those that are soluble are isolated by further evaporation of the water. As the products used in this reaction are insoluble in cold water, this system was considered ideal for product isolation. In a setup similar to that of the vacuum distillation experiment discussed above the activity of a $HNTf_2$ solution was tested before and after contact with superheated steam at 130 °C and 1 atm pressure for 3 h. Figure 6 shows that in this case the catalyst is either destroyed or removed from the ionic liquid as there is no activity in the steam-distilled ionic liquid. However these small scale studies did show that clean product recovery was possible.

Recycle and Scale Up Studies. A preliminary comparison of the three methods indicated that the zeolite-catalysed reaction was the least expensive in terms of catalyst cost (based on September 2007 Sigma Aldrich prices). This is mostly due to the high costs associated with the indium chloride and indium triflate salts as well as the high price of $HNTf_2$ relative to that of its lithium salt which is used in the production of the ionic liquid. Of the product extraction strategies the steam distillation proved to be the most effective for meeting the criteria in terms of overall purity and colour.

Larger-scale studies on the recycle of both zeolite and ionic liquid were carried out using the miniplant, Figure 7. Figure 8

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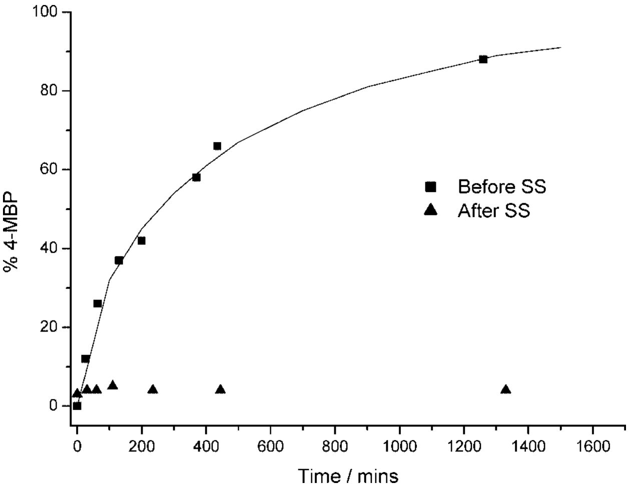

Figure 6. **Effect of steam distillation on the activity of [C_2mim][NTf_2] doped with $HNTf_2$ as the catalyst system for the benzoylation of anisole. Reaction conditions: temperature 90 °C, 1.5 mol dm^{-3} anisole, 3.1 mol dm^{-3} benzoic anhydride.**

shows the recycle of the zeolite using fresh batches of ionic liquid for runs 1 and 2 and the recycle of the zeolite and ionic liquid for run 3. In each case, the zeolite was regenerated between reactions by first washing with acetonitrile and then heating to 500 °C under air. Both the regenerated zeolite and the ionic liquid show good recyclability.

As found for the small PFR, operation of the larger fixed bed in the miniplant in continuous mode, Figure 9, shows that there is a rapid decrease in conversion with time on stream, demonstrating the exchange of the acidic proton on the surface of the zeolite with the cation of the ionic liquid. However, even after 1300 min on stream, some activity remains. The temperature was then increased from 90 to 130 °C, and as expected, the concentration of product in the outlet stream increased again followed by a slower decrease in conversion than that observed at 90 °C.

In the miniplant, the separator was operated at atmospheric pressure using a steam flow of approximately 32 g min^{-1} where it was shown that the anisole was removed at 130 °C, the benzoic acid at 150 °C and 4-methoxybenzophenone at 250 °C. The anisole was separated by simple decantation from the separation tank, whereas the benzoic acid was soluble in the hot condensed steam but was easily recovered by further cooling and filtration. Within the distillation vessel any unreacted benzoic anhydride was converted to benzoic acid under the conditions of the separation. The 4-methoxybenzophenone was recovered as an oily liquid which could be either decanted from the hot water or if cooled isolated by filtration. This fraction was then further purified by washing with 2 M sodium hydroxide solution giving a pale-cream powder. In this way 4-methoxybenzophenone was isolated in 99.5% purity with 94.7% selectivity to the 4-isomer.

In contrast to the orange-coloured benzoic acid which was filtered from the cooled reaction mixture, on using steam distillation, white needlelike crystals were obtained. However, some loss of the ionic liquid was observed (~5% by weight over the 2 h separation period), and it is unclear if this was due to decomposition of the ionic liquid, vaporisation[32] of the ionic liquid, or mechanical loss due to entrainment in the high-velocity steam.

Conclusions

There are a number of routes available for the benzoylation of anisole when using ionic liquids when performed in batch mode, with each route presenting increased rates when compared to similar systems without the addition of the ionic liquid. Our preliminary studies using chloroindate ionic liquid melts as well as metal triflates and zeolites in [C_2mim][NTf_2] indicated that the zeolite process was the most cost-effective in terms of the catalyst cost even though this resulted in the loss of ionic liquid due to exchange with the catalyst surface. Previous studies have shown that approximately 49% of the acid sites on the zeolite were exchanged with [C_2mim] with 76.6 mg of $HNTf_2$ acid produced per gram of zeolite used. This translates to approximately 12.9 g (0.033 mol) of ionic liquid consumed per kg (4.71 mol) of product (based on a 90% conversion in a typical batch experiment). It should be noted that much cheaper cations could however be used for this exchange. While the bulk of the activity stems from the generation of this acid there is evidence that some heterogeneous activity remains although the level of activity is considerably lower than nonionic liquid system when excess anisole is used as the solvent.

When considering continuous operation, where product extraction and ionic liquid recycle are taken into account, the normally quoted advantages of ionic liquids, in terms of low volatility and high solubility of reactants, become disadvantageous as they complicate product recovery and ionic liquid recycle. Of the separation strategies investigated here i.e. precipitation/crystallisation, solvent extraction, direct distillation and vacuum/steam-distillation, only the latter method was able to recover product of suitable quality. However, this too resulted in additional losses of ionic liquid due either to its slight volatility or more likely due to physical entrainment from the steam-distillation vessel. It is interesting to note that the first commercial ionic liquid processes i.e. BASF's BASIL process[33] is a two phase process where by the ionic liquid is the product and phase separates from the reaction mixture. Similarly IFP's butenes dimerisation (Difasol) process uses a liquid−liquid biphasic reaction using an ionic liquid catalyst.[34] Therefore one could conclude that efficient and simple product separation is the most significant factor for the commercial exploitation of ionic liquids.

Despite the fact the ionic liquids have been shown not to be as good as nonionic liquid routes for the Friedel−Crafts benzoylation of anisole we have shown that such ionic liquid processes can be scaled up effectively to >300 g/batch using zeolite catalysts and that they can be recycled numerous times with losses attributed to a mixture of exchange and mechanical losses. It can also be noted that after 250 h of operation, between batch and continuous operation no corrosion of the pump head or valves was observed.

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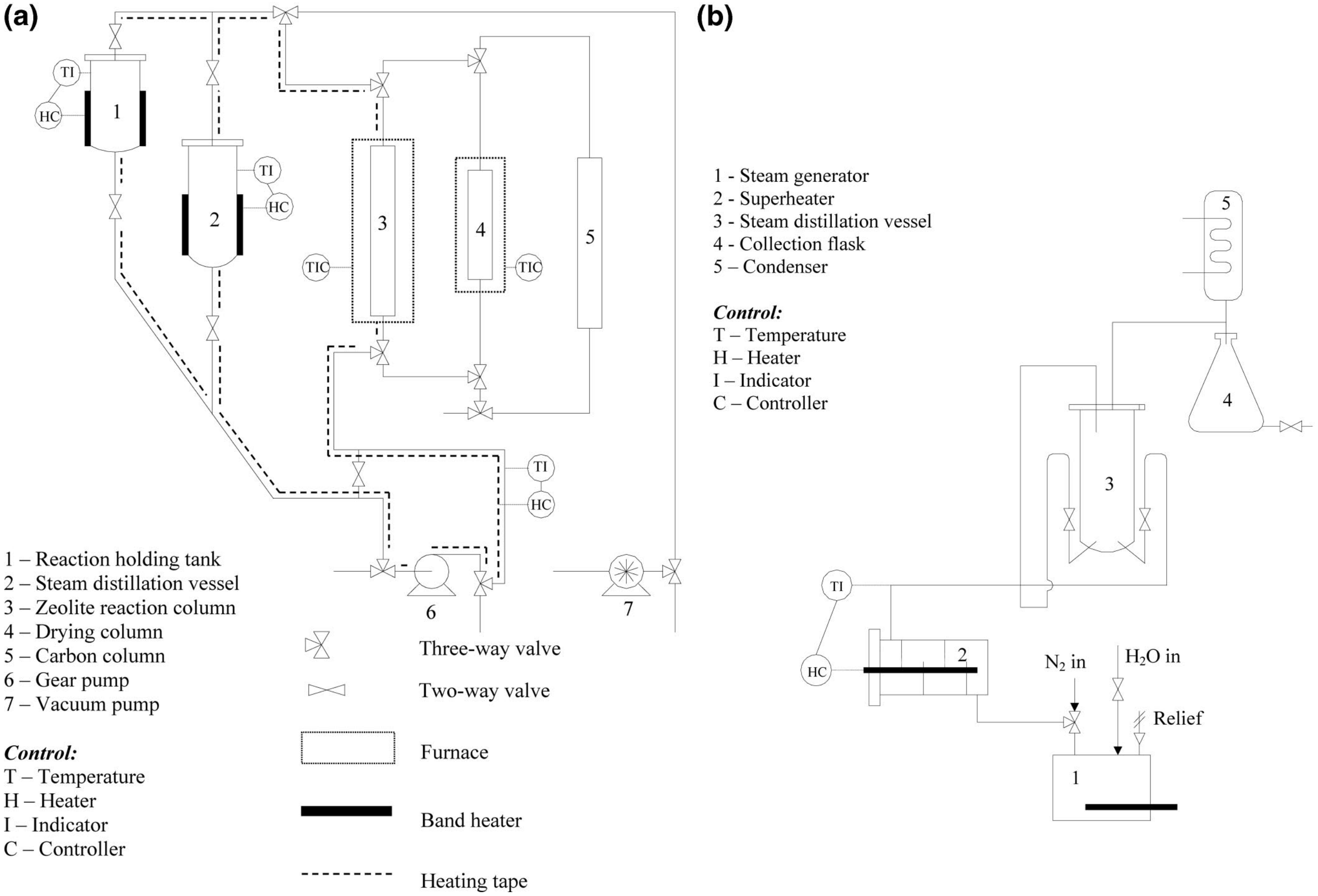

Figure 7. **Schematic diagram of the miniplant.**

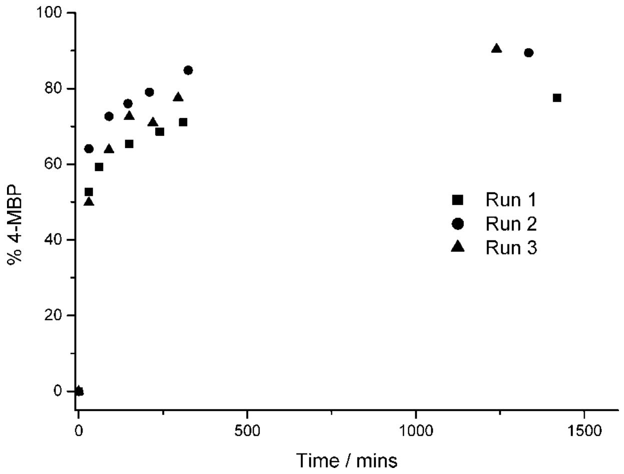

Figure 8. **Batch recycle studies carried out on the miniplant. Reaction conditions: temperature 90 °C, 1.6 mol dm^{-3} anisole, 3.3 mol dm^{-3} benzoic anhydride, 9 g of zeolite, flow rate 500 cm^3 min^{-1}.**

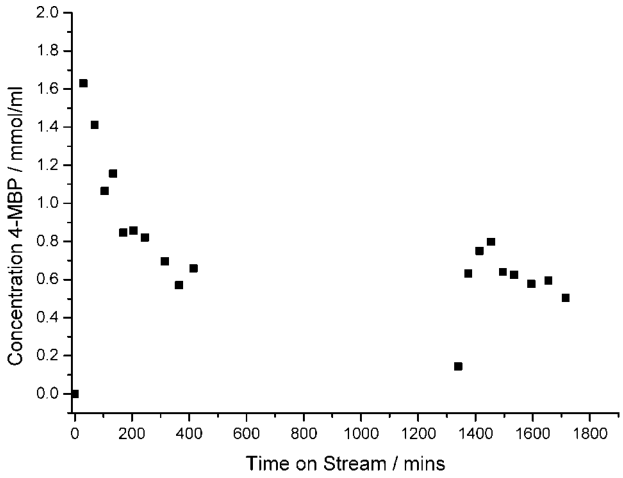

Figure 9. **Outlet concentration of 4-methoxybenzophenone (4-MBP) from continuous reaction carried out on the miniplant. Reaction conditions: temperature 90 °C, 1.6 mol dm^{-3} anisole, 3.3 mol dm^{-3} benzoic anhydride, 9 g of zeolite, flow rate 24 cm^3 h^{-1}, residence time 30 min.**

Experimental Section

Materials. Anisole (99%) and benzoic anhydride (98%) were obtained from Lancaster. H-USY-29 zeolite samples were provided from QUILL industrial partners and were calcined in air at 500 °C overnight prior to use. The measured BET surface area and pore volume of the catalyst were determined as 625.8 m^2 g^{-1} and 0.396 cm^3 g^{-1}, respectively. Where required, the zeolite pellets were formed from the powder by compression to 6 tons crushed and then sieved to the appropriate particle size. The ionic liquids, 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($[C_2mim][NTf_2]$) and 1-butyl-3-methyl imidazolium chloroindate, ($[C_4mim]Cl-InCl_3$ (mole fraction of $InCl_3$, $X(InCl_3) = 0.67$)), were synthesised according to a standard literature procedure.[7,35] Prior to use ionic liquids were dried in vacuo at 60 °C for more than 4 h and contained

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(35) Bonhôte, P.; Dias, A. P.; Papageorgiou, N.; Kalyanasundram, K.; Grätzel, M. *Inorg. Chem.* **1996**, *1168*, 1178.

<0.01 wt % water, determined by Karl Fischer analysis. The densities of the ionic liquid and reagent mixtures, used to calculate concentrations, were obtained using an Anton Parr DMA4500 densitometer.

Small-Scale Reaction Procedure. The procedure for the small-scale continuous flow experiments in a plug flow reactor (PFR) was as described previously.[16]

The miniplant (1.2 m × 1.5 m), Figure 7a, was accommodated in a fume hood, and all pipe work, unions, and valves were constructed from 1/4″ stainless steel. Reagents [C_2mim][NTf_2] (0.21 mol), anisole (0.39 mol), and benzoic anhydride (0.78 mol) were transferred from the feed tank to the holding tank using a peristaltic pump (Watson-Marlow, 101U) and a gear pump (March May with a Fluid o Tech MGK209XPS17 gear head) was used to circulate reaction mixture at a flow rate of 500 cm^3 min^{-1} round the reaction loop. The holding tank (500 cm^3) and steam-distillation vessel (1000 cm^3) were constructed from Pyrex glass with lids of mild steel lined with PTFE to minimise corrosion. The catalyst bed (1/2″ OD pipe) and drying column were heated by Carbolite furnaces, and the glass vessels were heated by band heaters. To prevent precipitation of benzoic acid from the reaction mixture below 70 °C, all pipe work in the reaction line was trace heated.

The catalyst bed was charged with 9 g of zeolite which had a particle size in the range 650−800 μm. The drying column was filled with 4 Å molecular sieve, and the carbon column contained activated charcoal granules. Fine mesh was used to keep the material in place.

The miniplant was designed to be operable as a batch or continuous system. When running as a batch process, a solution of the reagents and solvent were placed in the feed tank and passed round the heating loop until the required temperature was reached. At this point the reaction mixture was passed over the catalyst bed and round the reaction loop. On completion of the reaction, the mixture was transferred to the steam-distillation vessel for product isolation in batch mode. To operate the system as a continuous process, the feedstock was fed into the reactor via a piston pump at 24 cm^3 h^{-1}. In each case, samples were taken from an additional sampling valve at the top of the catalyst bed as a function of reaction time.

A schematic for the steam-distillation line is shown in Figure 7b. The superheater consists of two Watlow FIREROD cartridge heaters and a series of four baffles housed in a custom-made stainless steel vessel. Steam distillation was achieved by passing wet steam, generated in a 4.5 dm^3 2.3 kW boiler at a flow of ~64 g min^{-1} through the superheater. The power to the cartridge heaters was adjusted until the desired temperature was obtained. In order to achieve temperatures in excess of 200 °C the power to the boiler, and thus steam flow, was reduced to 50% of maximum. The superheated steam flow was split into three, two of which were introduced to the base of the steam-distillation vessel and adjusted to facilitate suitable mixing and the third was introduced via the top of the vessel. The exit steam was condensed and stored in a modified 2 dm^3 conical flask. Once complete, the ionic liquid left in the steam-distillation vessel was pumped through the drying column and the charcoal column for purification before being stored in the reaction holding tank for further reaction. The zeolite was reactivated in the fixed bed by first washing with acetonitrile to remove excess ionic liquid and then by passing a slow stream of compressed air through the system at 500 °C over the catalyst bed.

Catalytic reactions carried out using the ionic liquid, 1-butyl-3-methyl imidazolium chloroindate ([C_4mim]Cl−$InCl_3$ ($X(InCl_3) = 0.67$)) (3.50 g), were carried out in a round-bottomed flask equipped with a magnetic stirrer, at 80 °C, with anisole (0.113 mol) and benzoic anhydride (0.124 mol), giving a free indium content of 5 mol % with respect to anisole. The system was recycled by adding excess anisole and removing the ionic liquid by washing with water at least five times with an equal mass of water to ionic liquid. The aqueous extracts were combined and concentrated in vacuo to yield the original chloroindate ionic liquid. Fresh anisole and benzoic anhydride were added, and the system was recycled in this way, over 6 runs.

Offline analysis was carried out using an Agilent HPLC system with a diode array detector set at 224 nm. Samples of known mass (~30 mg) were removed over time and dissolved in acetonitrile (10 cm^3), an Eclipse XDB-C8 column with an eluent of methanol/water (60:40) at a flow rate of 1.0 cm^3 min^{-1} was used. Quantification of the conversions was performed using calibration curves for anisole and 4-methoxybenzophenone from known standards. In all cases conversions are reported as the percentage conversion to 4-methoxybenzophenone. For all reactions, mass balances based on anisole and 4-methoxybenzophenone of greater than 95% were obtained.

Solvent Extraction. Screening of different solvents for extracting the product, 4-methoxybenzophenone, from [C_2mim][NTf_2] was performed by stirring a mixture of 4-methoxybenzophenone (1 g) and the ionic liquid (10 g) for approximately 1 h to ensure complete dissolution. An aliquot (1.1 g) was taken to which the desired extraction solvent (3 g) was added. This mixture was stirred in a sealed baffled vessel for 2 h at 1000 rpm (magnetic stirring) and 20 °C. The stirrer was stopped, and the liquid was allowed to phase separate for a further 4 h. Aliquots of known mass were taken from each layer and prepared for analysis by ^{1}H NMR and HPLC by dissolution in 10 cm^3 deuterated acetonitrile and protonated acetonitrile, respectively.

In a set of similar experiments, ternary equilibria data were generated for the ionic liquid−mesitylene−4-methoxybenzophenone system. Initially 4-methoxybenzophenone was added to a stirred solution (600 rpm) of ionic liquid and mesitylene until the solution was observed to go cloudy, thereby indicating the formation of a second liquid phase. Further addition of product results in two distinct phases being formed. Tie lines represent the equilibrium concentrations in each of the two phases.

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