Organic Process Research & Development **2010,** *14,* 716–721

Ionic Liquids as Phase-Transfer Catalysts: Etherification Reaction of 1-Octanol with 1-Chlorobutane

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Abstract:

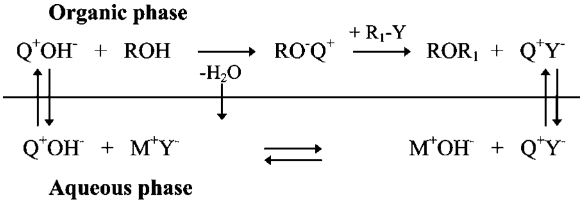
Various ionic liquids have been examined along with some traditional phase-transfer catalysts, such as Aliquat reagents, in a standard liquid−liquid phase-transfer catalysis (LLPTC) reaction. A standard *O*-alkylation LLPTC reaction was chosen because of its relatively high yields and low incident of reaction side products. As expected, quaternary tetraalkyl ammonium catalysts all resulted in high conversion to product. Aliquat HTA-1, a high temperature phase-transfer catalyst normally used in nonaqueous reactions, resulted in yields only slightly higher than the noncatalyzed reaction. Substituted pyrrolidinium salts had relatively good catalytic activity, while substituted pyridinium and imidazolium catalysts showed either very little or no catalytic activity. Catalysts with fixed cationic charges resulted in high conversion for the etherification reactions; however, compounds with an aromatic π-bonding system were not suitable as phase-transfer catalysts.

Introduction

Ionic liquids (ILs) are becoming increasingly used in "green" chemistry as solvents and catalysts due to their unique properties.[1−4] The most basic definition of an IL, a salt which melts below 100 °C, encompasses a large variety of compounds.[2] While ILs are commonly considered a new and exciting class of compounds, many compounds used in chemistry throughout the 20th century can be considered ionic liquids, specifically: certain ammonium, phosphonium, and sulfonium salts.

Tetraalkyl ammonium ILs have been used as liquid/liquid phase-transfer catalysts since the pioneering work of Starks, Mąkosza, and Brändström.[5−7] Liquid/liquid phase-transfer catalysis (PTC) uses the addition of a catalyst to assist the migration of anionic reactants from one liquid phase to another liquid phase where a reaction can take place. The scope of PTC reactions has grown dramatically in the past decade. Phase-transfer catalysis has been applied to a variety of reactions including alkylations,[8−11] nucleophilic substitutions,[12−15] oxidations,[16−18] reductions,[19] polymerizations,[20,21] etc.

Scheme 1. **Extraction mechanism of a phase-transfer catalysis etherification of a water-immiscible alcohol using a tetraalkyl ammonium catalyst**



The extraction mechanism shown in Scheme 1 illustrates the PTC mechanism for an etherification reaction of a water-immiscible alcohol using a tetraalkyl ammonium (quat) catalyst, Q^+, to transport the base across the phase boundary where it can react with the alcohol to form an alkoxide.[22,23] The alkoxide can then react with an alkyl halide, R-Y, which is also acting as a solvent. The organophilic ion pair, Q^+OH^-, distributes between the organic phase and the boundary with the aqueous phase. Once in the organic phase, OH^- reacts with enhanced reactivity due to three factors. The most important factor is that when OH^- is transferred, it has very little water of hydration. The reduction of the hydration shell of OH^- results in increased reactivity which can be orders of magnitude higher.[22] Second,

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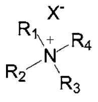
Table 1. **Ionic liquid phase-transfer catalysts**



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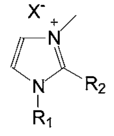

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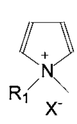

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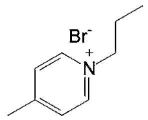

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cmpd	synonym
1a, $R_1 = R_2 = R_3 = R_4$ = butyl, X = bromide	Aliquat 100
1b, $R_1 = R_2 = R_3$ = butyl, R_4 = methyl, X = chloride	Aliquat 175
1c, $R_1 = R_2 = R_3$ = octyl, R_4 = methyl, X = bromide	Aliquat 138
1d, $R_1 = R_2 = R_3$ = octyl/decyl, R_4 = methyl, X = chloride	Aliquat 336
1e, proprietary formula	Aliquat HTA-1
2a, R_1 = ethyl, R_2 = H, X = bromide	[emim][Br]
2b, R_1 = butyl, R_2 = H, X = chloride	[bmim][Cl]
2b, R_1 = butyl, R_2 = H, X = bromide	[bmim][Br]
2b, R_1 = butyl, R_2 = H, X = hexafluorophosphate	[bmim][PF_6]
2e, R_1 = octyl, R_2 = H, X = chloride	[omim][Cl]
2f, R_1 = butyl, R_2 = methyl, X = chloride	[bdimim][Cl]
3a, R_1 = ethyl, X = bromide	[empyrrol][Br]
3b, R_1 = butyl, X = bromide	[bmpyrrol][Br]
3c, R_1 = octyl, X = chloride	[ompyrrol][Cl]
4	[4-mbp][Br]
5	PEG 500 dimethylether

the OH^- has a higher reactivity due to the looser ion pair with Q^+ than with alkali metals such as sodium or potassium. Finally, reactivity between OH^- and R−OH is increased due to their proximity in the same phase as compared to when the reaction occurs at an interface. According to the extraction mechanism, once the desired reaction occurs, the quat pairs with the leaving group (Y^-) and transfers it to the aqueous phase. The extraction mechanism completes the catalytic cycle with an ion exchange in which the quat exchanges OH^- for Y^- resulting in the Q^+OH^- ion pair that is ready to be extracted completely into the organic phase and react with R−Y.

In this study, we were interested in determining the possibility of using traditional ILs as phase-transfer catalysts. We chose a Williamson etherification as a model reaction. Conversion rates for Williamson etherification reactions are greatly increased when tetraalkyl ammonium catalysts are used because of the improved transfer of water-soluble base into the organic phase. The reaction conditions were similar to the etherification reactions conducted by Freedman and Dubois,[24] and were chosen because of the relatively high yields and low incident of side reaction products. A complete list of the ionic liquid catalysts used is in Table 1.

The molecular structure and charge distribution of the catalyst are important factors for transferring anions out of an aqueous phase into a nonpolar organic phase across the interface.[25] Quat salts (Aliquat 336, Aliquat 100, and Aliquat 175) are commonly used phase-transfer catalysts in the chemical industry. The reasons for the high demand for quats are their low costs, wide applicability and availability, high catalytic activity, and good selectivity. The traditional IL compounds (**2a**−**f**, **3a**−**c**, **4**) are highly polar and nonvolatile, even at elevated temperatures.[26] The imidazolium (**2a**−**f**), pyrrolium (**3a**−**c**), and pyridinium (**4**) salts also contain tetravalent nitrogen cations and a smaller inorganic anion, which are structures similar to the Aliquat compounds and could conceivably function as phase-transfer catalysts. A PEG 500 diether (alkyl-capped polyethylene glycol oligomer, M_n = 500 g/mol) was also tested as polyethylene glycols and their capped derivatives often perform well as phase-transfer catalysts.[25]

Experimental Section

Polyethylene glycol dimethyl ether and all of the ionic liquids are commonly available compounds and were obtained from Merck KGaA. Aliquat reagents were supplied by Cognis Corporation. Analytical data was obtained using a Agilent Technologies 6890 N GC with FID equipped with a Zebron 7HM-G002-11 ZB-5 column. The temperature program included a 2 min hold at 60 °C followed by a ramp of 20 °C/min up to 250 °C and a second ramp of 40 °C/min up to 340 °C ending with a 5.25 min hold time.

The standard PTC *O*-Alkylation reaction used follows a similar procedure previously reported by Freedman and DuBois,[24] for the etherification of a linear alcohol with a linear alkyl halide. A general procedure for the reactions is given here. To a 250 mL round-bottom flask heated to 65 °C under nitrogen was added 23.05 g of 1-octanol (0.177 mol), 4.27 g of *n*-decane (0.030 mol, used as an internal standard for the gas chromatograph), and 116.8 g of a 50% w/w aqueous KOH solution (0.884 mol of 95% KOH). The reaction contents were stirred at 500 rpm. If the catalyst contained water, solid KOH was added in order to achieve a 50% w/w aqueous solution. A quantity of catalyst (6 mol %) was added to the reaction mixture and allowed to dissolve into the organic phase. An excess of 1-chlorobutane (19.63 g, 0.212 mol) was then added to the reaction flask. Samples of the reaction mixture were taken at various intervals and analysed by gas chromatography.

Results and Discussion

The etherification reaction given in Scheme 2 was used as a model reaction to determine the phase-transfer catalytic behavior of various ionic liquids. Some common ionic liquids

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Scheme 2. **Etherification reaction using ionic liquids as phase-transfer catalysts**

$$\text{n-}C_8H_{17}OH + C_4H_9Cl \xrightarrow[\text{50\% KOH}]{\text{Ionic liquid}} C_8H_{17}OC_4H_9$$

were chosen for this work; tetraalkyl ammonium salts (**1a−e**), imidazolium salts (**2a−f**), pyrrolidinium salts (**3a−c**), and a pyridinium salt (**4**). Oligomeric polyethylene glycol ether was also tested for comparison (Figure 1).

Tetraalkyl ammonium-based Aliquat reagents, with the exception of Aliquat HTA-1, resulted in high conversions to the resulting ether after 300 min of agitation. The conversions ranged from 87% to 96%, with Aliquat 100 giving the highest conversion. These results are consistent with yields of other etherification reactions (*O*-alkylations) using Aliquat reagents as phase-transfer catalysts.[24,27,28] Using the extraction mechanism discussed in the introduction, the quaternary ammonium compounds are able to efficiently transfer base (OH^-) into the organic phase where it can extract a proton from the alcohol. The resulting alkoxide then quickly reacts to form the butyl octyl ether. While Aliquat HTA-1 has been used as a catalyst for etherification,[29] the reaction conditions typically use non-aqueous systems at temperatures over 100 °C. HTA-1, a proprietary substituted guanidine ammonium compound, does not have the standard Aliquat structure (tetraalkyl ammonium salt), and it is not clear why there is no apparent catalytic activity. However, it is our experience that HTA-1 decomposes in aqueous base at higher temperatures.

All the imidazolium salts (**2a−f**), and the pyridinium salt (**4**) resulted in conversions that were not significantly higher than the blank reaction performed without catalyst. The lack of catalytic activity was noted for all imidazolium compounds regardless of anion character or substituent alkyl chain length. Pyrrolidinium salts (**3a−c**) showed relatively good catalytic behavior. The conversion to the ether varied from 68% to 90%, and the increase in etherification conversion was related to increasing alkyl chain length. The PEG 500 diether showed moderate catalytic capability. The polyethylene glycol ether oligomers act as phase-transfer catalysts by forming an organic soluble complex by associating with the alkali cation of the K^+X^- ion pair. This is similar to an open-chain crown ether in PTC applications and was included in this work because it has been shown to catalyze various reactions involving proton extractions.[25] PEG 500 dimethyl ether data have been added solely for comparison to data of the other phase-transfer catalysts.

Phase-transfer-catalyzed etherification reactions are generally completed very quickly even when using mild conditions. Aliquat and pyrrolidinium catalysts, with the exception of HTA-1, showed steady increase in conversion to the ether up to 120−180 min, at which time the reactions had reached their maximum conversion (Figure 2). For the imidazolium and pyridinium catalysts (with the exception of BDIMM Cl which had only slightly higher conversion to the ether) the conversion rates were not different from that of the blank (Figure 3).

Various factors influence the catalytic effectiveness of phase-transfer catalysts. Accessibility of the positive charge of the nitrogen cation for complexation with the reacting anion, distribution of the ion pairs or complex in the organic phase, polarizability of the positive charge of the cation (i.e., through resonance in the case of imidazolium, pyridinium, and HTA-1), and the polarity of the organic phase are important factors in determining the extent of anion transfer from the aqueous phase to the organic phase as well as the separation of the ion pair when the alkoxide is reacting presumably during the rate-

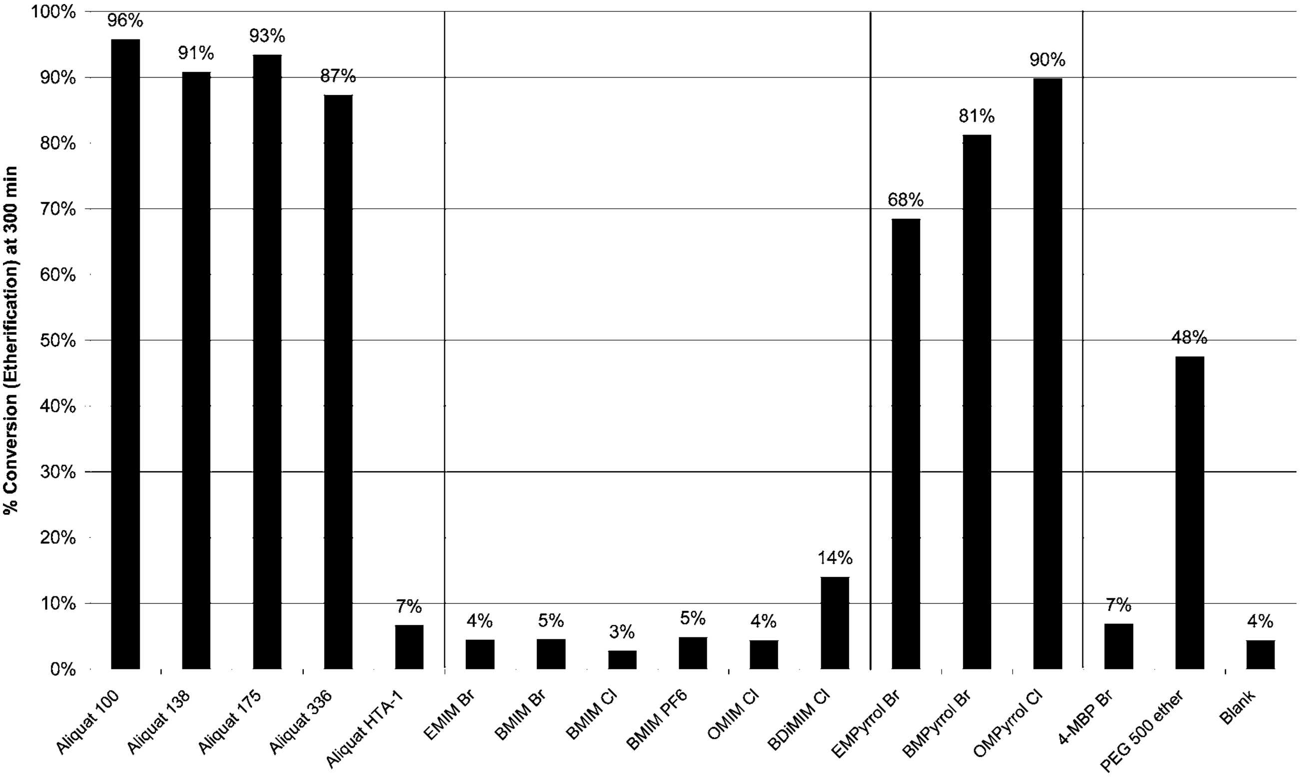

Figure 1. **Results of the etherification reactions after 300 min while stirring (500 rpm) at 65 °C.**

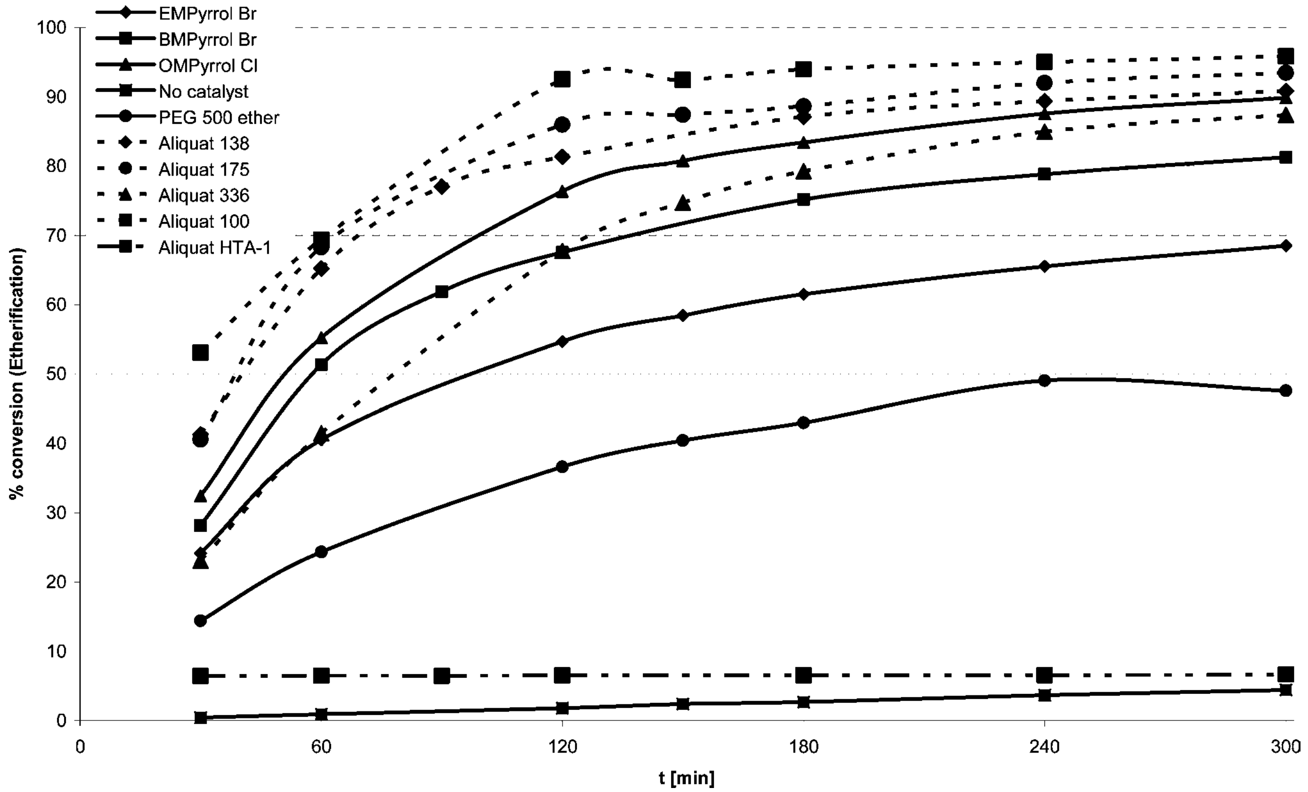

Figure 2. **Ether % conversion as a function of time for Aliquat and pyrrolidinium catalysts at 65 °C with a stir rate of 500 rpm.**

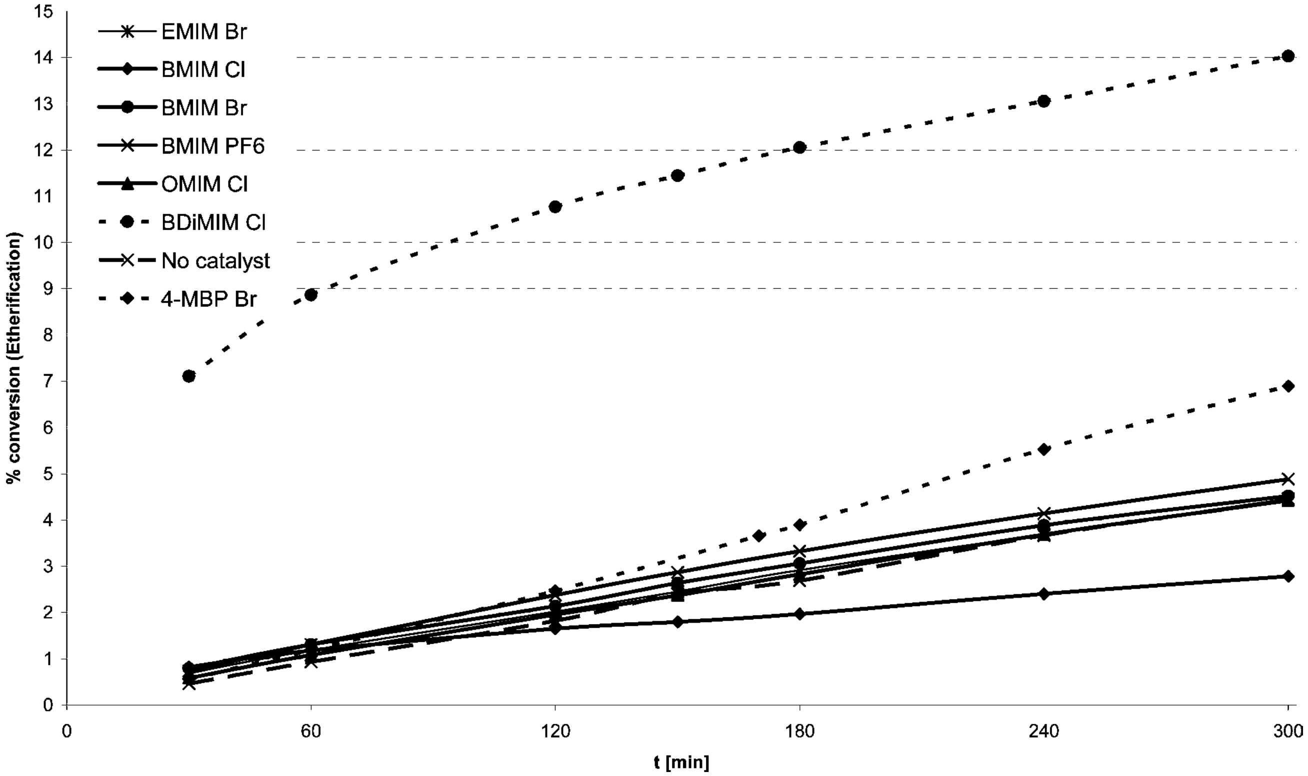

Figure 3. **Ether % conversion as a function of time for imidazolium and pyridinium catalysts at 65 °C with a stir rate of 500 rpm.**

determining step. In addition, the presence of bromide in some of the phase-transfer catalysts can form butyl bromide in situ which reacts faster than butyl chloride, and a bromide cocatalyst effect may enhance the rate of this PTC reaction. This effect is sometimes responsible for higher reactivity of Aliquat 100 (bromide counteranion) in comparison to that of Aliquat 336 or Aliquat 175, the latter two of which have chloride as the counteranion.

Quat	q-value	C#
Aliquat® 100	1.00	16
Aliquat® 175	1.75	13
Aliquat® 138	1.38	25
Aliquat® 336	1.30-1.38	25-32

Figure 4. ***q*-Value and *C#* for Aliquat reagents. Aliquat 336 has a range for the *q*-value and *C#,* since it is a mixture of quaternary amines that have three C-8 and/or C-10 chains.**

These factors will determine whether a reaction proceeds at an acceptable rate or fails to proceed at all.

Determining the optimum accessibility and organophilicity of a catalyst can be essential in some PTC reactions. In the case of the Aliquat catalysts, varying the length of the alkyl chains results in the positively charged nitrogen becoming either more or less accessible. In addition, the length of the alkyl chains affects the overall organophilicity of the quat, which is the measure of the preferential distribution of the quat complex in the organic phase or possible formation of a small third phase with very high concentration of quat alkoxide and alkylating agent that would greatly enhance reactivity. A measure of the organophilicity and accessibility of quats has been proposed by Halpern,[22] and has been used extensively in the PTC literature. The accessibility of a quat (*q*-value) is calculated as the sum of the reciprocals of the number of carbons on each of the four chains of the quat (eq 1). Essentially, the higher the *q*-value the more accessible the cation becomes. Quats with a *q*-value greater than 1 are considered to have a moderate to high accessibility, while quats with a *q*-value lower than 1 are considered to have a low accessibility. Organophilicity (represented as a *C#*) is calculated as the sum of the carbons on each of the four chains of the quat (eq 2). Quats, and quat complexes, with *C#* greater than 16 are considered to have a moderate to high organophilicity. While the Aliquat reagents in Figure 4 spanned the ranges of both accessibility and *C#* (Figure 4), all of the reagents resulted in high conversion to the ether. Aliquats 100 and 175 had slightly higher conversions in which case the accessibility is of less importance (as they have both the lowest and highest accessibility, respectively), and the reactions are favored by catalysts with less organophilicity.

$$q\text{-value} = ((C_nH_{2n+1})_iN^+) = \sum_{i=1}^{4}\frac{1}{n_i}(\text{e.g., Aliquat 100 } q\text{-value} = \frac{1}{4}+\frac{1}{4}+\frac{1}{4}+\frac{1}{4} = 1.0) \quad (1)$$

$$C\# = ((C_nH_{2n+1})_iN^+) = \sum_{i=1}^{4} n_i(\text{e.g., Aliquat 100 } C\# = 4+4+4+4 = 16) \quad (2)$$

Ionic liquids containing tetravalent nitrogen hetereocycles do not behave in the same manner as the quaternary tetraalkyl Aliquat compounds. The tetravalent ammonium heterocycles (**2a−f, 3a−c,** and **4**) incorporate the nitrogen cation into a conjugated ring system. In the case of the imidazolium cations (**2a−f**) and pyridinium cation (**4**) these conjugated systems are aromatic, while the pyrrolidinium cations are not aromatic and are possibly antiaromatic. Aromatic tetravalent nitrogen compounds resulted in low ether conversion in all cases, and the nonaromatic ammonium compounds resulted in high conversions to the desired product. Aromaticity of the pyridinium catalyst results from a π-electron system which closely resembles benzene, where the nonbonded electrons used to form the dative bond with the alkyl chain are orthogonal to the conjugated π-system. While pyrrole is aromatic and has a π-electron system similar to that of the cyclopentadienyl anion because the nonbonded electrons of the nitrogen are in a p-orbital (four sp^2-hybridized carbons with four p-orbitals plus a nitrogen atom that is sp^2-hybridized yielding six p-electrons), the pyrrolidinium cation is not aromatic. Once the nonbonded electrons in the p-orbital have formed a dative bond with the carbon atom of the alkyl chain to form the cation, the system becomes a conjugated four p-electron heterocycle which should be destabilized by resonance. Imidazolium cations contain two nitrogens where one nitrogen atom is behaving similarly to a pyridinium nitrogen and the other to a pyrrole nitrogen. The resulting conjugated π-system is aromatic. Altering the length of the substituent alkyl chains in order to adjust the accessibility of the cation and the organophilicity of the pyridinium and imidazolium catalysts had no affect on the etherification reaction, while increasing the alkyl chain length of pyrrolidinium catalysts increased the conversion percentage dramatically from 68% to 90%.

Since the mechanism of the phase-transfer catalysis for this class of ionic liquids has not been previously addressed, we offer the following concepts to explain the lack of catalytic activity of pyridinium and imadazolium ILs in this system: the cation might be resonance stabilized (charge is delocalized) enough so that it is unable to exchange for the hydroxide ion, the alkoxide formed from the proton extraction forms a stable counterion for the quat, or the geometry of the conjugated ring inhibits some aspect of the PTC reaction. Considering the lack of catalytic activity in this reaction, aromatic heterocyclic ammonium compounds do not appear to be suitable for PTC strong base reactions.

While Aliquats 100, 175, 138, and 336 catalyzed the etherification reaction in this work as expected, there are limitations to their use as phase-transfer catalysts. The major drawback to using quaternary tetraalkyl ammonium salts is their decomposition at relatively low temperatures (typically these compounds are used at reaction temperatures below 80 °C). Identifying phase-transfer catalysts, such as the pyrrolidinium salts, which have higher decomposition temperatures, may expand the scope of PTC reactions.

Conclusions

The results of this investigation have shown that, as expected, Aliquat-type quaternary tetraalkyl ammonium salts offer very high catalytic activity for the above specified etherification reaction. Nonaromatic heterocyclic pyrrolidinium salts also resulted in high catalytic activity, whereas aromatic heterocyclic tetravalent nitrogen catalysts (imidazolium- and pyridinium-

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(28) Meyer, O.; Heitger, H. U.S. Patent 6,835,857, 2004; CAS (2003): 717800.

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based salts) did not demonstrate any significant catalytic activity. Cation structure dominated catalytic behaviour. Catalysts with fixed cations showed very high catalytic activity for etherification reactions, while compounds with a cation that is part of an aromatic π-bonding system do not appear to be suitable as phase-transfer catalysts in *O*-alkylation reactions. The pyrrolidinium catalysts had increasing catalytic activity with increasing organophilicity, although the overall organophilicity of these compounds would still be lower than that of most of the Aliquat catalysts.

Acknowledgment

This work was supported by the Department of Process Development of the Cognis Deutschland GmbH & Co. KG, Niederrhein University of Applied Science (Krefeld); Faculty of Technical Chemistry, and Dr. Marc E. Halpern, PTC Organics Inc.

Received for review February 2, 2010.

OP100031U