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Short communication

Gasometric titration for dimethylaluminum chloride analysis

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ABSTRACT

A gasometric titration method was developed to quantitate active alkylaluminum content in dimethylaluminum chloride solution to perform the stoichiometry calculation for the reaction charge. The procedure was reproducible with good precision, and the results showed good correlation with ICP-MS method. The gasometric titration is a simple, inexpensive alternative to analysis via ICP-MS which provides more selective analysis of methylaluminum species without the need for inertion.

1. Introduction

Dimethylaluminum chloride, also called chlorodimethylaluminum, is a highly hazardous pyrophoric organic compound and strong Lewis acid. It is commercially available neat or as solution in hydrocarbon solvents. Neat dimethylauminum chloride is an extremely pyrophoric liquid and immediately ignites spontaneously to produce copious corrosive fumes. Dimethylaluminum chloride in all forms is extremely flammable, and thus must be kept away from sparks, flames, or any source of ignition [1–5]. Even the more concentrated solutions (2 M) are pyrophoric, while the more dilute solutions produce smoke upon exposure to air. Since dimethylaluminum chloride is highly reactive toward air, moisture, and other oxygen compounds, the neat liquid form as well as its solutions must be handled under inert gas (Ar or N_2) to exclude oxygen and water. Dimethylaluminum chloride solutions are reasonably stable and may be titrated by standard analytical methods [6]. Since dimethylaluminum chloride can formally act as a proton scavenger, it reacts with water to give methane and HCl. Therefore, on some vendor certificates of analysis (COA), dimethylaluminum chloride is assayed by titrating Cl^- with silver nitrate, or via acid-base titration with a color indicator. Alternatively, the purity is determined by back titration of aluminum [7]. Ethylenediaminetetraacetic acid (EDTA) and aluminum are allowed to react in the hot solution for several minutes, and then excess EDTA is titrated with Zn^{2+}. However, no analytical methods exist to specifically assay for the active methylaluminum content, which refers to aluminum in the form of organoaluminum species that catalyzes the desired chemical transformation such as dimethylaluminum chloride or trimethylaluminum.

Over the years, we have found dimethylaluminum chloride to be useful in a number of chemical transformations to afford the desired target products selectively in good yields. Dimethylaluminum chloride has been shown to be useful in Lewis acid catalyzed reactions such as Friedel-Crafts acylations, ene reactions and aldol reactions [1]. Unfortunately, we have observed side reactions in our chemistry due to nucleophilic additions of the methyl group to carbonyl compounds, despite the diminished nucleophilic activity of the methyl group relative to the ethyl group in diethylaluminum chloride. Specifically, we have encountered such issues in the Friedel-Crafts acylation of indoles with acyl chlorides where an excess of dimethylaluminum chloride led to undesired methyl addition to the ketone products and polymeric by-products [8]. Because of this, it is desirable to have an accurate and easy assay for dimethylaluminum chloride, specifically for organo-aluminum content. In our case, a dimethylaluminum chloride charge of 0.5 equivalents proved optimal in terms of conversion to desired product, yield and reaction rate.

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Dimethylaluminum chloride can be prepared by charging trimethylaluminum to a slurry of aluminum chloride in a solvent such as *n*-heptane so that the following reaction takes place [1]:

$$2AlMe_3 + AlCl_3 \rightarrow 3AlMe_2Cl \quad (1)$$

Any solids can then be removed via filtration resulting in a dimethylaluminum chloride solution ($AlMe_2Cl$). In the resulting product, trimethylaluminum ($AlMe_3$) and methyl aluminum dichloride ($AlMeCl_2$) could potentially exist as side products; however, these two species do not co-exist as they will convert to dimethylaluminum chloride upon contact. The other reactant, aluminum chloride ($AlCl_3$) cannot exist in solution at any appreciable level due to its low solubility in heptane. The resulting product was characterized by the vendor via acid-base titration utilizing a phenolphthalein indicator.

Based on the dimethylaluminum chloride potency on the vendor release COA, 0.5 equiv. of dimethylaluminum chloride was charged but resulted in sluggish reaction. Time-consuming range finding experiments (0.40, 0.45, 0.50, and 0.55 equiv.) were performed and 0.45 equiv. was found to be optimum, which indicated a potency higher than what was listed on the vendor COA. By doing spiking experiments, it was also found that when active alkylaluminum content is within 10% of the theoretical value in the dimethylaluminum chloride sample, then the reaction rate was acceptable. However, beyond this range, the reaction became sluggish. The root cause of the higher potency was suspected to be due to residual trimethylaluminum in the dimethylaluminum chloride sample, which was not titratable by NaOH. When more than 10% of trimethylaluminum co-exists in dimethylaluminum chloride, the reaction slowed down due to overcharge of the alkylaluminum species. Small amounts (<10%) of trimethylaluminum in dimethylaluminum chloride did not appreciably impact the chemistry, but the use of pure trimethylaluminum gave somewhat inferior results. Most importantly, it was the total organo-aluminum content of the reagent that impacted the reaction. To provide a better quality control of charged material, we have developed a simple gasometric titration method [9,10] for more accurate dimethylaluminum chloride characterization. Instead of measuring HCl by acid-base titration, we established a new procedure to measure the total alkylaluminum content in the sample as evolved methane. When the methane content is within the targeted 10% range, the total aluminum charge is within 10% range leading to the desired reaction rate. The gasometric titration results were in agreement with the ICP-MS (inductively coupled plasma mass spectrometer) results. The method is reproducible, easy to conduct without requiring expensive instrumentation or special training, and can be easily transferred to a vendor that does not have an operational ICP-MS. Furthermore, since methylaluminum reagents such as dimethylaluminum chloride and trimethylaluminum can be useful as methyl transfer agents as in the addition of a methyl group to a ketone, the ability to specifically measure active alkylaluminum content via gasometric titration is valuable.

2. Experimental

2.1. Instrumentation

A gasometric titration system was set up in the lab for active methylaluminum content determination via volumetric methane measurement. NMR spectra were recorded using a Bruker 500 MHz spectrometer with Quattro Nucleus Probe (QNP). A PerkinElmer Elan 6000 inductively coupled plasma mass spectrometer (ICP-MS) equipped with an AS-91 autosampler was used for ICP-MS analysis. The instrumental conditions and general method parameters are listed in Table 1.

Table 1
Elan 6000 instrumental conditions and method parameters.

RF power (W)	1300
Coolant argon flow (L/min)	15.0
Auxiliary argon flow (L/min)	1
Nebulizer argon flow (L/min)	0.86–1.06
Sample introduction system	Cross flow nebulizer with Scott spray chamber
Operating frequency (MHz)	40
Sample uptake rate (mL/min)	1.5
Detector mode	Dual mode
Sampler/skimmer cones	Platinum
Scanning mode	Peak hopping
Number of points per peak	1
Dwell time (ms)	15
Sweeps per reading	40
Number of replicate	2

2.2. Reagents and materials

Dimethylaluminum chloride (1.0 M in hexanes), Trimethylaluminum solution (2.0 M in heptane), 1.0 M HCl, and Chloroform-*d* ($CDCl_3$) were purchased from Sigma Aldrich. Concentrated nitric acid (70%, trace metal grade) was purchased from Seastar (Sidney, B.C., Canada). Aluminum standard (certified 1000 μg/mL in 2% HNO_3) and chloride standard (Certified 1000 μg/mL in water) were obtained from High Purity Standards (Charleston, SC). Deionized water was prepared by passing distilled water through a Milli-Q water system (Millipore, Bedford, MA). Flexible teflon tubing (¼" ID, 1/8" Wall) and septum (Sleeve Stopper Size 24) were purchased from Fisher scientific (Pittsburgh, PA, USA). All the drug substances and their intermediates used in this study were obtained from Merck Sharp & Dohme Corp. (Rahway, NJ, USA).

2.3. Sample preparation

Dimethylaluminum chloride and trimethylaluminum mixture solutions were prepared following the procedure in Table 2 below. The final molar ratios of the mixture solutions were 95:5, 90:10, and 85:15, respectively.

ICP-MS calibration standard (10 μg/mL for all Al and Cl) was prepared by quantitatively diluting standard solutions in 10% nitric acid matrix. The 10% nitric acid solution was also used as the calibration blank. Standards were prepared in duplicate. ICP-MS samples were prepared preferably in a glove box. A syringe was used to accurately weigh approximately 100 mg of sample (about 0.100 mL) directly into a polypropylene sample container containing 10 mL of 10% nitric acid and mix well. Standards and samples were prepared in duplicate.

2.4. Gasometric titration procedure

The gasometric system consisted of an acid-dispensing and gas-measuring burette (50 mL), a 125 mL separatory funnel with teflon stop cock, a gas-tight syringe (0.5–1.0 mL), and flexible Teflon tubing.

1) Set up apparatus as shown in Fig. 1 filled with a sufficient quantity of 1 M HCl to mostly fill the separatory funnel (ca 10–20 mL remaining headpace), to completely fill the Teflon tubing and a small portion (ca 5 mL) of the buret. Since only 2 equivalents of HCl are required per equivalent of dimethylaluminum chloride, there is enough aqueous HCl to completely consume the aluminum reagent (0.1 mL).
2) Adjust the heights of the separatory funnel or buret so that levels of liquid are at the same heights in both the separatory funnel and the buret, then read the volume level of HCl in the buret.