Concentration determination of methyl magnesium chloride and other Grignard reagents by potentiometric titration with in-line characterization of reaction species by FTIR spectroscopy

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Abstract

A potentiometric titration method for methyl magnesium chloride and other Grignard reagents based on the reaction with 2-butanol in THF has been developed and validated. The method employs a commercially available platinum electrode, using an electrolyte compatible with non-aqueous solvents. Well-defined titration curves were obtained, along with excellent method precision. The endpoint was precisely determined based on the first derivative of the titration curve. Different solvents such as THF, diethyl ether and methylene chloride provided similar results with regard to sharpness of the endpoint and method precision. The method was applied to a wide array of Grignard reagents including methyl magnesium bromide, ethyl magnesium chloride, propyl magnesium chloride, vinyl magnesium chloride, phenyl magnesium chloride, and benzyl magnesium chloride with similar precision and accuracy. Application of in-line FTIR was demonstrated for in situ monitoring of the titration reaction, allowing characterization of the reaction species. An authentic spectrum of the MeMgCl–THF complex was obtained using spectral subtraction and the vibrational absorbance bands were identified. FTIR also provided an alternative for detecting the titration endpoint, and the titration results so obtained, provided a cross-validation of the accuracy of the potentiometric titration. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Methyl magnesium chloride; Automated titration; In-line FTIR; Grignard reagent titration

1. Introduction

Methylmagnesium chloride (CH_3MgCl) is a very important Grignard reagent that can be used as a methylation reagent [1]. Accurate charging of the reagent is often critical to the synthetic process in order to optimize yield and purity of the product. Thus, accurate and reliable measurement of the concentration of Grignard reagent, especially after a period of storage of this air- and moisture-sensitive reagent, is an important part of quality control.

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A survey of literature indicated that a broad array of analytical methods have been reported for quantitative analysis of organomagnesium and organolithium reagents in the past. These methods include the iodination method for alkyllithium solutions by Clifford and Olsen [2], the double titration method by Gilman and Haubein [3], the vanadium pentoxide method for oxidimetric determination of alkyllithium solutions by Collins et al. [4], the high frequency titration method using acetone for organolithiums by Watson and Eastham [5], gas chromatography (GC) method for methyllithium and methylmagnesium compounds after derivatization by House and Respess [6], and the high performance liquid chromatography (HPLC) method following derivatization reactions for analysis of vinylmagnesium halide by Egekeze et al. [7]. These methods are generally more complicated in sample preparation. The only direct method developed by Watson and Eastham [8] involves the reaction of the Grignard reagent with an alcohol.

Although the direct titration method has been the preferred and most widely accepted procedure (due to the method's simplicity and speed) for total base determination of alkylmagnesium halides, the choices for endpoint determination have been very limited. Only oscillometric technique (involving high frequency measurements) [5] and color indication [8] have been reported for endpoint determination in the titration of alkylmagnesium halide. The measurement of high frequency is not attractive because it is believed to be applicable only to compounds containing lithium–carbon bonds. In addition, this method can be very time-consuming. The use of color indicators such as 1,10-phenanthroline and 2,2′-biquinoline [8] to determine the endpoint suffers from poor reproducibility and ruggedness. Our experiments with methyl magnesium chloride (3.0 M in THF) using 2,2′-biquinoline as a color indicator did not produce distinct and reproducible endpoint (due to formation of a pinkish precipitate during the reaction with 2-butanol). The endpoint determination based on color change is therefore subject to considerable human error, and the method is not precise and robust.

Chevrot et al. have reported the use of a pure hydrogen electrode (glass electrode with fixed hydrogen pressure) to determine the end point [9,10]. However, the exact type of hydrogen electrode described by Chevrot is not commercially available. Therefore, we modified the original method by employing a commercially available platinum electrode for the endpoint determination. The titration was automated for repetitive routine analyses. The method was validated in terms of precision, repeatability, linearity (independent of sample size), titration rate, solvent type and accuracy by comparing results with an independent method. Application of this method to the analysis of various other Grignard reagents was also demonstrated.

In addition, we simultaneously monitored the titration by an in situ ReactIR™ system, which yielded a more complete reaction profile and provided spectral information. The in-line FTIR technique developed in recent years [11] is a powerful tool to provide real-time information about a reaction for which qualitative and quantitative spectral analyses of complex, non-isolated mixtures can be achieved. Ende et al. have reported using FTIR to monitor scale-up of Grignard formation and hydrolysis [12] and Buhr has suggested the use of in situ FTIR analysis as a suitable analytical method for the determination of the concentration of Grignard reagents in fast reactions [13]. In our study, in-line FTIR spectroscopy was used as an independent technique, not only to confirm the titration results obtained via the potentiometric endpoint detection, but also to monitor the titration reaction by first obtaining authentic spectra of the various species involved. These findings may lead to a better understanding of Grignard reactions in complex mixtures and be transferable to in-line reaction monitoring of scale-up processes.

2. Experimental

2.1. Reaction of Grignard reagents with 2-butanol

Grignard reagents react vigorously with alcohols and can be directly titrated with a standard

solution of 2-butanol to a well defined, stoichiometric endpoint.

$$R–Mg–X + 2\text{-BuOH} \rightarrow RH + 2\text{-Bu–O–Mg–X}$$
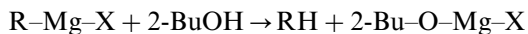
where R = alkyl or aromatic group such as methyl, ethyl, propyl, phenyl, benzyl, and vinyl, and X = Cl, Br, or I.

2.2. Reagents and solutions

Grignard reagents were purchased from Aldrich/Sigma Chemical Company (Milwaukee, WI, USA) in 100-ml bottles with SurelSeal™ septa and used within 2 weeks of receipt. No visible turbidity was observed in the fresh Grignard reagent bottles. All other reagents and solvents for titration were analytical grade chemicals purchased from Aldrich/Sigma Chemical. Tetrahydrofuran (THF) contained no butylated hydroxytoluene (BHT). The water content in THF, toluene, methylene chloride and diethyl ether was determined by Karl Fischer titration to be less than 200 μg/ml before use. The 2-butanol was dried over molecular sieves (3–5 Å) for at least 2 h until the water content was below 200 μg/ml as determined by Karl Fischer titration.

A solution of 2-butanol (0.8721 M) in THF as the titrant was prepared by pipetting 40 ml of dried 2-butanol into a 500-ml volumetric flask and diluting to volume with THF. For the study of solvent matrix effects, the titrant was prepared in either diethyl ether or toluene, to match the solvent in which the Grignard reagent was prepared.

2.3. Instrumentation

2.3.1. Automated potentiometric titration

An automated titrator (model 716 DSM titrino) from Brinkmann (New York, NY, USA) was used in this study. A Metrohm combined platinum wire electrode (Pt/ − 5...70 °C, 3 M KCl) was purchased from Brinkmann (cat. # 6.0402.100). The inner chamber of the electrode was rinsed with THF and dried at our laboratory. A concentrated lithium chloride (∼ 3 M) solution in THF was then filled into this chamber to produce an electrode suitable for non-aqueous titration. A few drops of 0.1 N silver nitrate solution were added to the inner chamber (Ag/AgCl reference electrode inside) to form a silver chloride precipitate, which connected the salt bridge. The electrode was soaked in a 0.1 N nitric acid solution in water between and after analyses. Reagent addition rate was a constant and generally set at 1.0 ml/min in the standard procedure for methylmagnesium chloride titration. A stainless steel syringe needle, 18-gauge, 4-in. long, with deflecting tip and Luer hub (Aldrich), was fit onto a 5-ml syringe for sampling.

2.3.2. In-line FTIR

A ReactIR™ 1000 spectrometer with a Di-Comp diamond ATR immersion probe (Mettler-ASI Applied System, Millersville, MD, USA) was used in the study. The data were collected in a sequence at a rate of 1 spectrum per 30 s in the range of 4000–600 cm^{-1}. Each spectrum represents an average of 16 scans with a spectral resolution of 4 cm^{-1}. Typically, a total of 100 spectra were taken during the course of titration.

2.4. Titration procedure

The following procedure was used for Grignard solutions at or near 3.0 M in THF. For more dilute solutions, a larger sample volume was used to achieve comparable accuracy and precision.

The setup of the titration vessel is shown in Fig. 1. The three-necked round-bottom flask (250 ml), containing a 3-cm Teflon-coated magnetic stirring bar, was dried in a drying oven (105 °C) for at least 1 h and cooled in a desiccator to room temperature before use. Alternatively, the vessel was pre-washed with acetone followed by THF to remove residual moisture on the vessel wall. THF (70 ml) was charged into the vessel and gentle stirring was applied. The stirring rate was controlled between range 2 and 4 with a 728 Metrohm stirring plate. The platinum electrode was inserted through the central neck (capped with rubber serum stopper)

and carefully positioned with the electrode tip immersed in the solvent below the surface at the vortex and above the stirring bar. Since Grignard reagents react readily with moisture and carbon dioxide in air, the reagents and titration mixture were protected from the atmosphere by constantly purging the titration vessel with nitrogen. The inlet and outlet of the nitrogen purge were two hypodermic needles inserted through the rubber serum stoppers on the two sidearms of the three-necked flask. The flow rate of the nitrogen was adjusted to approximately 20 ml/min (measured by the flowmeter connected to the vent) so that the head space above the liquid was flushed gently and continuously with nitrogen. The bubbler was used to provide visual confirmation that the nitrogen purge was uninterrupted. The vent was expressed in a well-ventilated fume hood. The Teflon dispenser of the titrant was inserted through the same rubber stopper holding the nitrogen inlet and the tip of the dispenser was submerged below the solvent surface. After closing the vessel, it was purged with nitrogen for approximately 3 min to remove any air.

A suitable volume (approximately 5 ml) of methylmagnesium chloride solution (3.0 M) was withdrawn from the sample bottle by syringe and weighed (with the syringe and needle intact) on an analytical balance to obtain the gross weight. Then the sample was introduced via the syringe, which punched through the stopper on one sidearm of the titration vessel. The introduction of the sample was accomplished in a period of approximately 1 min. Care was taken to prevent the syringe tip from touching the solvent or the vessel wall. The syringe with needle was weighed again following delivery of the sample to obtain the weight of the sample (W). The titration was then started immediately and the volume of titrant used was recorded.

The reaction between methylmagnesium chloride and 2-butanol formed methane (gas bubbles) and the solution gradually turned cloudy. A grayish precipitation could be observed near the endpoint. The endpoint was determined based on the first derivative of the potentiometric curve using the computer software of the Brinkmann titrator. The titration was performed in duplicates or triplicates. The molarity of the sample was calculated as
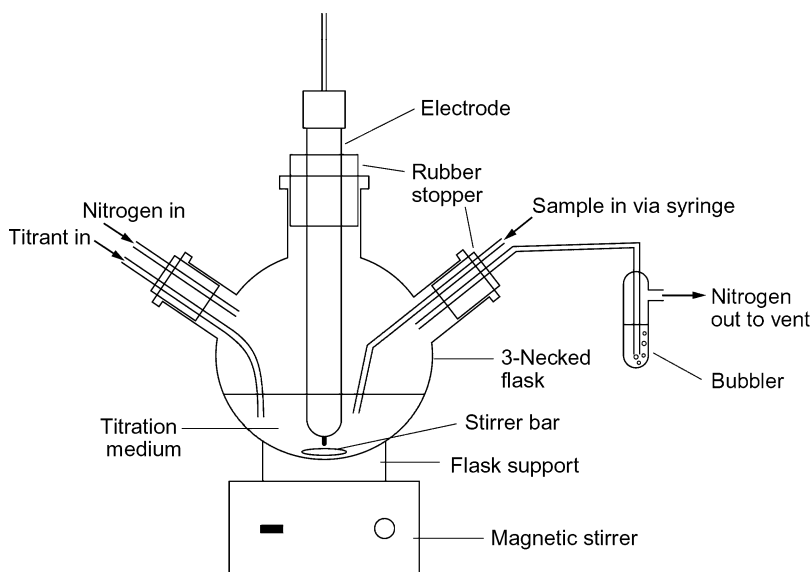

Fig. 1. Automated titration vessel setup.

$$M = \frac{(V)(M_{std})(d)}{(W)}$$

where M, molarity of MeMgCl in the sample; V, total volume of titrant used (ml); M_{std}, molarity of 2-butanol in titrant (0.8721 M); d, density of sample (g/ml) which was obtained from the manufacture's certificate of analysis; W = weight of sample (g).

A typical titration could be finished in less than 20 min. For routine analysis of large numbers of samples or repetitive analyses of a single sample, a partial titration method was developed to reduce analysis time to less than 10 min for each titration. This was done by accurately adding approximately two third of the expected volume of titrant in a much faster rate using the manual control button on the titrator, followed by a slower titration of the remaining Grignard reagent. This technique not only reduced analysis time, but also minimized potential decomposition of the sample upon standing.

The titration procedure can be reversed if necessary. During the course of study, we encountered some problems with MeMgI which is not soluble in THF. We performed the titration in THF by reversing the order of reagent addition. MeMgI diethyl ether solution was added at 1.0 ml/min into a measured amount of 2-butanol standard solution with excellent results.

2.5. Procedure for in-line FTIR monitoring in conjunction with potentiometric titration

The titration vessel setup was similar to that shown in Fig. 1, with the vessel being slightly modified so that a fourth sidearm was added. The ATR probe (DiComp) was inserted directly into the titration vessel from the extra sidearm, through an air-tight Teflon adaptor. The probe was carefully positioned so that the tip was submerged in the solvent and away from the vortex. The background was collected using a nitrogen purge, before adding the solvent to the vessel. Solvent (70 ml THF) was added to the vessel and the spectrum of the solvent was collected. A known amount of Grignard reagent was then added using the procedure described in

Section 2.3 and a spectrum of the solution was collected. The automated potentiometric titration and acquisition of sequential FTIR spectra were then initiated simultaneously, spectra recorded periodically (every 30 s). After detecting the endpoint potentiometrically, the titration and spectral acquisition were stopped.

In our study, FTIR spectral analysis was performed using GRAMS/32 software (Galactic Industries Corporation, Salem, NH), with the reaction spectra deconvoluted for the component spectra and the corresponding reaction profiles of the components constructed using ConcIRt (version 2), an add-on software of this FTIR instrument. With the FTIR technique, the titration endpoint was determined based on the first derivative of the extrapolated FTIR reaction profile of 2-butanol, which had a very similar shape as the potentiometric titration curve. The molarity of the Grignard reagent was calculated as

$$M = \frac{(R)(T)(M_{std})(d)}{(W)}$$

where M, molarity of MeMgCl in the sample; R, rate of titrant addition (ml/min), T, time needed to reach titration endpoint (min); M_{std}, molarity of 2-butanol in titrant (0.8721M); d = density of sample (g/ml); W, weight of sample (g).

3. Results and discussion

3.1. Potentiometric titration

MeMgCl solution (3.0 M) was titrated according to the procedure described in Section 2, a typical curve of potential versus titrant volume is shown in Fig. 2. The effect of solvent, titration rate and sample size on the final result are discussed here and the method validation, in terms of repeatability, precision, and accuracy, is reported. The method was found to be applicable to other common Grignard reagents.

3.1.1. Effect of solvent on method precision
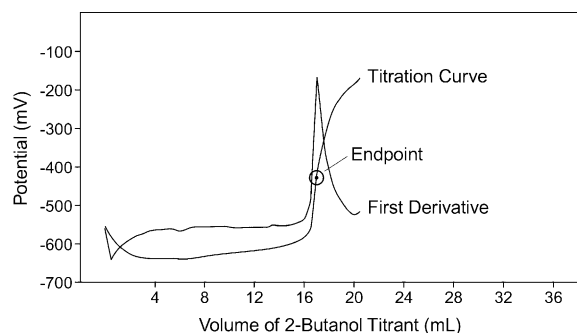Grignard compounds are exclusively available

Fig. 2. Potentiometric titration curve of MeMgCl (3.0 M in THF) with 2-butanol. Solid line, titration curve. Dashed line, first derivative of the titration curve.

as solutions, typically in diethyl ether, THF, and sometimes THF/toluene mixtures. A Grignard compound exists in solutions as an equilibrium mixture of mono, bi- and polynuclear solvated species [14]. The equilibrium between these species is known as Schlenk's equilibrium.

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons R_2Mg \cdot MgX_2$$

The exact composition of this equilibrium is influenced by the solvent's Lewis basicity and complexing power as well as the nature of the R group. However, in the case of primary alkyl Grignard compounds with chloride or bromide, the most important factor determining the position of the Schlenk equilibrium is the solvent [14]. Due to the possibility of co-existence of multiple species in a sample solution, it was of interest to investigate the effect of solvent on the shape of the potentiometric titration curve and possible influence on its concentration determination using the 2-butanol titration method. The 2-butanol standard was prepared in the same solvent as the vessel solvent. The titration curves obtained using

the solvents THF, toluene, methylene chloride, and diethyl ether were all very comparable to that shown in Fig. 2. The results in Table 1 clearly indicate that the solvents studied had little effect on the assay results. However, we found that the platinum electrode gave the best performance in THF in terms of the speed of electrode response and solubility of the compounds involved in the titration. Therefore, THF is the most suitable solvent for this titration.

3.1.2. Effect of titration rate

The rate of a titration should be consistent with the rate of electrode response and the frequency of data acquisition of the instrument, especially for non-aqueous titrations. If the titration rate is too fast, far surpassing the rate of electrode response, ill-shaped titration curve may be produced, affecting the endpoint determination. If the titration rate is too slow, the analysis becomes tediously long and the compound will have a greater chance of being consumed by possible contaminants from the ambient. The advantage of an automated titration is that the titration rate can be well controlled by controlling the rate of titrant delivery. During our initial method development, some problems regarding the odd shape of the titration curve were encountered when the titration rate was faster than 5 ml/min. This was probably due to the delayed response of the platinum electrode in the anhydrous organic solvent. Once the titration rate was reduced to 3 ml/min or lower, the problem disappeared. Our study showed that when titration rate was controlled in the range of 0.5–3.0 ml/min, consistent assay results were obtained (Table 2) within ± 0.1 M variation. The titration rate at 1.0 ml/min was

Table 1
Titration results obtained on a MeMgCl sample (3.0 M in THF) using different vessel solvents

Experiment number	Sample size (g)	Vessel solvent	Concentration[a] (M)
1	5	Tetrahydrofuran	2.91 ± 0.11 (5)
2	5	Toluene	2.86 ± 0.01 (3)
3	5	Methylene chloride	2.81 ± 0.04 (3)
4	3	Diethyl ether	2.93 ± 0.03 (2)

[a] The numbers in parentheses represent the number of replicates.

Table 2
Titration results obtained on a MeMgCl sample (3.0 M in THF) using different titration rate

Experiment number	Sample size (g)	Titration rate (ml/min)	Concentration[a] (M)
1	5	3	2.97 ± 0.06 (3)
2	5	2	2.86 ± 0.04 (5)
3	5	1	3.04 ± 0.05 (3)
4	5	0.5	2.93 ± 0.05 (2)

[a] The numbers in parentheses represent the number of replicates.

selected to accomplish high precision within a reasonable period of analysis time.

3.1.3. Effect of sample size

Effect of sample size on molarity determination for MeMgCl solution (3.0 M in THF) was determined by varying the sample size in the range encompassing 60–200% of the target sample size of 5 g. Results are shown in Table 3. As shown, titration results are independent of the sample size in this range (2.3% R.S.D.).

3.1.4. Precision/repeatability

The precision of the method on MeMgCl has been validated using five determinations of the concentration by two analysts in two different days (Table 4). Excellent precision was demonstrated (R.S.D.% of < 1.0%).

3.1.5. Accuracy

The accuracy of the method was verified independently by in-situ FTIR method as discussed in Section 3.2.

3.1.6. Results of other Grignard reagents

We applied the automated potentiometric titration method to other commercially available Grignard reagents. A 10-ml sample aliquot (with concentration of 1.0–3.0 M) was used for each titration. In Table 5, the results are shown and compared with those determined using the FTIR technique for endpoint detection. The potentiometric titration for these reagents consistently exhibited well-defined titration curves and sharp endpoints (Fig. 3). The results obtained using FTIR endpoint detection confirmed the accuracy of the potentiometric titration method.

3.1.7. Sources of error

Experimental error originates mainly from the following sources: malfunction of the platinum electrode, interferences from moisture, oxygen and carbon dioxide, and sample handling. Malfunction of the platinum electrode, indicated by weak potentiometric breaks and sluggishness of electrode response, is largely due to surface contamination and deactivation. The surface of the platinum electrode should be kept clean and free from any deposition. Before and after each analysis, the electrode should be soaked in a dilute nitric acid aqueous solution (~ 0.1 N) for at least 5 min. The performance of the electrode has been found to be reproducible during our 2-year study.

3.2. Monitoring titration by FTIR

FTIR is a powerful tool for in-line monitoring of reaction processes [11–13]. In our study, in situ FTIR technique was used to monitor the titration

Table 3
Titration results obtained on a MeMgCl sample (3.0 M in THF) using different sample size

Experiment number	Sample size (g)	Concentration[a] (M)
1	10	2.96 ± 0.02 (2)
2	6	3.04 ± 0.05 (2)
3	5	2.86 ± 0.04 (5)
4	3	2.93 ± 0.03 (2)
5	2	2.99 ± 0.08 (2)
Mean		2.96
S.D.		0.067
R.S.D.%		2.3

[a] The numbers in parentheses represent the number of replicates.

Table 4
Precision of the titration method for MeMgCl (3.0 M in THF)

Experiment number	Sample size (g)	Concentration (Molarity)
1	5	2.88
2	5	2.89
3	5	2.90
4	5	2.83
5	5	2.86[a]
Mean		2.87
S.D.		0.028
R.S.D.%		0.97

[a] Determination by second chemist.

process and verify the accuracy of the potentio-
metric titration method.

The course of the titration was monitored di-
rectly via the in situ FTIR probe inserted in the
titration vessel. Fig. 4 shows a typical 3D plot of
the titration mixture with MeMgCl being titrated
by 2-butanol in THF. A series of FTIR spectra in
the region of 1700–650 cm^{-1} in absorbance mode
were obtained over the course of the titration.
Spectral analysis was performed using ConcIRT
(version 2), an add-on software of the ReactIR
instrument, to produce the relative concentration
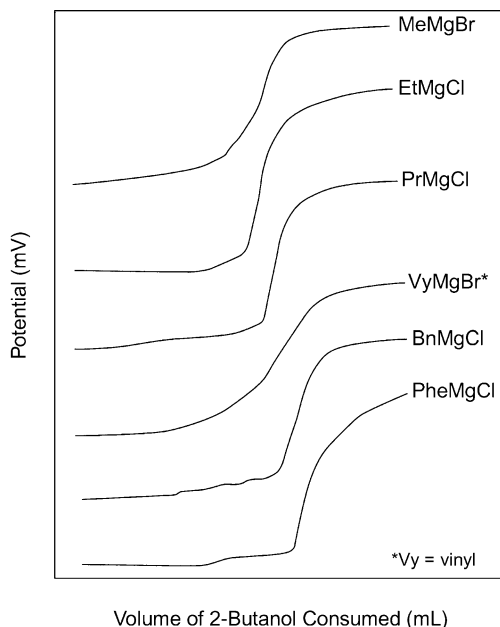curve of each soluble component (Fig. 5). During

Fig. 3. Potentiometric titration curves for other Grignard
reagents.

a normal titration (Fig. 5), the THF (vessel sol-
vent) was added first and its concentration re-
mained constant up to time 'A', at which
MeMgCl was added and the concentration of

Table 5
Comparison of titration results obtained using potentiometric and ReactIR endpoint detection techniques

| Compounds titrated	Concentration determined using potentiometric endpoint detection (M)	Concentration determined using reactIR endpoint detection (M)
Methylmagnesium bromide (1.4 M in THF)	1.42	1.34
Methylmagnesium chloride (3.0 M in THF)	3.04	2.99
Methylmagnesium iodide (3.0 M in diethyl ether)	2.95	3.05
Ethylmagnesium chloride (2.0 M in THF)	2.09	1.94
Propylmagnesium chloride (2.0 M in THF)	1.93	2.03
Vinylmagnesium bromide (1.0 M in THF)	0.97	1.04
Phenylmagnesium chloride (1.7 M in THF)	1.66	1.68
Benzylemagnesium chloride (2.0 M in THF)	1.96	1.94
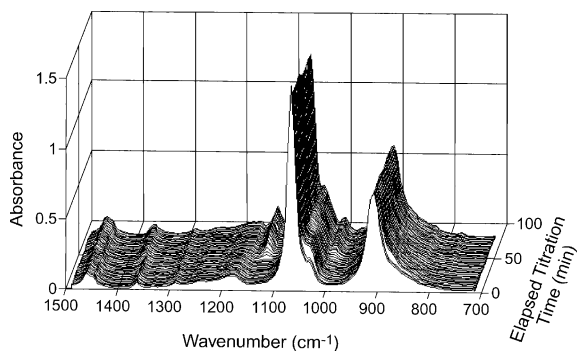
Fig. 4. 3D spectra of MeMgCl with 2-butanol by ReactIR in the fingerprint region.

THF decreased (due to the dilution effect) and that of MeMgCl correspondingly increased. The addition of MeMgCl stopped at time 'B', at which time the concentrations of THF and MeMgCl leveled off. At time 'C', the addition of 2-butanol titrant was started. From this point, the THF concentration started increasing (since 2-butanol titrant contained THF as the solvent), that of MeMgCl began to decrease (since MeMgCl was being consumed) and the concentration of 2-bu-
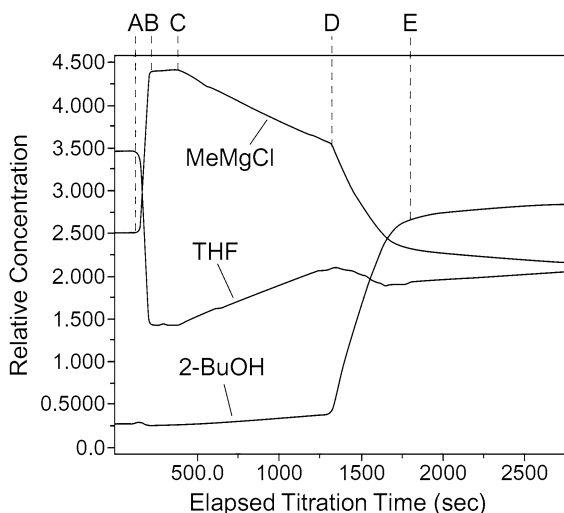
Fig. 5. Concentration profiles (normalized) of the various species involved in the titration measured by ReactIR. Time A, adding MeMgCl into vessel. Time B, addition of MeMgCl completed. Time C, starting titration with 2-butanol in THF. Time D, titration near completion Time E, titration completed.

tanol remained essentially unchanged (since 2-butanol is consumed immediately). When the titration was near completion at time 'D', the concentration of 2-butanol started to increase dramatically as excess 2-butanol started to accumulate and the concentration of MeMgCl started to decrease at a faster rate. At time 'E', the titration was completed and the concentrations of 2-butanol and MeMgCl began to level off. The concentration profile of 2-butanol behaved similarly to the potentiometric titration curve and was therefore used to determine the titration endpoint (at time 'E'). The volume of titrant used to reach the endpoint was calculated based on the titration rate (ml/s) and the time used to add the titrant.

The identification of the curves in Fig. 5 was based on spectral calculation and comparison with authentic materials. The reaction products, namely methane (a gas) and 2-butyloxyl magnesium chloride (a precipitate), were invisible to the FTIR probe since only soluble species could be detected. Based on a 3D plot such as that in Fig. 4, the computer software was able to identify and provide spectra of the components for which concentrations were changing. In our study, the calculated spectra of the changing components were then compared with those of authentic materials. The calculated spectra of THF and 2-butanol matched the spectra of THF and 2-butanol obtained separately using the same instrument. To identify the curve for MeMgCl, the spectrum of MeMgCl in THF solution was taken and compared with that of THF background solvent (Fig. 6a). The vibrational spectra, such as infrared and Raman spectra of methyl and ethyl Grignard reagents have been studied thoroughly and the vibrational assignment has been determined previously by many research groups as reviewed in reference [15]. The characteristic bands due to the C–Mg and Mg–X stretching vibration in ether solution at 300 K, which appear near or below 600 cm^{-1}[16], were beyond the measuring range of our ReactIR system (4000–650 cm^{-1}). Only the bands due to C–H stretching and deformation vibrations in the R group could possibly be observed by the ReactIR system used in our study. Although the C–H bands arising from the methyl group in MeMgCl (3000–2800 and 1461 cm^{-1})
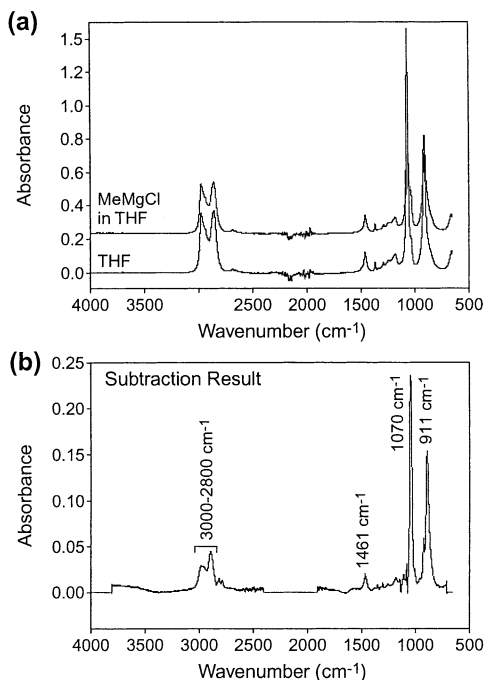
(a)

(b)

Fig. 6. Overlaid spectra of THF and MeMgCl THF solution (a) and IR spectrum of MeMgCl–THF complex after subtracting spectrum of THF (b).

were essentially indistinguishable from those of the background solvent (Fig. 6a), we were able to apply a spectral subtraction technique to obtain an interesting spectrum (Fig. 6b) in the region of $4000–700$ cm^{-1}, the subtraction result (Fig. 6b) matching the calculated spectrum of the component labeled as MeMgCl in Fig. 5. Several characteristic absorbance regions can be recognized in Fig. 6b, which represents the authentic spectrum of MeMgCl–THF complex. The group of small peaks in the $3000–2800$ cm^{-1} region are due to typical C–H stretching vibrations. A weak band at 1461 cm^{-1} is due to C–H asymmetric deformation vibration. The two strong absorbance bands at 1037 and 884 cm^{-1} are due to shifting of the two dominate bands of THF at 1070 and 911 cm^{-1} (the bands at 1070 and 911 cm^{-1} are due to C–O–C stretching and ring breathing, respectively [17]). The band shifting is an evidence of the ether molecule chemically incorporating into the structure of the Grignard compound by donating a pair of electrons from the oxygen to the magne-
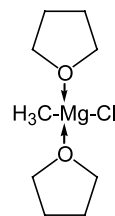

Fig. 7. Illustration of the THF molecules complexed with MeMgCl.

sium (Fig. 7). This 'charge transfer effect' puts more restrain on the C–O–C group, leading to the slight shift of the bands to lower wavenumbers. The shift of the C–O–C bands of THF in the Grignard complex caused by the charge transfer effect was also observed by Ende et al. during a Grignard synthesis process in THF [12]. Similar studies on the MeMgBr in diethyl ether solutions by Kress and Novak also strongly suggested the existence of the etherate structure [18,19].

To confirm the validity of the identification of the MeMgCl species using the computer software, a reversed titration was performed. A MeMgCl (3.0 M) solution in THF was continuously charged into 20 ml of 2-butanol solution. The concentration profiles obtained (Fig. 8) were in a reversed fashion as compared with those in Fig. 5,
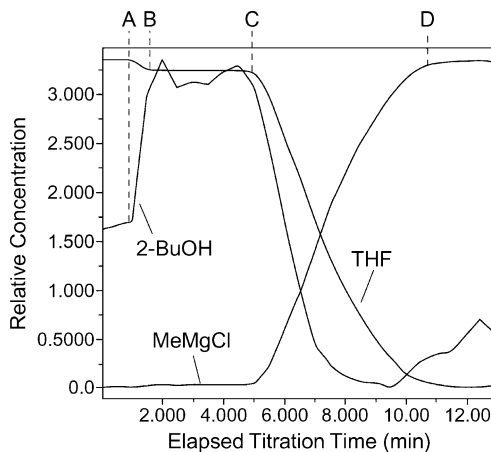

Fig. 8. Concentration profiles (normalized) of the various species involved in the reversed titration measured by ReactIR. Time A, adding 2-butanol into vessel. Time B, addition of 2-butanol completed. Time C, titration near completion. Time D, titration completed.

in agreement with the predicted pattern. The calculated spectrum of the species represented by the MeMgCl curve in Fig. 8 once again matched that of the MeMgCl–THF complex shown in Fig. 6b.

In addition, the spectra of MeMgCl and MeMgBr solutions in THF were found to be essentially the same in the region of 4000–700 cm^{-1}. This is understandable since the band for Mg–X appears below 600 cm^{-1} and is outside our spectrum window.

For the purpose of cross checking the accuracy of the potentiometric titration, the concentrations of various Grignard reagents were determined using the FTIR technique for endpoint detection based on the concentration profile of 2-butanol, as illustrated in Fig. 5. The titration results obtained by potentiometric endpoint detection agreed reasonably well with those obtained using FTIR endpoint detection (Table 5).

4. Conclusions

The determination of the concentration of methylmagnesium chloride solutions and an array of other Grignard reagents by direct titration with 2-butanol can be automated. The endpoint can be accurately determined potentiometrically using a platinum electrode. The potentiometric titration is reproducible and less subject to human error. The method worked well at the titration rate from 0.5 to 3.0 ml/min in THF, diethyl ether and a THF/toluene mixture and was able to cover a sample size between 3 and 10 ml at 3 M concentration. The analysis could be performed in less than 10 min. The method was validated and determined to be suitable for transfer to factory. Attention should be paid to sample handling in order to minimize contamination from solvents, vessels and atmosphere.

In addition, we have successfully demonstrated the application of FTIR spectroscopy for monitoring the reaction between MeMgCl and 2-butanol in situ. FTIR spectroscopy combined with the mathematical spectral deconvolution techniques yielded results comparable to those obtained by potentiometric endpoint detection. Spectral characterization of the compounds of interests provided new and unique information about the species involved in the titration reaction. An authentic spectrum of the MeMgCl–THF complex was obtained using spectral subtraction technique and the absorbance bands were identified. The major advantage of the FTIR technique is that it can provide real-time information and requires little or no sample preparation. This technique has a great potential for in-line monitoring of similar reactions on a manufacturing scale.

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