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Quantitative analysis of dimethyl titanocene by iodometric titration, gas chromatography and NMR

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Abstract

In this study we report the use of an automated iodometric titration method and a novel gas chromatography (GC) method for the quantitative analysis of dimethyl titanocene (DMT), a key raw material in drug synthesis. Both approaches are based on the reaction of DMT in toluene or tetrahydrofuran solutions with iodine. In the case of iodometric titration, excess iodine is titrated with a standardized aqueous sodium thiosulfate solution to a potentiometric end-point for the determination of DMT concentration. Alternatively, GC is employed to measure the concentration of iodomethane, a product of the reaction between DMT and iodine, in order to determine the concentration of DMT in the solution. Excellent agreement between iodometric titration, GC and NMR results using several DMT samples confirms the accuracy of the two methods and strongly supports the use of either method as a replacement to the expensive NMR for quantitative DMT analysis. The relatively few sources of error associated with the two methods, their ubiquitous nature and ease of application in routine analysis make them the analytical methods of choice, among all. Both methods have been validated according to ICH requirements. The use of iodometric titration method for DMT analysis is demonstrated with a couple of applications.

Keywords: Organotitanium; Dimethyltitanocene; NMR; Iodometric titration; Gas chromatography; Quantitative analysis

1. Introduction

Dicyclopentadienyl derivatives of titanium are particularly attractive as raw materials in bulk drug synthesis in the pharmaceutical industry. Such titanium-based reagents have been used for methylenating a variety of carbonyl compounds, including esters, ketones and amides [1–6]. One such reagent, dimethyltitanocene (DMT), was shown to be effective for olefinations [6]. Subsequently, the use of DMT for olefinations has gained popularity [7–10] over other organotitanium compounds, such as Tebbe [1] and Grubbs [3] reagents, as it is not only much easier to prepare but is also free of acidic byproducts. Recently, an improved and relatively safe method

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for DMT preparation has been developed and demonstrated successfully at pilot plant scale [11]. In our pharmaceutical application of interest, DMT is used in the olefination of ester intermediate of MK-0869 drug candidate, a Substance-P antagonist being developed by Merck for chemotherapy-induced emesis [12,13]. The mechanism of such ester olefinations using DMT has been studied in detail [14].

The use of DMT in drug synthesis warrants the employment of a robust analytical method for accurately quantifying DMT. In our R&D laboratories, NMR has been used for the determination of DMT concentration in toluene/tetrahydrofuran (THF) solutions [11]. Since NMR is a very expensive tool, a need was clearly identified to develop an alternative inexpensive technique for quantitative DMT analysis.

Survey of the scientific literature indicated the use of wet-chemical methods for the analysis of organometallic compounds. Clifford and Olsen [15] developed an iodometric titration method for quantitative determination of organolithium and organosodium compounds based on the reaction of such compounds with diethyl ether solution of iodine. In this method, an excess of a standardized diethyl ether solution of iodine was reacted with the organometallic solution to be analyzed under inert atmosphere, followed by manual titration of excess iodine with a standardized aqueous sodium thiosulfate solution to a starch end-point. The authors claimed that their titration method was faster and probably more accurate than existing titration methods based on hydrolysis [16] and carbonation [17] of organometallics. However, they acknowledged that there was no absolute method against which the analyses could be checked to confirm the accuracy of the results. Bryukhanova and coworkers [18] further applied this technique to quantify dicyclopentadienyl derivatives of titanium in benzene, toluene and THF solvents. They demonstrated that fourfold excess of iodine with respect to organotitanium compound yielded more accurate results.

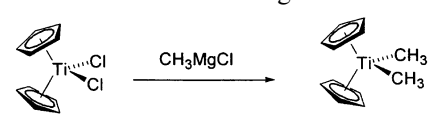
Nonetheless, the precision of this two-phase iodometric titration method relies heavily on the accuracy of the starch end-point determined by manual titration. Due to the formation of a black precipitate during the reaction of iodine with DMT, this end-point determination is subject to considerable human error. As a result, the method is not precise and robust. It does not meet the strict requirements for commercial drug production and, therefore, cannot be readily adopted in the pharmaceutical industry in its current form.

The need for an analytical tool that is precise, accurate, robust, ubiquitous as well as convenient for routine analysis prompted us to further investigate analytical methods based on the reaction of iodine with DMT as a means of quantitatively assaying DMT solutions. This paper presents the development of two such methods, namely an improved iodometric titration method and a novel gas chromatography method, for quantitative DMT analysis. The original iodometric titration method has been modified and automated for higher precision as well as ease of use. A gas chromatographic method has also been developed and employed to provide an alternative means of determining the concentration of DMT. Results obtained by using these methods are compared with NMR results in order to test the accuracy of the methods. The applications of the above-mentioned methods, sources of error and validation results are also described in detail.

2. Experimental section

2.1. Dimethyl titanocene synthesis

Titanocene dichloride and methyl magnesium chloride (CH_3MgCl, 3 M in THF) were purchased from Boulder Scientific, Boulder, CO and used as received. Analytical grade toluene was obtained from EM Science, Gibbstown, NJ and dried with 3 Å sieves to less than 150 μg/ml water (by Karl Fisher titration) before use. DMT was prepared according to the procedure described recently [11] and summarized in the following:



Cp_2TiCl_2
Titanocene dichloride
MW=248.98

$Cp_2Ti(CH_3)_2$
Dimethyltitanocene
MW=208.14

To a well-stirred cold suspension (− 5°C) of titanocene dichloride (249 g, 1.00 mol) in toluene (2.75 l) under inert atmosphere was added 750 ml of CH_3MgCl (3.0 M in THF, 2.25 mol) over 1 h, while maintaining the temperature below 8°C. The resulting orange slurry was aged at 0–5°C for 1 h, or until the insoluble purple titanocene dichloride had dissolved completely to form a solution of DMT in toluene/THF. A normal phase HPLC method, was employed to confirm reaction completion and quantify the presence of monochloro monomethyl titanocene reaction intermediate and a dimeric byproduct. Typically, the product was very pure with only traces of reaction intermediate and byproduct. The reaction solution was quenched with aqueous ammonium chloride (700 ml) under a blanket of nitrogen and worked up with two aqueous extractions to remove quench mixture and interfacial emulsions followed by vacuum distillation to concentrate and remove water. Several DMT solutions of varying concentrations (6–22 wt%) were prepared from the batch and analyzed for analytical method development.

2.2. NMR

All spectra measurements were carried out by ^1H NMR spectroscopy at 250.13 MHz frequency in $CDCl_3$ (Cambridge Isotope Laboratories, Andover, Massachusetts, USA). An aliquot of 0.075 ml of DMT solution was added to 0.6 ml of $CDCl_3$ (stored over K_2CO_3 to remove HCl). The sample was transferred into a 5 mm NMR tube and analyzed by ^1H NMR. Acquisition of proton spectra incorporated a 10 s relaxation delay between pulses. NMR spectra were recorded on Bruker AM 250 spectrometer. The chemical shifts are reported in ppm relative to residual $CHCl_3$ ($\delta = 7.27$ ppm). For DMT wt% measurement, peaks for DMT cyclopentadienyl (Cp) group (6.1 ppm, 10H) and DMT methyl group (0.0 ppm, 6H) were integrated against peak for toluene methyl group (2.5 ppm, 3H). DMT wt% result was calculated using the following equation

$$\mathrm{wt\%} = \frac{\dfrac{\left(\dfrac{A_{\mathrm{Cp,DMT}}}{10} + \dfrac{A_{\mathrm{CH_3,DMT}}}{6}\right)}{2}}{\left[\dfrac{\left(\dfrac{A_{\mathrm{Cp,DMT}}}{10} + \dfrac{A_{\mathrm{CH_3,DMT}}}{6}\right)}{2}(\mathrm{MW_{DMT}})\right] + \left(\dfrac{A_{\mathrm{CH_3,Toluene}}}{3}\right)(\mathrm{MW_{Toluene}})}(\mathrm{MW_{DMT}})(100), \quad (1)$$

where $A_{\mathrm{Cp,DMT}}$, peak area of DMT Cp group; $A_{\mathrm{CH_3,DMT}}$, peak area of DMT methyl group; $A_{\mathrm{CH_3,Toluene}}$, peak area of toluene methyl group; $\mathrm{MW_{DMT}}$, MW of DMT and $\mathrm{MW_{Toluene}}$, MW of toluene. Precision of NMR analysis based on four wt% measurement was determined to be $< 3.5\%$.

2.3. Iodometric titration

Instrumentation consisted of an automated model 716 DMS titrino titrator from Brinkmann, Westbury, NY. A Metrohm combined metal, Platinum electrode (6.0415.100, Pt/ − 5…70°C, 3 M KCl) from Brinkmann, was used for potentiometric titration. Titrant delivery was set at a minimum increment of 30 μl with variable volume addition depending on the slope of the curve. The maximum rate of delivery was 40 ml/min. Time between additions was determined by a signal drift of 30 mV/min. or an equilibration time of 32 s. The stirring speed was regulated between 3 and 5 range with a 728 Metrohm stirrer using a 3.5 cm magnetic stirrer bar. Data analysis was performed using Brinkmann software.

All reagents for titration were analytical grade chemicals purchased from Aldrich Chemical, Milwaukee, WI unless otherwise stated. Standardized aqueous sodium thiosulfate ($Na_2S_2O_3$) solution (0.0975 N) stored at room temperature was used as the titrant. Aqueous potassium iodide (KI) solution (120 g/l) was prepared by dissolving 120 g of KI (EM Science, Gibbstown, NJ) in 1 l of deionized water and stored in amber bottle at room temperature. A solution of iodine in toluene (~ 0.2 N) was prepared in a volumetric flask by dissolving about

12.69 g of iodine (MW = 253.8) in 200 ml toluene and diluting to a final volume of 500 ml with toluene. The solution was standardized by mixing 10 ml of the solution in a 150 ml beaker with 10 ml of toluene, 50 ml of aqueous KI solution and 10 ml of deionized water, and titrating with 0.1 N aqueous $Na_2S_2O_3$ to a potentiometric end-point. Continuous stirring during titration was maintained to ensure fast equilibrium between aqueous and organic phases. The standardized iodine solution in toluene was stored in amber bottle at room temperature.

The DMT sample for titration was prepared in the following manner. In a 150 ml beaker with magnetic stirrer, 10 ml of toluene and 10 ml of standardized iodine solution (0.2 N) were pipeted and the solution tared on the balance. Then, approximately 400 μl of DMT solution to be analyzed (containing ~7 wt% DMT) was added drop-wise to the solution and accurately weighed (~400 mg). The reaction mixture was stirred for 1 min. To this were added 50 ml of aqueous KI solution and 10 ml of deionized water to provide an aqueous titration medium as well as to increase the solubility of unreacted iodine into the aqueous phase. The final mixture was titrated at room temperature with 0.1 N aqueous $Na_2S_2O_3$ solution to a potentiometric end-point. Continuous stirring during titration was maintained to ensure efficient mixing of the two phases.

The concentration of DMT was determined from the amount of iodine consumed in reaction II

$$\underset{\substack{\text{DMT}\\ \text{MW} = 208.14}}{Cp_2Ti(CH_3)_2} + 2I_2 = \underset{\substack{\text{Iodomethane}\\ \text{MW} = 141.94}}{Cp_2TiI_2 + 2CH_3I}$$

as

$$\text{wt\%} = \frac{[(N_I V_I) - (N_T V_T)]}{(4)(W_S)}(\text{MW}_{DMT})(100) \qquad (2)$$

where N_I, normality of the standardized iodine solution in toluene; N_T, normality of titrant, i.e. aqueous $Na_2S_2O_3$ solution; V_I, volume of the standardized iodine solution in ml; V_T, volume of aqueous $Na_2S_2O_3$ solution consumed during titration in ml; MW_{DMT}, MW of DMT and W_S, weight of DMT solution to be analyzed in milligrams (~400 mg). For accuracy, titration of the sample was performed in duplicate. In all experiments iodine solution in toluene was standardized once before and once after the titration of each DMT sample.

2.4. Gas chromatography

An HP 5890 gas chromatograph from Hewlett Packard, Wilmington, DE equipped with a flame ionization detector (FID) was employed for DMT analysis by GC. A 30 m long Rtx-Volatiles capillary column with internal diameter of 0.53 mm and film thickness of 2.0 μm was obtained from Restek, Bellefonte, PA. The following method parameters were used. The GC oven temperature was programmed to initially hold the column temperature at 35°C for 7 min, then to ramp it up at a rate of 40°C/min to 120°C and finally to hold the column at that temperature for 4 min. Injection mode was splitless with injector temperature set at 150°C. The output of the FID detector was set at 1 μAmp/Volt and the detector temperature was 250°C. High purity grade helium from Air Gas, Harrisburg, PA was used as the carrier gas. The flow rate of helium through the capillary column was 6 ml/min. Autosampler settings included injection volume of 1.0 μl, duplicate injections per vial, 6 sample pre-washes and 6 toluene post-washes. The run time of the GC method was 14 min. Nelson system from Perkin Elmer, Cupertino, CA equipped with an AccessChrom software was employed for chromatographic data acquisition.

Analytical grade iodomethane stabilized with copper was obtained from Aldrich, Milwaukee, Wisconsin, USA. It is light sensitive and should be protected from moisture. Since it is highly toxic, vesicant, possibly carcinogenic, mutagenic and readily absorbed through skin, it should be handled in the fume hood. Iodomethane was stored in amber bottle in the refrigerator and allowed to warm up to room temperature before use. Iodomethane external standard (0.1% v/v) was prepared in toluene by spiking 10 μl of iodomethane in a 10 ml volumetric flask containing 5 ml toluene and diluting to volume with toluene.

The DMT sample for analysis was prepared as follows. In a scintillation vial 10 ml of 0.2 N iodine solution in toluene was tared on the balance. DMT solution to be analyzed (containing ~ 7 wt% DMT) was accurately weighed (~ 200 mg) and added drop-wise into the scintillation vial using a 200 μl pipeter. The vial was capped and shaken for 1 min. Then, the reaction mixture was immediately injected neat into the GC.

The DMT wt% was determined from the amount of iodomethane evolved during reaction II as

$$\text{wt\%} = \frac{(A_S)(V_{\%STD})\,(d)\,(V_I + V_S)\,(MW_{DMT})}{2(A_{STD})\,(MW_I)\,(W_S)} \quad (3)$$

where A_S, average area count of iodomethane peak in the sample; A_{STD}, average area count of iodomethane peak in iodomethane external standard, $V_{\%STD}$ = %(v/v) iodomethane external standard, d, density of iodomethane (2.28 g/ml); V_I, volume of (0.2 N) standardized iodine solution in toluene in ml (10 ml), V_S, volume of DMT solution to be analyzed in ml (0.2 ml), MW_{DMT}, MW of DMT; MW_I, MW of iodomethane and W_S, weight of DMT solution to be analyzed in grams (~ 0.2 g).

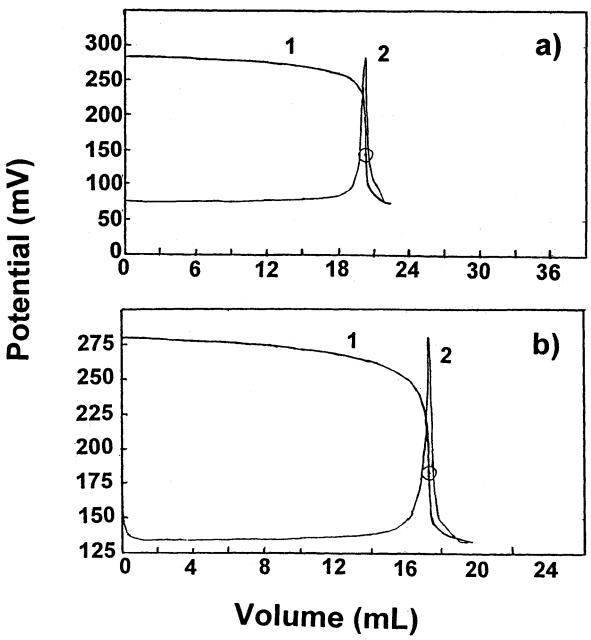


Fig. 1. Automated iodometric titration of (a) iodine solution in toluene (10 ml, 0.2 N); and (b) DMT sample. 1, Potentiometric titration curve; 2, Derivative of titration curve; Instrument: Automated 716 DMS titrino from Brinkman; Electrode: Platinum from Metrohm (6.0415.100, Pt/-5…70°C, 3 M KCl); Titrant: Standardized aqueous sodium thiosulfate solution (0.0975 N); DMT sample preparation: DMT solution (400 μl) weighed and added to 10 ml of iodine solution in toluene (0.2 N), 10 ml of toluene, 50 ml of aqueous KI solution (120 g/l) and 10 ml deionized water, stirred for 1 min.

3. Results and discussion

3.1. Automation of iodometric titration for DMT analysis

The original iodometric titration method [15,18] was employed to determine its precision and reproducibility in quantitative analysis of DMT solution in toluene/THF. Due to the presence of two phases and a black precipitate formed during the reaction of DMT with iodine, it was difficult to visually observe the starch end-point accurately during titration. This resulted in a much larger deviation in DMT wt% results from titration to titration. For instance, the wt% results from triplicate measurements of the DMT sample showed RSD > 5.0%, indicating that the manual titration method with visual detection of end-point was grossly imprecise.

An automated titrator along with combined platinum electrode was subsequently used for DMT analysis to enhance the precision and reproducibility of the method to an acceptable level. With this automated set-up, experiments were designed to select the various parameters, such as the amount of iodine solution used, amount of DMT solution added, stirring speed and reaction time. Based on these experiments, a set of optimal conditions was chosen which yielded results with highest precision and reproducibility. These conditions have been described in detail in the experimental section.

Titrations of iodine standard solution in toluene and DMT sample to be analyzed were performed according to the procedure described in the experimental section. Fig. 1 illustrates titration curves obtained by the automated titrator for the iodine standard solution in toluene and the

Table 1
Precision of iodometric titration method for DMT analysis based on 5 determinations

Number	DMT solution amount (μl)	DMT wt%
1	400	7.50
2	400	7.64
3[a]	400	7.58
4[a]	400	7.73
5[a]	300	7.66
Mean	–	7.62
%RSD	–	1.14

[a] DMT wt% determined by second chemist.

Table 2
Linearity of iodometric titration method based on amount of DMT solution analyzed

Number	DMT solution amount (μl)	DMT wt%
1	200	7.35
2	250	7.54
3	300	7.17
4	350	7.33
5	400	7.40
6	500	7.39
Mean	–	7.36
%RSD	–	1.63

DMT sample. As seen, the curves are smooth with sharp inflection points, allowing for easy potentiometric determination of the end-point. Precision of the titration method was evaluated on the basis of 5 determinations of DMT performed by two chemists on the same day. From data presented in Table 1, it is seen that automated iodometric titration of DMT exhibits acceptable precision/reproducibility of $< 1.5\%$ RSD, confirming its superiority over manual titration method.

The automated iodometric titration method for DMT analysis was also validated in terms of linearity and robustness. Linearity of the method was investigated by varying the DMT solution size in the range encompassing 50–125% of the target solution size of 400 μl. Weight percentage results obtained by iodometric titration of DMT solution using 200, 250, 300, 350, 400 and 500 μl of the sample are listed in Table 2. As seen, assay results are linear in the size range with a 1.6% RSD. The method was tested for robustness and stability of sample preparation by titrating the DMT sample after the elapse of a certain time from sample preparation. Six samples were prepared from the same DMT solution out of which two were titrated immediately after sample preparation. The other four samples were titrated at regular intervals of time. Table 3 lists DMT wt% results obtained by iodometric titration of these six samples. The assay results listed in Table 3 indicate that iodometric titration significantly overestimates DMT concentration when the assay is performed a long time after sample preparation due to loss of iodine by evaporation. It is concluded that the method is robust if titration is performed within 5 min of sample preparation to avoid iodine evaporation.

The following sources of error associated with iodometric titration were identified. As demonstrated in an earlier study [18], an excess of iodine should be maintained and the DMT solution added drop-wise to the iodine solution in order to minimize undesirable coupling reactions [15] that may affect the quantitation of DMT. It is recommended that the iodine standard solution be titrated each time prior to the titration of DMT sample in order to correct for the systematic error caused by possible evaporation of iodine. The stirring speed

Table 3
Results of studies on robustness of iodometric titration method

Number	DMT solution amount (μl)	Time from sample preparation (min)	DMT wt%
1	400	0	7.51
2	400	0	7.47
3	400	3	7.55
4	400	5	7.60
5	400	30	8.76
6	400	1 day	11. 21

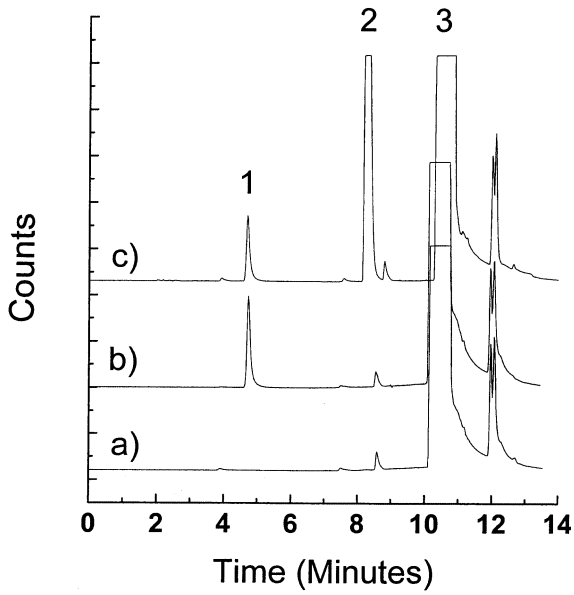


Fig. 2. Chromatograms of (a) blank toluene solution; (b) 0.1% (v/v) iodomethane standard in toluene; and (c) DMT sample. Sample components: (1) Iodomethane; (2), Tetrahydrofuran; (3) Toluene. Instrument: HP 5890; Column: Rtx-Volatiles, 30 m, 0.53 mm I.D. and 2.0 μm film thickness; Detector: FID at 250°C; Injector: Splitless at 150°C; Carrier gas: Helium at 6.0 ml/min; Temperature gradient: Initial temperature at 35°C for 7 min, then 40°C/min ramp to 120°C with 4 min hold at final temperature; Injection volume: 1.0 μl; DMT sample preparation: DMT solution (200 μl) weighed and added to10 ml of iodine solution in toluene (0.2 N), shaken for 1 min.

should be regulated to avoid splashing, at the same time, to enhance the mass transfer of excess iodine from organic to aqueous phase. Finally, the formation of precipitate could coat the electrode, resulting in a poor titration curve that may affect the measurement of the end-point. For this reason, it is recommended that the electrode be rinsed with dilute aqueous nitric acid solution and wiped clean with a cloth after use. For accuracy, DMT wt% result from the average of two measurements must be reported for each DMT sample.

3.2. Gas chromatography for quantitative DMT analysis

A new approach using GC was developed as a referee method to determine the wt% of DMT and to test the accuracy of titration results. According to this approach, DMT is reacted with iodine and the reaction product, iodomethane, is monitored by GC. By using an external iodomethane standard, the concentration of iodomethane in the reaction sample is measured which then allows the determination of DMT wt% in the sample according to Eq. (2).

Fig. 2 illustrates the chromatograms obtained by GC for a toluene blank, a 0.1% (v/v) iodomethane external standard and a DMT sample prepared according to the procedure described in the experimental section. The retention times of iodomethane, THF and toluene peaks under current experimental conditions were determined as 5.0, 9.0 and 11.9 min, respectively. It is seen from the chromatograms in Fig. 2 that the iodomethane peak is well resolved and separated from neighboring peaks, thus allowing for accurate determination of its peak area.

The GC method for DMT analysis was validated with respect to precision, reproducibility, limit of quantitation (LOQ), limit of detection (LOD), linearity and recovery using the conditions listed in the experimental section. Injection precision of the GC method was evaluated by performing six replicate injections of 0.01% (v/v) and four replicate

Table 4
Injection precision of GC method for determination of iodomethane

Iodomethane standard conc. (%v/v)	Injection #	Area count of iodomethane
0.01	1	171605
	2	171776
	3	171092
	4	167976
	5	177220
	6	179072
	Average	173124
	S.D.	4169
	%RSD	2.4
0.1	1	1734414
	2	1710202
	3	1687026
	4	1731110
	Average	1715688
	S.D.	21910
	%RSD	1.3

Table 5
Reproducibility of GC method for DMT analysis based on four DMT Wt% determinations

Number	DMT wt%[a]
1	26.8
2	27.5
3[b]	26.9
4	27.1
Mean	27.0
%RSD	1.1

[a] Data represents average of three injections.
[b] DMT wt% determined by second chemist.

injections of 0.1% (v/v) iodomethane standards and calculating the % RSD of iodomethane peak area counts. Table 4 lists the results of the injection precision study. As seen, the GC method for DMT analysis is precise with a maximum of 2.4% RSD for the iodomethane peak at 0.01% (v/v) level and 1.3% RSD at 0.1% (v/v) level. The reproducibility of the method was established based on 4 DMT wt% determinations of the same DMT solution performed by two chemists on the same day. DMT wt% data presented in Table 5 indicates that the GC method is reproducible with RSD < 1.2%. In order to establish the LOQ, LOD and linearity of the GC method, a stock solution of 1.0% (v/v) iodomethane standard was prepared and diluted several times to obtain 0.2, 0.1, 0.05, 0.01, 0.005, 0.001, 0.0005 and 0.0001% (v/v) iodomethane standards. Triplicate injections of each standard solution were made under established chromatographic conditions. Table 6 lists the iodomethane peak area counts, %RSD and response factors for

Table 6
Linearity[a], limit of detection and limit of quantitation of GC method for DMT analysis

Conc. of iodomethane (%v/v)	Peak area count	Average peak area count and %RSD	Response factor
0.0001 (LOD)	1802 2988 3322	Avg. = 2704 %RSD = 29.5	27 040 000
0.0005 (LOQ)	9362 7352 7851	Avg. = 8188 %RSD = 12.8	16 376 000
0.001 (10 × LOQ)	16524 15622 16348	Avg. = 16165 %RSD = 3.0	16 165 000
0.005	82230 80112 81738	Avg. = 81360 %RSD = 1.4	16 272 000
0.01	171605 171776 171092	Avg. = 171491 %RSD = 0.2	17 149 100
0.05	1023254 1009202 986102	Avg. = 1006186 %RSD = 1.9	20 123 720
0.1	1724414 1710202 1687026	Avg. = 1710547 %RSD = 1.3	17 105 470
0.2	3448000 3462810 3444920	Avg. = 3451910 %RSD = 0.3	17 259 550

[a] $r^2 = 0.99899$.

Table 7
Recovery of iodomethane by GC

Iodomethane conc. spiked (%v/v)	Conc. recovered after spiking (%v/v)	Recovery (%)
0.01	0.01017	101.7
0.001	0.001025	102.5

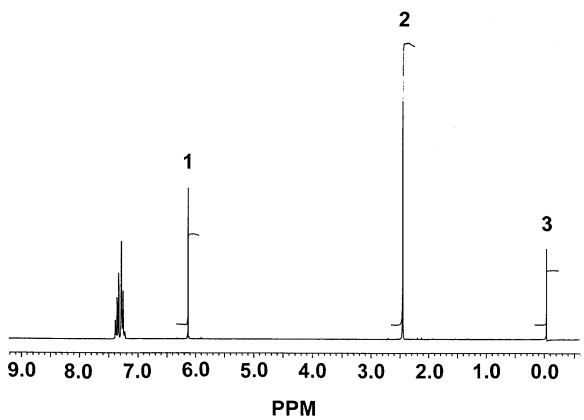


Fig. 3. ^{1}H NMR spectra of DMT sample in $CDCl_3$ at 250 MHz with 10 s relaxation delay. Instrument: 250MHz Bruker AM; Integrated Peaks: (1) Cyclopentadienyl (Cp) group from DMT (6.1 ppm, 10 H); (2) methyl group from toluene (2.5 ppm, 3 H); (3) methyl group from DMT (0.0 ppm, 6H). DMT sample preparation: DMT solution (0.075 ml) added to 0.6 ml of $CDCl_3$, then transferred to a 5 mm capped NMR tube.

Table 8
Comparison of DMT wt% results obtained by iodometric titration, GC and NMR

DMT Solution #	DMT wt% Results[a]		
	Iodometric titration	GC	NMR
1	20.1	20.5	20.5
2	11.5	11.8	
3	6.4		6.4
4	6.0	6.0	5.8
5	6.3		6.2
6	6.9	7.1	7.2
7	6.9	7.0	7.0

[a] Data represents average of three measurements.

all the standard solutions. LOD was established as 0.0001%(v/v), on the basis of signal-to-noise ratio $\geq$3:1. The following criteria were used to establish the LOQ of the method: (a) signal-to-noise ratio $\geq$10:1; (b) deviation of the response factor of iodomethane at the LOQ is $\leq$20% compared to that in a 10 times concentrated solution; and (c) %RSD for area counts of iodomethane at the LOQ is $\leq$15% for a minimum of three injections. From data presented in Table 6, the LOQ was determined to be 0.0005% (v/v) of iodomethane. The method was found to be linear in the concentration range between 0.2% (v/v) and the LOQ with $r^2 = 0.99899$. Finally, the accuracy of the GC method for DMT analysis was tested by performing iodomethane recovery experiment. A known concentration of iodomethane stock solution (0.1% v/v) was spiked into toluene at 0.01% and 0.001% solvent levels. Injections were made in triplicate under standard chromatographic conditions. Concentrations of spiked iodomethane were determined using the 0.01% (v/v) iodomethane standard for recovery calculations. The results of the spiking experiment are summarized in Table 7. It is seen that the GC method for DMT analysis is accurate as determined by 101.7% and 102.5% recovery of iodomethane spiked at 0.01% and 0.001% (v/v) levels in toluene, respectively.

There are relatively fewer sources of error associated with GC. The iodomethane standard should be prepared at room temperature since iodomethane has a low boiling point of 42.5°C. The volume of iodine solution as well as that of DMT solution to be analyzed should be measured accurately as these values are used in the calculation of DMT wt% in Eq. (3).

3.3. Comparison of titration, GC and NMR results

In order to test the accuracy of the above analytical methods based on the reaction of iodine with DMT, bridging studies were conducted that were aimed at comparing the results of these methods to those obtained by an independent method such as NMR. In this endeavor, automated iodometric titration, GC and NMR were used to analyze several DMT samples. NMR results were calculated using Eq. (1) and peak

area data obtained from the spectra by integrating DMT cyclopentadienyl and methyl signals against toluene methyl signal as shown in Fig. 3. Eqs. (2) and (3) were used to calculate the DMT wt% results from titration and GC data, respectively. DMT wt% results thus obtained by the employment of such disparate techniques are listed in Table 8 for comparison. It is seen that the wt% results obtained by the three techniques are in excellent agreement with each other and the average deviation is less than 4%, attributable mainly to experimental errors associated with the various methods. The results of bridging studies unambiguously confirm the accuracy of automated iodometric titration and GC analytical methods and strongly support their use as a replacement for the expensive NMR in quantitative DMT analysis.

4. Applications

4.1. Yield and productivity characteristics of various DMT synthetic processes

The automated iodometric titration method was employed to study the yield and productivity characteristics of the DMT synthetic process. In the early stage of process development, typical DMT yields of 85–90% were obtained. In an effort to further enhance the DMT yields and increase volumetric production, several modified processes for DMT synthesis were investigated. Some of these modifications involved re-crystallization of titanocene dichloride raw material to remove impurities, replacement of toluene by THF as the slurry solvent for titanocene dichloride to enhance DMT solubility and performing the reaction at a concentrated scale to enhance volumetric productivity. Table 9 lists the DMT wt% results of solutions prepared from various modified processes and their corresponding yields. Also listed is data obtained for the unmodified DMT synthetic process using 90 g/l of titanocene dichloride solution in toluene (denoted in the Table by '1X Toluene, 12 g scale'). It is seen from data presented in Table 9 that the DMT synthetic process utilizing 90 g/l of recrystallized titanocene dichloride in THF (to remove impurities) gives the highest yield of 97%. However, purifying titanocene dichloride raw material before use is cost-intensive and therefore not practical for large-scale production. On the other hand, DMT synthetic process utilizing 180 g/l of non-purified titanocene dichloride in THF and 0.5 g/g of celite to remove insolubles appears to be quite appealing as it not only provides a higher DMT yield of 93% compared to 89% from the unmodified synthetic process but also offers a means to increase DMT productivity significantly by a factor of two.

4.2. Stability of DMT

A primary concern of the DMT synthetic process involving THF is the stability of the organic phase due to higher water content. To address this issue, the decomposition of DMT with time was studied as a function of THF, water content, and temperature. Automated iodometric titration method was employed to analyze the various solutions. DMT samples for stability study were prepared as fol-

Table 9
DMT wt% and corresponding yields of final product obtained from various DMT synthetic processes

DMT process #	Process modifications	Wt% of DMT solution[a]	Yield
1	0.2X[b] THF, 8 g scale		90
2	0.2X Toluene, 8 g scale		93
3	1X Toluene, 12 g scale	16.5	89
4	1X Toluene, recrystallized titanocene dichloride, 10 g scale	12.9	93
5	1X THF, recrystallized titanocene dichloride, 10 g scale	18.2	97
6	2X THF, 0.5 g Celite per g titanocene dichloride, 20 g scale	28.4	93

[a] DMT wt% results represent average of three iodometric titration measurements.
[b] Notation X refers to 90 g/l of titanocene dichloride solution used in the unmodified DMT synthetic process # 3.

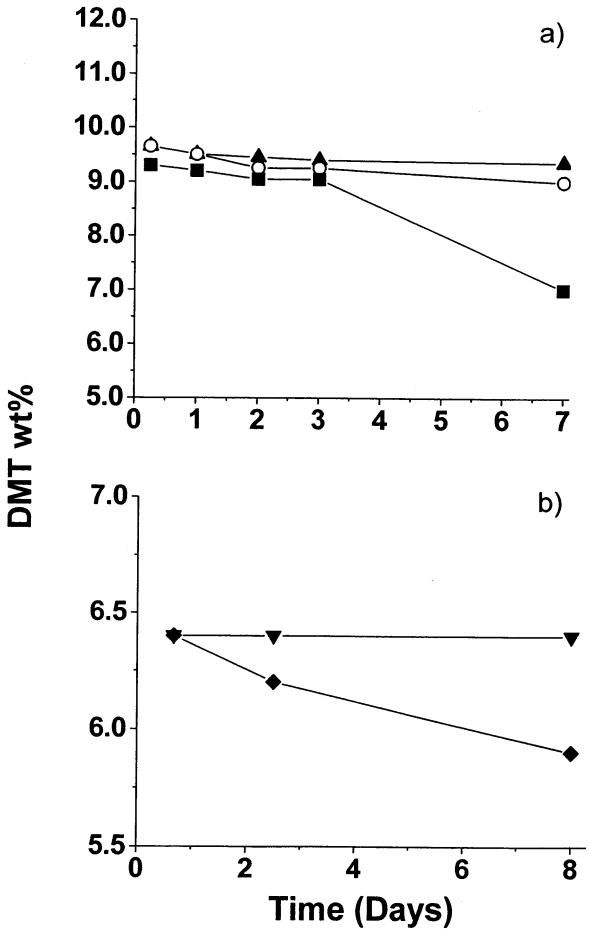


Fig. 4. Plots of DMT wt% as a function of time for the DMT solution (a) agitated in the presence of aqueous phase at 5°C with (○) 20%(v/v) THF and (■) 60%(v/v) THF; and (b) in the absence of aqueous phase with 50% (v/v) THF at (▼) −20°C and (◆) 5°C. Data for stability of DMT solution in toluene at 5°C in the absence of aqueous phase is represented by (▲) symbol.

lows. The DMT batch prepared after extractions and work-up by utilizing the unmodified process was first concentrated to obtain a stock solution of 20 wt% DMT in toluene. To this stock solution, known amounts of toluene, THF and water were added to obtain various DMT samples of roughly the same DMT concentration. Temperature studies were conducted at refrigerator (5°C) and freezer (−20°C) conditions.

Two sets of stability studies were conducted. In the first set of studies, the stability of various DMT samples was investigated at 5°C as a function of THF concentration in the presence of an aqueous phase under agitated conditions. In other words, all DMT samples containing THF and water were agitated until the end of the study so that intimate contact between the organic and the aqueous phase was always maintained. For reference, stability data of DMT solution in toluene stored at 5°C in the absence of aqueous phase was obtained by iodometric titration. In the second set of studies, the aqueous phase was removed to minimize contact with the organic layer. Furthermore, decomposition of DMT in the presence of THF was investigated at both −20°C and 5°C.

Fig. 4a illustrates the dependence of DMT wt% as a function of time for three DMT samples stored at refrigerator condition. Iodometric titration analysis of DMT solution in toluene in the absence of water (represented by ▲ symbol in Fig. 4a) indicates that the solution is stable for at least a week, with a DMT loss of only 0.4% per day. On the other hand, DMT sample with 20% (v/v) THF and agitated in the presence of aqueous phase (represented by ○ symbol in Fig. 4a) shows a larger drop in DMT concentration over time. Increasing the THF content to 60%(v/v) (represented by ■ symbol in Fig. 4a) results in further decrease and a much greater DMT loss per day compared to the DMT solution in toluene as determined by iodometric titration, indicating a decrease in DMT stability with increase in THF. This is expected since the presence of THF increases the solubility of water in the organic phase, resulting in further decomposition of DMT.

For comparison, DMT samples with THF were analyzed in the absence of aqueous phase at two different temperatures. Fig. 4b illustrates the stability of DMT solution with 50%(v/v) THF at 5°C and −20°C as a function of time. It is seen that although DMT solution at 5°C is not quite stable even in the absence of aqueous phase, the rate of DMT decomposition is significantly arrested by lowering the temperature to −20°C.

From the discussion of the above studies, it is concluded that limiting the contact between the organic and the aqueous phase combined with decreasing the content of THF in the final DMT

solution results in significant improvement in DMT stability. Furthermore, lowering the temperature of storage also assists in slowing the rate of DMT decomposition if THF is present in DMT solution. Based on these results, the most practical and inexpensive approach for maintaining DMT stability is to cut the aqueous layer after DMT reaction quench and extraction, concentrate the organic layer to remove THF and water and store the DMT solution at 5°C. This approach significantly arrests the DMT decomposition to $\leq 0.5\%$ per day as compared to a DMT loss of as much as 3.5% per day under extreme conditions.

5. Conclusion

For quantitative dimethyltitanocene (DMT) analysis two analytical methods based on the reaction of DMT with iodine have been developed and validated, namely automated iodometric titration and gas chromatography. They are precise, simple and convenient to use methods requiring readily available instruments. Both assays yield reproducible results that compare very favorably with those of NMR. The results of the present study strongly support their use for routine DMT analysis as a replacement for the expensive NMR.

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