Friedel-Crafts Reactions in Ambient-Temperature Molten Salts

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Mixtures of 1-methyl-3-ethylimidazolium chloride and aluminum chloride are ionic liquids that melt below room temperature. They may be used as solvent and catalyst for Friedel-Crafts reactions. The scope of the reactions was studied relative to alkylating and acylating agents and to aromatic substrates. The nature of the catalyst that promotes the reactions was established.

Introduction

Completely ionic liquids are not the usual solvent for organic reactions. Most ionic liquids are liquid only at high temperatures and offer little advantage over the more commonly used aqueous or organic media. Most work on organic reactions in molten salts have employed eutectic mixtures, but they still require temperatures above 200 °C. For example, Kikkawa and co-workers have used binary, ternary, and quaternary chloride melts to crack, eliminate, and chlorinate organic compounds, but at temperatures never less than 205 °C.[1] Organic reactions have been performed in binary alkali-metal chloride-aluminum chloride salts, which are lower melting, but still require temperatures over 100 °C.[2] In recent years some salts have been discovered and characterized that are liquid at and below room temperature. The most common class of these low melting ionic compounds are the chloroaluminates, composed of an organic chloride salt and aluminum chloride.[3] We report here that these low melting ionic liquids may be used as solvent and catalyst for Friedel-Crafts reactions.

Recently, we have been studying the structure, physical properties, and chemistry of chloroaluminate melts consisting of mixtures of 1,3-dialkylimidazolium chloride and aluminum chloride.[4,5] These mixtures are liquid at room temperature, and some compositions melt substantially below 0 °C. Comprehensive viscosity determinations for the entire range of melt compositions have been accomplished and previously reported.[5] Because the binary mixture of 1-methyl-3-ethylimidazolium chloride and aluminum chloride ("MeEtImCl-$AlCl_3$") has a particularly favorable combination of physical properties and ease of preparation, it was selected over other chloroaluminates for this study. Numerous other substituted imidazolium and pyridinium chlorides form molten salts with aluminum chloride but do not possess the favorable physical properties we sought for this investigation. In addition, the MeEtImCl-$AlCl_3$ molten salts have a wide range of Lewis acidity, which makes them convenient systems for investigating Friedel-Crafts reactions.[6]

The species present in chloroaluminate molten salts are well-known. Fannin,[7] Mamantov,[8] and Osteryoung[9] have clearly established the chloroaluminate species in $AlCl_3$-NaCl melts through potentiometric investigations and vapor pressure measurements. Raman spectroscopy has been used to demonstrate the anions present in $AlCl_3$-1-(1-butyl)pyridinium chloride (BuPy) melts. Osteryoung showed that, in a 1:1 mixture, aluminum is present entirely in the tetrachloroaluminate form and, in the 2:1 melt, only the heptachloroaluminate form exists.[10] Aluminum-27 NMR studies by Gray and Maciel supported these assignments.[11] In addition, Matsumoto and Ichikawa also used aluminum-27 NMR and concluded that in basic melts only $AlCl_4^-$ exists, in acidic melts, i.e., $AlCl_3$ mole fraction greater than 0.5, both $AlCl_4^-$ and $Al_2Cl_7^-$ are present, and in the 0.67 melt, only $Al_2Cl_7^-$ is present.[12] Similar NMR studies have been conducted by Wilkes et al. in the MeEtImCl melts.[13] An important point is that $AlCl_3$ or Al_2Cl_6 were not detected in room-temperature melts having $AlCl_3$ mole fraction less than 0.67.

The acid-base properties of this system are described by the equilibrium

$$2AlCl_4^- \rightleftharpoons Al_2Cl_7^- + Cl^-$$

where $Al_2Cl_7^-$ is the lewis acid and Cl^- the Lewis base. The equilibrium constant in BuPy melts was initially shown to be of the order of magnitude of 10^{-13} [14] and later revised to 10^{-15} to 10^{-19}.[15] Hussey et al.[6] report the equilibrium constant in the MeEtImCl melt to be 5×10^{-17} at 40 °C.

We also noted that the MeEtImCl-$AlCl_3$ mixtures dissolved a wide variety of organic compounds and stabilized organic radical cations.

Results and Discussion

The venerable Friedel-Crafts electrophilic alkylation and acylation reactions are normally run in an inert solvent and catalyzed by suspended or dissolved $AlCl_3$. Here we describe the reactivity and extent of these simple reactions employing the unusual MeEtImCl-$AlCl_3$ catalysts and solvent system. In studying the alkylation and acylation reactions, we noted that basic melts exhibited no catalytic activity, whereas acidic melts were extremely reactive. Since an acidic species is required to catalyze these reac-

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Table I. Alkylation of Benzene

alkylating agent (R-Cl)	N of melt	mole ratio R-Cl:benzene: melt	% alkylated products mono	di	tri	tetra	penta	hexa
R = methyl[a]	0.67	xs:1:1	1.5	58.5	1.5	26.8	1.4	10.2
R = ethyl[a]	0.67	xs:1:1	11.5	10.8	33.4	24.4		1.5
R = *n*-propyl[b]	0.60	1.25:1.25:1	24.8	19.9	55.3			
R = *n*-butyl[b,c]	0.60	1.33:1.33:1	25.0	26.3	48.7			
R = cyclohexyl	0.60	10:10:1	35.0	30.0	34.4			
R = benzyl[d]	0.60	0.78:1.17:1	50.0	34.5	15.6			

[a] Run at reflux temperature of alkyl chloride. [b] Room temperature, drybox conditions, exothermic with evolution of gas. [c] Only *sec*-butyl-alkylated products were found. [d] Tar formation, small amount of alkylated product isolated.

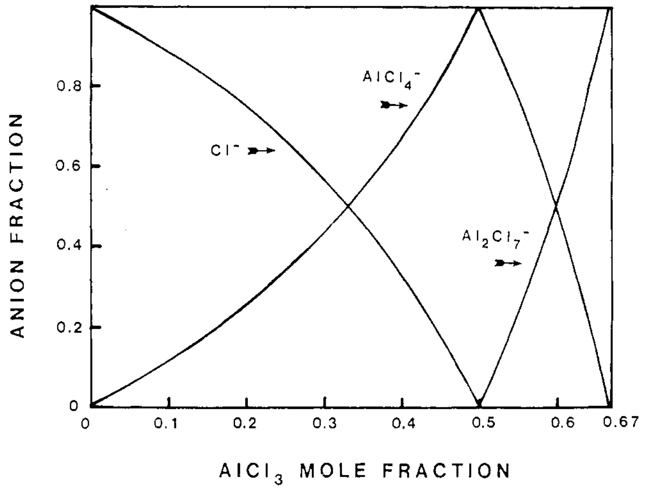

Figure 1. Calculated anion fractions vs. mole fraction $AlCl_3$ in chloroaluminate melts.

tions, compositions of the MeEtIm melt where $AlCl_3$ was in excess over the MeEtImCl were used. In chloroaluminate melts the Lewis acid species present in $AlCl_3$-rich compositions is well established and known to be $Al_2Cl_7^-$. We usually express the melt composition as apparent $AlCl_3$ mole fraction, N, realizing that free $AlCl_3$ does not exist in the melt. An $N = 0.67$ melt is prepared by adding 2 mol of $AlCl_3$ to 1 mol of MeEtImCl. Likewise an $N = 0.50$ melt is prepared by combining 1 mol of each; $N < 0.5$ implies a basic melt. Figure 1 describes the calculated anion composition vs. $AlCl_3$ mole fraction in these chloraluminate melts.

In order to determine the scope of Friedel–Crafts alkylations, we tested a series of alkylating agents. Primary and secondary alkyl halides were added to mixtures of melt and benzene under anhydrous conditions. Alkylated benzenes were observed after reactions with methyl chloride, ethyl chloride, *n*-propyl chloride, *n*-butyl chloride, cyclohexyl chloride, and benzyl chloride (see Table I). Gaseous HCl was evolved during all of the alkylation reactions. It is noteworthy that some of the alkylations were performed at −25 °C, with the melt still liquid. In addition to monoalkylation products, polyalkylated benzenes were present in the reaction products. For example, excess ethyl chloride reacted with benzene to produce the following ethylbenzenes: mono (12%), di (11%), tri (33%), tetra (24%), penta (17%), and hexa (2%). Methyl chloride produced an interesting array of products where principally even numbers of alkylations occur. Methylation of toluene also alkylates even numbers of times and therefore gives products with odd numbers of alkyl groups. We have no explanation for this and we could not find any reports of similar phenomena in the literature.

Polyalkylation can be accounted for by considering the enhanced activity of the alkylated product. An excess of aromatic substrate minimized polyalkylation. For example, a tenfold excess of benzene over *n*-propyl chloride, in the presence of the 0.67 melt, produced predominately monopropylbenzene (95%) with only 5% polypropylated products. The monopropylbenzene consisted of 70% isopropylbenzene and 30% *n*-propylbenzene. The presence of isopropylbenzene gives evidence of rearrangement of the primary carbonium ion to the more favorable secondary carbonium ion prior to ring substitution. The predominance of the rearranged product is an indication that the carbonium ion is formed, since reactions where ionization does not take place (i.e., where a "polarized covalent complex" is formed) show primarily the unrearranged product.[16] Rearrangement of *n*-butyl carbonium ion to secondary butyl carbonium ion also occurs in alkylation reactions with *n*-butyl chloride. Spontaneous formation of carbonium ions in 1-(1-butyl)pyridinium chloride–$AlCl_3$ melt has been reported,[17] so we believe that the alkylation proceeds by way of the completely dissociated carbonium ions in the reactions described here.

Comprehensive positional isomerization studies of the polyalkylated benzenes have not been done in the melt to detect intramolecular rearrangements. Under usual Friedel–Crafts conditions intermolecular migrations among polyalkylated benzenes can also occur, especially in the presence of excess catalyst, to produce a nonthermodynamically controlled product distribution.[18] The intermolecular migration usually occurs following protonation of the polyalkylbenzene at the carbon bearing an alkyl group with subsequent dissociation of the carbonium ion. The same process should not be possible in the aprotic chloroaluminate melts. An equimolar mixture of benzene and hexamethylbenzene in an acidic melt ($N = 0.67$) resulted in no toluene, xylenes, mesitylenes, etc.; thus there is no dissociation of the methyl substituents, probably due to lack of H^+ in the medium. Koch et al.[19] observed that Friedel–Crafts transalkylations could be initiated electrochemically in ethylpyridinium bromide–$AlCl_3$ melts, which are chemically similar to the MeEtIm melt described here.

The scope of substrates that may be alkylated was tested by reacting propyl chloride with benzene, toluene, chlorobenzene, and nitrobenzene in $N = 0.67$ MeEtImCl–$AlCl_3$ melt at 0 °C. All of the aromatic substrates were alkylated except nitrobenzene, which did not react at all. An increase in temperature of the nitrobenzene reaction simply increased the amount of propene formed from the elimination side reaction.

Friedel–Crafts acylations of aromatic compounds are also promoted by the MeEtImCl–$AlCl_3$ molten salts.

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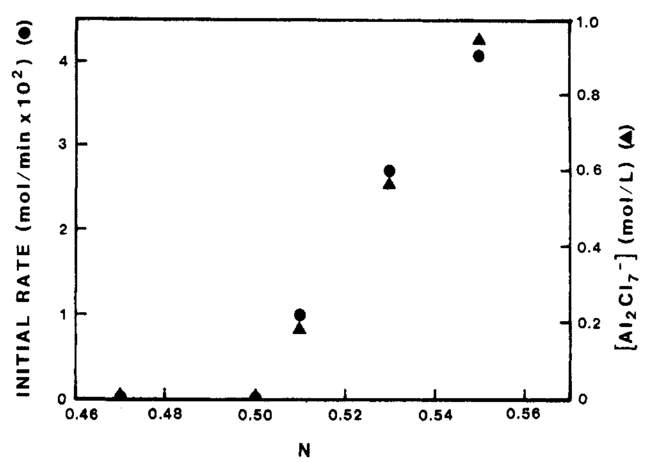

Figure 2. initial rate of benzene consumption (●) during acetylation by acetyl chloride in melts of varying composition, N. The $Al_2Cl_7^-$ concentration (▲) is shown for each reaction.

Acylation proved simpler than alkylation because the first substitution product deactivates the aromatic nucleus toward further ring substitution. We observed only monosubstitution when benzene and acetyl chloride were reacted in acidic MeEtIm melt.

We used the simplest of the acylation reactions, i.e., MeEtImCl-$AlCl_3$ catalyzed reaction of acetyl chloride with benzene to produce acetophenone, to determine the effect of the melt composition on the Friedel–Crafts reactions. The rate at which acetophenone was produced was dependent on the Lewis acidity of the melt, which was determined by the melt composition (vide infra). Melts of greater Lewis acidity (greater N) demonstrated greater catalytic activity than those of weaker acidity or ones that were neutral or basic. A series of experiments using constant amounts of reactants and melt but variable melt composition demonstrated the expected dependency. Figure 2 shows the initial rate of acetylation of benzene plotted vs. N. No substitution occurred in melts where $N \leq 0.5$, and the initial rates of reactions were found to increase as the acidity of the melt increased. These observations are almost certainly due to the increasing concentration of the actual catalytic species in the melt. The calculated concentrations[20] of $Al_2Cl_7^-$ in the melts also are plotted in Figure 2, and the correlation of [$Al_2Cl_7^-$] with initial rate suggests that $Al_2Cl_7^-$ is the catalyst responsible for promoting the reaction. We examined the reaction between the melt and acetyl chloride by nuclear magnetic resonance (NMR) spectrometry in order to learn some details about the nature of the catalyst in the melt and the electrophile that is produced from the acetyl chloride. Observation of the proton NMR resonance of the methyl group in the acetyl chloride (or its reaction product) was useful, since it was a singlet well separated from the proton resonances of the imidazolium ions in the melts. Figure 3 shows the dependence on the acetyl proton chemical shift on the relative concentrations of acetyl chloride (CH_3COCl) and $Al_2Cl_7^-$ in the mixture. At low concentrations of acetyl chloride, the acetyl resonance was shifted downfield and did not change much with increasing concentration. At high [CH_3COCl], the resonance moved upfield with increasing relative concentration. The threshold that delineated these two types of behavior was where [CH_3COCl] was equal to the [$Al_2Cl_7^-$] in the mixutre (zero on the plot in Figure 3). This is very suggestive of a stoichiometric reaction between the CH_3COCl and $Al_2Cl_7^-$, which is probably the actual catalyst in the melt. This is a very useful fact, because we can now easily select the reactivity of the medium toward Friedel–Crafts substitution by adjusting the N of the melt used.

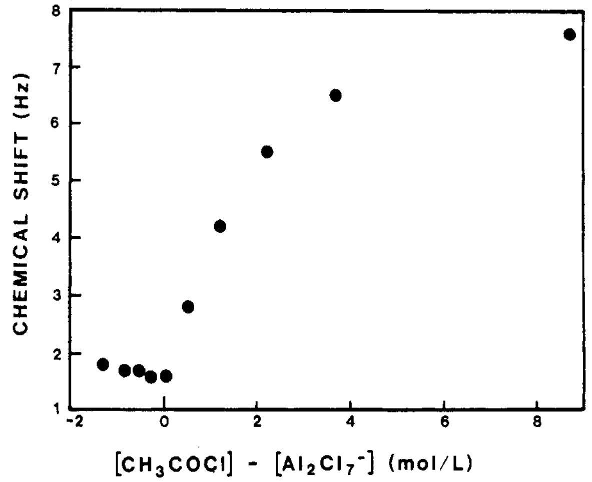

Figure 3. ^1H NMR chemical shifts of acetyl chloride in melts of varying composition. Shifts are referenced to the CH_3 of the N-ethyl of the imidazolium cation. The abcissa is the difference between the acetyl chloride and heptachloroaluminate concentrations in order to emphasize the equimolar point.

When an acidic MeEtIm melt was combined with an amount of CH_3COCl equal to the amount of $Al_2Cl_7^-$ present and the mixture was allowed to stand, we observed the slow formation of needle crystals. The isolated crystals were very reactive when added to benzene or toluene, producing the acetylated product. Full characterization of these crystals is now in progress, but preliminary results indicate that the solid is the crystalline form of the electrophile produced in the melt during the acetylation reactions.

The data in Figure 3, the reactivity of acetyl chloride, and the formation of the reactive crystals suggest that the reaction between CH_3COCl and $Al_2Cl_7^-$ generate the electrophile CH_3CO^+ (1-oxoethylium):

$$CH_3COCl + Al_2Cl_7^- \rightarrow CH_3CO^+ + 2AlCl_4^-$$

Alternatively, an undissociated reactive complex of $CH_3COCl \cdots Al_2Cl_7^-$ or the less likely diacetylacetylium cation[21] might be formed. The ^1H NMR chemical shift of CH_3CO^+ has been measured,[22] but in an entirely different solvent and with a different reference. Olah reported that CH_3CO^+ was shifted 1.9 ppm downfield from its parent CH_3COF. We see a 1.0 ppm downfield shift from the parent CH_3COCl, which we cannot interpret unambiguously as the completely dissociated CH_3CO^+.

The classic nature of Friedel–Crafts electrophilic aromatic substitution reactions in chloroaluminate melts was further demonstrated through relative reactivity measurements. In competitive propylation, toluene was found to be 1.9 times more reactive than benzene, and chloro-

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[20] The concentration of $Al_2Cl_7^-$ may be calculated from

$$[\mathrm{Al_2Cl_7^-}] = \frac{\rho(2N - 1)}{(1 - N)M_{\mathrm{ImCl}} + NM_{\mathrm{AlCl_3}}}$$

for $N > 0.5$ and [$Al_2Cl_7^-$] = 0 for $N < 0.5$ where ρ is the melt density,[4b] M_{ImCl} is the molecular weight of 1-methyl-3-ethylimidazolium chloride, and $M_{\mathrm{AlCl_3}}$ is the molecular weight of aluminium chloride. Actually, in neutral and basic melts some $Al_2Cl_7^-$ is present due to the $2AlCl_4^- = Al_2Cl_7^- + Cl^-$ equilibrium. The concentrations are extremely low ($<10^{-7}$ M) and may be neglected.

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benzene was approximately 0.55 times as reactive as benzene. The relative rates suggest that a highly reactive electrophile is produced during the reaction. Such reactive attack by electrophiles are relatively nonselective for aromatic compounds that are activated or deactivated by substituents, and therefore, relative rates are usually within the same order of magnitude. A competitive rate experiment for acetylation also gave the expected order of reactivity for benzene, toluene, and chlorobenzene. The relative rates were 1, 37, and 0.015, respectively. Here the substituents are exerting more kinetic control in the reaction.

In all of the experiments described so far the $Al_2Cl_7^-$ was present in large excess, because the melt was used as the solvent. True catalysis by the $Al_2Cl_7^-$ was demonstrated by a series of turnover experiments where the composition of the melt was adjusted so that it provided less $Al_2Cl_7^-$ than the amount of substrate. A reaction that contained benzene, acetyl chloride, and $Al_2Cl_7^-$ in the proportions of 1.1:1.0:0.5, respectively, afforded complete conversion of the benzene to acetophenone in less than 5 min. A second reaction using the proportions 1.1:1.0:0.1 still afforded a yield of acetophenone greater than the $Al_2Cl_7^-$ would permit if consumed, but at a rate 20 times slower than the first experiment.

Conclusion

The imidazolium chloroaluminate room-temperature molten salts provide a medium for Friedel–Crafts alkylations and acylations that is both the solvent and catalyst. Because the Lewis acid species in the melt is well characterized, the catalyst for the Friedel–Crafts reactions can be clearly identified as $Al_2Cl_7^-$. This is consistent with the fact that pure $AlCl_3$ is not an effective catalyst in Friedel–Crafts reactions, why traces of a co-catalyst are necessary, and why a twofold excess of $AlCl_3$ promotes greater yields.[23] In the case of acetylation, the reactive electrophile can be isolated as a crystalline material. We propose the following mechanism for the acylation of an aromatic compound, Ar–H, by the acyl chloride, RCO–Cl, catalyzed by the melt:

$$\mathrm{RCO{-}Cl} + \mathrm{Al_2Cl_7^-} \rightarrow \mathrm{RCO^+} + 2\mathrm{AlCl_4^-}$$

$$\mathrm{RCO^+} + \mathrm{Ar{-}H} \rightleftharpoons \mathrm{H{-}Ar^+{-}CO{-}R}$$

$$\mathrm{H{-}Ar^+{-}COR} + \mathrm{AlCl_4^-} \rightleftharpoons \mathrm{Ar{-}CO{-}R} + \mathrm{HCl} + \mathrm{AlCl_3}$$

$$\mathrm{AlCl_3} + \mathrm{AlCl_4^-} \rightarrow \mathrm{Al_2Cl_7^-}$$

$$\mathrm{RCO{-}Cl} + \mathrm{Ar{-}H} \rightarrow \mathrm{Ar{-}CO{-}R} + \mathrm{HCl}$$

We believe that the first and last steps are very rapid and virtually quantitative. The cationic intermediate shown as a product of the first step may not be the completely ionized acylium, but instead the reaction may produce other species of equivalent stoichiometry and reactivity.

Experimental Section

The 1-methyl-3-ethylimidazolium chloroaluminate melts were prepared as described earlier.[4] All melt preparations were done in a helium- or argon-filled glovebox maintained at <10 ppm combined water and oxygen. The organic reactions were performed on the bench top under a stream of dry nitrogen.

General Friedel–Crafts reaction procedure: The aromatic Friedel–Crafts substrate was added to a weighted quantity of melt (0.1–5 g). The alkylating agent was added either at room temperature or at the reflux temperature of the alkyl chloride. For kinetics determinations an aliquot of the reaction mixture (usually 0.1 or 0.2 mL) was removed, added to 2 mL of water to quench the reaction, and made basic with 6 m NaOH. The mixture was extracted with 5 mL of diethyl ether and dried over anhydrous $MgSO_4$.

The products were analyzed by GC/MS on a Hewlet–Packard Model 5985 mass spectrometer equipped with a 3 ft column packed with 2% OV-101. NMR spectra were obtained on a Varian T-60 or JEOL FX90Q spectrometer.

Registry No. Benzene, 71-43-2; methyl chloride, 74-87-3; ethyl chloride, 75-00-3; *n*-propyl chloride, 540-54-5; *n*-butyl chloride, 109-69-3; cyclohexyl chloride, 542-18-7; benzyl chloride, 100-44-7; 1-methyl-3-ethylimidazolium chloroaluminate, 87587-77-7; acetyl chloride, 75-36-5.

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Monitoring and Optimization of Deprotection Reactions of Peptides by Direct Sampling with Fast Atom Bombardment Mass Spectrometry[†]

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Deprotection is often one of the most critical reactions in peptide chemistry. Direct monitoring of these reactions using fast atom bombardment (FAB) mass spectrometry proved a suitable method to optimize reaction conditions. The use of the micromolar reaction scale efficiently reduces the amount of fully protected peptide needed. All investigations were carried out with cyclic analogues of biologically active peptides.

In organic chemistry and particularly in peptide chemistry the use of protecting groups is essential for the success of a synthesis, but their removal often presents a serious challenge. General procedures invariably have to be specifically adapted and optimized for each individual case to prevent incomplete deprotection and various side reactions. The optimization is frequently extremely time consuming and usually severely limited by the amounts needed to detect, separate, and characterize the different

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[†] Dedicated to Professor Ferdinand Bohlmann, TU Berlin, on the occasion of his 65th birthday.

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