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DOI:

[10.1021/acs.joc.0c02684](https://doi.org/10.1021/acs.joc.0c02684)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Hutchinson, G., Welsh, C. D. M., & Burés, J. (2020). Use of Standard Addition to Quantify In Situ FTIR Reaction Data. *The Journal of organic chemistry*. <https://doi.org/10.1021/acs.joc.0c02684>

Published in:

The Journal of organic chemistry

Citing this paper

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Use of Standard Addition to Quantify In Situ FTIR Reaction Data

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Supporting Information Placeholder

ABSTRACT: FTIR spectroscopy is a common in situ reaction monitoring technique used in modern academic and industrial environments. The FTIR signals collected during the course of a reaction are proportional to the concentration of the reaction components, but not intrinsically quantitative. To make FTIR data quantitative, precalibration or offline analyses of reaction samples are required, which diminishes the unique benefits of in situ reaction monitoring techniques. Herein, we report the use of standard addition as a convenient method to obtain quantitative FTIR data.

Spectroscopic in situ reaction monitoring techniques have several advantages when compared with offline analyses of reaction samples: sampling and quenching of the reaction are not required, unstable intermediates can be quantified, dozens of data points can be acquired and the results can be obtained almost instantaneously.¹ In situ FTIR has these advantages, but, in order to provide quantitative concentration profiles, it has to be calibrated.² Calibration curves can be used, but they are tedious to generate and can be inaccurate if the matrices of the calibration solutions and the reaction mixture differ significantly. Calibration curves are best used to monitor the same reaction several times, for example, in process control.³ However, calibration curves are not practical when monitoring diverse reactions, reactions run under different conditions (i.e. in mechanistic studies) or reactions with complicated matrices. In these cases, it is more convenient to estimate the background and the sensitivity in the linear dynamic range for each reaction using two points with known concentration of analyte. Usually, the concentrations of all the reaction components at the beginning of the reaction are known, but not at the end, as the reaction might not proceed to completion or could generate side products. Consequently, the reaction must be sampled at least once, often at the end of the reaction, to quantify the concentration of the analyte using an offline technique.⁴ The need for sampling and offline analysis lessens the intrinsic benefits of in situ FTIR spectroscopy. Alternatively, standard addition can determine the concentration of an analyte without sampling and offline analysis. Standard addition has been successfully used to determine by ATR-FTIR the concentration of analytes in static samples.⁵ *Herein, we report the use of standard additions to quantify the concentration of reaction components without the need for sampling and offline analyses.*

We selected the organocatalytic α -selenylation of aldehydes to demonstrate the effectiveness of a standard addition to in situ calibrate FTIR data. The selenylation reaction was described by Melchiorre and Córdova,^{6,7} and its mechanism was studied by Blackmond.⁸ We reacted *N*-(phenylseleno)phthalimide (**2**) with an excess of isovaleraldehyde (**1**) and AcOH in a vial fitted with the FTIR probe and initiated the reaction by adding the Jørgensen–Hayashi type catalyst **3** (Figure 1). To show the versatility of the method, we carried out two different standard addition calibrations: with a reactant, the *N*-(phenylseleno)phthalimide (**2**), and with a product, the phthalimide (**5**).

When monitoring the reaction by following the signal corresponding to a reactant, we started collecting spectra before adding the reactant in two portions, which constitute the standard additions. We collected consecutive FTIR spectra from before the addition of the stock solution of *N*-(phenylseleno)phthalimide (**2**) to the reaction mixture until the end of the reaction (Figure 1a). We applied the second derivative⁹ to the spectra to increase the resolution of the peaks (Figure 1b). Finally, we measured the signal height relative to zero at 862 cm⁻¹, which corresponds to the *N*-(phenylseleno)phthalimide (**2**) (Figure 1c) and adjusted the signal height before the addition of *N*-(phenylseleno)phthalimide (**2**) to 0 AU (Figure 1d).

The reaction profile in Figure 1d is a relative reaction profile (with arbitrary units on the Y-axis) that must be calibrated to become a reaction profile in absolute terms (with concentration units on the Y-axis). We calibrated the entire reaction profile using Equation 1:¹⁰

$$[\mathbf{2}]_t = \mathbf{k} \cdot \text{signal}(t); \mathbf{k} = \frac{n_{\text{SA}}}{\text{signal}_{\text{SA}} \cdot V_{\text{SA}}} \quad (1)$$

$\mathbf{k}$: inverse of the response factor

$\text{signal}(t)$: signal at time t (AU)

n_{SA} : amount of the standard added (mmol)

$\text{signal}_{\text{SA}}$: signal after the standard addition (AU)

V_{SA} : volume after the standard addition (mL)

a) Stacked FTIR absorbance spectra over time

b) More resolved peaks after applying the 2nd derivative

c) *N*-(Phenylseleno)phthalimide peak at 862 cm⁻¹ selected for analysis

d) Relative reaction profile of *N*-(phenylseleno)phthalimide

Figure 1. Treatment of FTIR data to extract a relative temporal reaction profile of disappearance of *N*-(phenylseleno)phthalimide (**2**).

We also calibrated the data using a traditional offline analysis technique, quantitative NMR of an end-point sample, for

Figure 2. The FTIR data calibrated by standard addition of the reagent **2** (blue) perfectly overlays with the data calibrated by NMR offline analysis (red).

comparison. Gratifyingly, the quantitative FTIR data we generated by standard addition calibration of the reactant **2** (blue circles, Figure 2) and offline quantitative NMR calibration (red diamonds, Figure 2) overlaid perfectly.

In some reactions, it may be necessary to follow the progress of the reaction by monitoring the signal of a product. In these cases, the calibration by standard addition of the product can be performed at the end of the reaction. As an example, we calibrated the reaction profile by addition of the byproduct **5**, phthalimide, in two portions at the end of the reaction. We collected consecutive FTIR spectra from the beginning of the reaction (Figure 3a) and we applied the second derivative to increase the resolution of the peaks (Figure 3b). We measured the signal height of the peak at 1036 cm⁻¹ (Figure 3c) relative to a single point baseline¹¹ (1058 cm⁻¹, red dot) and adjusted the signal height before the catalyst addition to 0 AU (Figure 3d).

profile using the standard addition of one of the products of the reaction, we used Equation 2.¹⁰

$$[4]_t = k \cdot \text{signal}(t); k = \frac{n_{SA}}{\text{signal}_{SA} \cdot V_{SA} - \text{signal}_E \cdot V_E} \quad (2)$$

k : inverse of the response factor

$\text{signal}(t)$: signal at time t (AU)

n_{SA} : amount of the standard added (mmol)

signal_{SA} : signal after the standard addition (AU)

V_{SA} : volume after the standard addition (mL)

signal_E : signal at the end of the reaction (AU)

V_E : volume of the reaction mixture (mL)

As in the first example, we also calibrated the data using quantitative NMR of an end-point sample, for comparison. The temporal concentration profiles generated using the calibration with standard addition of the byproduct 5 (blue circles, Figure 4) and offline quantitative NMR calibration (red diamonds, Figure 4) overlaid perfectly.

Figure 3. Treatment of FTIR data to extract a relative temporal reaction profile of appearance of phthalimide (5).

As in the previous example, the relative reaction profile (with arbitrary units on the Y-axis) in Figure 3d had to be calibrated to become a reaction profile in absolute terms (with concentration units in the Y-axis). To calibrate the entire

Figure 4. The FTIR data calibrated by standard addition of the byproduct 5 (blue) overlays with the data calibrated by NMR offline analysis (red).

Calibrating FTIR data is more important when the reaction does not arrive to completion because the variation of the signal during the reaction cannot be assumed to be 100%. To further test the calibration method by standard addition of reactants and products, we monitored the reaction carried out with a much smaller catalyst loading. This reaction did not achieve full conversion and better showed the need for a calibration method to obtain concentration profiles. In this reaction, the temporal reaction profiles obtained with an offline quantitative NMR calibration (red diamonds, Figure 5) matched the profiles obtained by calibration by a standard addition of a reactant (blue circles, Figure 5a) and by a standard addition of a product (blue circles, Figure 5b).

a) Calibration by standard addition of a reactant (2)

b) Calibration by standard addition of a product (5)

Figure 5. The reaction profiles obtained with calibration by standard addition of the reactant 2 (blue), by standard addition of byproduct 5 (blue) and by offline quantitative NMR (red) match.

We have described the use of the standard addition method to calibrate in situ FTIR data. The method is rapid, accurate, adequate for complicated matrices and does not require calibration curves or sampling and off-line analyses. This more convenient method to obtain temporal concentration profiles from in situ FTIR data should facilitate the mechanistic study of a variety of reactions. Other reaction monitoring techniques, such as in situ Raman and UV-vis spectroscopy, could also benefit from the use of this method. The application of orthogonal techniques, such as verifying analyte concentration by HPLC or qNMR, is still good practice and is required during the initial investigations of a new reaction to ensure the chosen signals adequately represent the reaction of interest.

Experimental

General Experimental: Unless otherwise specified, reagents and solvents were used as purchased from Merck, Alfa-Aesar and Fisher Scientific. CDCl₃ was dried over 4 Å activated molecular sieves and stored under nitrogen prior to use. The amine catalyst, (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether, was purified by flash column chromatography (100% CH₂Cl₂) to remove any deprotected alcohol. *N*-(Phenylseleno)phthalimide (NPSP) was recrystallized from CHCl₃, washed with cold isopropyl alcohol

and stored at $-18\text{ }^{\circ}\text{C}$ under nitrogen. The recrystallized NPSP was found to be 98% pure by NMR, and this has been accounted for in all concentration calculations. Isovaleraldehyde was freshly distilled under vacuum prior to use.

All FTIR spectra were taken with a Mettler Toledo ReactIR 15 equipped with a LN₂ MCT detector and a 9.5 mm AgX Fibre DiComp probe at 4 cm^{-1} resolution. The spectra were recorded every 45 s and each was comprised of 122 scans. The FTIR data underwent 2nd derivative processing using the standard function in the Mettler-Toledo iCIR software. This function applies a 7-point Savitzky-Golay filter and an inversion. The *N*-(phenylseleno)phthalimide (NPSP) was monitored using the height of the signal at 862 cm^{-1} relative to zero. The height of the signal at 1036 cm^{-1} relative to a single point baseline at 1058 cm^{-1} was used to monitor the concentration of phthalimide (NHP). A minimum of 5 data points before and after each addition were taken to ensure a reliable average. The NPSP and NHP were each added in two portions and the average of these two calibrations was reported. The average temperatures during the reactions were recorded by the FTIR probe.

All NMR spectra were recorded on a Bruker AVIII HD 400 MHz spectrometer with BBO prodigy probe. The ¹H NMR chemical shifts (δ) are quoted in ppm relative to residual solvent peaks (for CDCl₃, given in ppm: 7.26). Quantitative ¹H NMR (qNMR) was performed with a $d_1 = 25\text{ s}$ to ensure all species had fully relaxed. The analysis of reaction yield by qNMR used 1,1,2,2-tetrachloroethane as the internal standard.

Complete organocatalytic α -selenylation of isovaleraldehyde: A vial fitted with a septum, the ReactIR probe and a stirrer bar was charged successively with stock solutions of isovaleraldehyde (500 μL , 0.206 mmol, 5.6 equiv, CDCl₃), acetic acid (500 μL , 0.503 mmol, CDCl₃) and 1,1,2,2-tetrachloroethane (400 μL , 0.041 mmol, CDCl₃). Five consecutive FTIR spectra were taken before a stock solution of *N*-(phenylseleno)phthalimide (500 μL , 0.037 mmol, 1.0 equiv, CDCl₃) was added in two portions (200 μL , 300 μL). Five consecutive FTIR spectra were taken after both additions before a stock solution of (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidine-methanol trimethylsilyl ether (100 μL , 2.1×10^{-4} mmol, 0.6 mol%, CDCl₃) was added to initiate the reaction. FTIR spectra were recorded consecutively until the reaction appeared to end by visual analysis of the data. The stock solution of phthalimide (500 μL , 0.017 mmol, CDCl₃) was added in two portions (200 μL , 300 μL). Immediately after the second addition, a 0.6 mL aliquot of the reaction was taken, frozen in liquid N₂, and analyzed by qNMR. The spectroscopic data of the reduced product, 3-methyl-2-(phenylselenyl)butanol, matched that from the literature.⁶

Incomplete organocatalytic α -selenylation of isovaleraldehyde: A vial fitted with a septum, the ReactIR probe and a stirrer bar was charged successively with stock solutions of isovaleraldehyde (500 μL , 0.385 mmol, 10 equiv, CDCl₃), acetic acid (500 μL , 1.997 mmol, CDCl₃) and 1,1,2,2-tetrachloroethane (400 μL , 0.041 mmol, CDCl₃). Five consecutive FTIR spectra were taken before a stock solution of *N*-(phenylseleno)phthalimide (500 μL , 0.037 mmol, 1.0 equiv, CDCl₃) was added in two portions (200 μL , 300 μL). Five consecutive FTIR spectra were taken after each addition before a stock solution of (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidine-methanol trimethylsilyl ether (100 μL , 3.8×10^{-5} mmol, 0.1 mol%, CDCl₃) was added to initiate the reaction. FTIR spectra were recorded consecutively until the reaction appeared to stall by visual analysis of the data. The stock solution of

phthalimide (500 μL , 0.017 mmol, CDCl₃) was added in two portions (200 μL , 300 μL). Immediately after the second addition, a 0.6 mL aliquot of the reaction was taken, frozen in liquid N₂, and analyzed by qNMR. The spectroscopic data of the reduced product, 3-methyl-2-(phenylselenyl)butanol, matched that from the literature.⁶

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at: Experimental details, tabulated data and mathematical derivations (PDF)

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Notes

The authors state that there are no conflicts to declare.

ACKNOWLEDGMENT

The research leading to these results has received funding from the EPSRC projects EP/S005315/1 and EP/R513131/1.

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(10) See Supporting Information.

(11) For the product, the signal height was measured relative to a single point baseline to mitigate the change in signal caused by nearby peaks and to ensure the signal height was proportional to the concentration of product. For the reactant, the signal height was proportional to the concentration of reactant without baseline correction.