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Identification of Infrared Spectral Features Related to Solution Structure for Utilization in Solubility and Supersaturation Measurements

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Abstract:

Infrared spectra are abundant with information about the chemical nature and the molecular structure of chemical systems. Any perturbation to a chemical system is reflected in the infrared spectrum by subtle variations in band positions and shapes. The current contribution demonstrates that such features can be used for the measurement of system variables of crystallization processes such as solubility and supersaturation. In addition, the study demonstrates the consistency of the measurements made using a multitude of IR spectral features.

1. Introduction

Recently, the utility of *in situ* ATR FTIR spectroscopy for the measurement of important crystallization system variables such as supersaturation, solubility, and the metastable limit was demonstrated by Dunuwila et al.[1] and Dunuwila and Berglund.[2,3] The feasibility of the technique toward process development and eventually control of batch crystallization processes that will provide for improved product quality/reproducibility, time savings, and cost containment was established. The current work demonstrates the broader scope of ATR FTIR spectroscopy as a multidimensional tool for use in crystallization research and development.

Infrared-active molecular vibrations absorb infrared radiation, thus generating a characteristic IR spectrum. Therefore, IR spectra reflect the chemical nature and the molecular structure of chemical systems.[4] Reactions, changes in composition, the introduction of new species, and temperature affect the molecular vibrational structure of a chemical system. These changes are reflected in numerous forms in the IR spectrum. In many cases, peak intensity changes generally associated with compositional changes may be prominent and can be used for measurement of crystallization phenomena as in the cases presented by Dunuwila et al.[1] and Dunuwila and Berglund.[2] Changes in molecular structure are manifested in more subtle spectral features such as variations in band positions and shapes.[5] These features, in addition to providing valuable insight to the organization of solute and solvent molecules in supersaturated solutions, may be extremely useful as a tool for measuring crystallization parameters. This is particularly true for solute−solvent systems that have overlapping IR bands where peak intensity changes may be difficult to isolate for band-ratioing.

The primary objective of this paper is to demonstrate the multidimensionality of IR spectra with respect to features available for measurement of crystallization system variables such as solubility and supersaturation. Aqueous maleic acid was used as the crystallizing system in this investigation. Several parameters suitable for measurement of solubility and supersaturation were identified, and the results are presented.

2. Materials and Methods

All details regarding the experimental setup and instrumentation were given by Dunuwila and Berglund.[2] The protocols for the accumulation of solubility data and data corresponding to the constant concentration lines are outlined below.

2.1. Measurement of Solubility in Slurries. Solubility was measured in a slurry, *in situ*, at temperatures ranging from 30 to 70 °C. An equilibration time of about 1 h was allowed for the slurry at each temperature setting. A slurry equilibration time of 1 h was determined to be sufficient by monitoring the system approaching equilibrium both from supersaturation and from undersaturation. At each temperature, 10 spectra were scanned. Therefore, the plotted data represent the average of 10 measurements.

2.2. Measurement of Constant Concentration Lines. Appropriate amounts (weight) of maleic acid and distilled water were placed in a 2 L crystallizer and heated to a homogeneous solution. The solution was cooled while solution ATR FTIR spectra were accumulated *in situ*, every 2 min, until it spontaneously nucleated. The cooling rate was 1.3 °C/min and was the maximum allowed by the capacity of the chiller. A series of such experiments ranging from 50% to 65% maleic acid by weight were conducted.

2.3. Data Processing. Derivative Spectra. The derivative spectra of ATR FTIR absorbtion spectra were obtained. The peak positions of all the identified maleic acid vibrational modes and the useful peak intensities (intensities used to compute PIR_1 and PIR_2) were extracted from the derivative spectra and tabulated. This otherwise tedious task was simplified by using the user programmable OBEY programming utility available in the Perkin-Elmer IRDM software.

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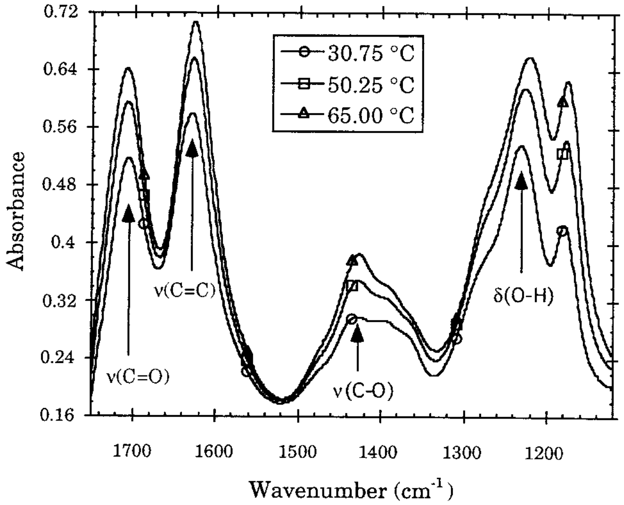

Figure 1. ***In situ,* slurry ATR FTIR spectra of aqueous maleic acid at saturation in the low-frequency region.**

3. Results and Discussion

3.1. Derivative Spectroscopy. Spectral data can be cluttered by interferences and artifacts that appear in the form of polynomial shapes such as sloping lines or quadratic curves.[6] The derivative of the spectrum, which is 1 order higher than the polynomial shape, resolves some of the finer details concealed by the polynomial shapes. For example, the first derivative removes sloping lines, and the second derivative removes quadratic curves and adds clarity to the spectrum. As such, derivative spectra can reveal a host of information otherwise hidden or not readily apparent in the original spectra and can be used to extract both qualitative and quantitative information. Derivative spectroscopy is a standard menu option in most FTIR software.

Figure 1 gives the ATR FTIR spectra (lower frequency window) of saturated aqueous maleic acid at various temperatures. Band assignments are indicated by the arrows.[5−12] These spectra are used to illustrate the functionality of derivative spectroscopy.

Consider the ν(C=O) peak that occurs in the vicinity of 1700 cm^{-1}. It appears to be a single peak devoid of any other feature such as shoulders. However, the first-derivative profile given in Figure 2 reveals information plausibly hidden by an artifact in the form of a polynomial shape. The most striking feature is the enhancement of a shoulder on the high-frequency side of the ν(C=O) peak that is manifested as two peaks in the positive component of the derivative profile. A peak intensity ratio (PIR) can be defined using the ratio of the derivative absorbance peak intensity at 1740 cm^{-1} to that at 1720 cm^{-1} (PIR$_1$) for the measurement of crystallization system variables. Since peak intensities are measured relative to a base line, one was arbitrarily defined at 0.005 (BL1) on the derivative absorbance axis. The solubility and the constant concentration lines of aqueous maleic acid with respect to PIR$_1$, measured *in situ,* are given in Figure 3. This parameter is clearly a function of temperature and independent of concentration. Therefore, the concentration lines coincide with the solubility line. Consequently, this parameter is not suitable for the measurement of supersaturation of aqueous maleic acid. However, the results are presented to demonstrate the scope of derivative spectroscopy in enhancing spectral features that may be used to measure crystallization system variables of many other systems.

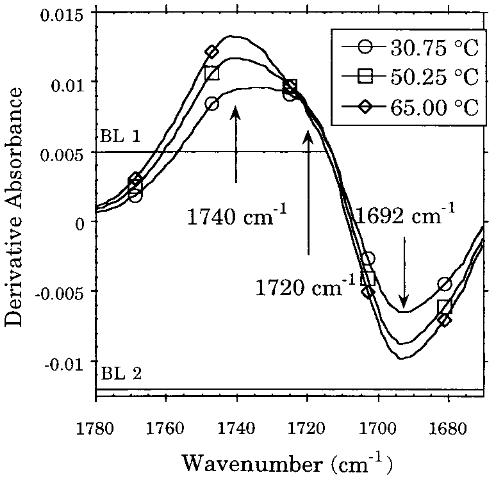

Figure 2. **First-derivative profiles of the ν(C=O) vibrational mode from Figure 1. BL1 = 0.005 and BL2 = −0.012 were the base lines used for PIR$_1$ and PIR$_2$, respectively. PIR$_1$ = (DA at 1740 cm^{-1} − BL1)/(DA at 1720 cm^{-1} − BL1). PIR$_2$ = (DA at 1740 cm^{-1} − BL2)/(DA at 1692 cm^{-1} − BL2). DA = derivative absorbance.**

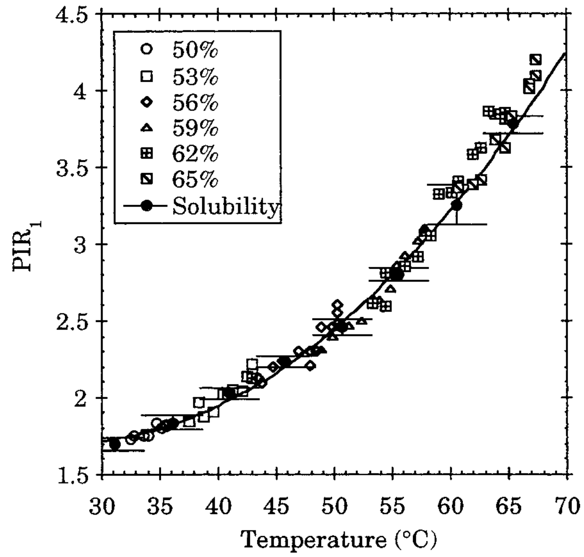

Figure 3. **Solubility and concentration lines of maleic acid with respect to PIR$_1$ measured *in situ*. In addition, solubility was measured in a slurry. PIR$_1$ = (DA at 1740 cm^{-1} − BL1)/(DA at 1720 cm^{-1} − BL1). DA = derivative absorbance.**

Alternatively, a second parameter can be defined using the features of the first derivative of the ν(C=O) mode. The defined parameter is the ratio (PIR$_2$) of the derivative absorbance peak intensity at 1740 cm^{-1} to that at 1692 cm^{-1} with the base line adjusted to −0.012 (BL2) as indicated in Figure 2. Essentially, this parameter reflects the relative changes between the high-frequency side of the ν(C=O) peak and the low-frequency side. The solubility and the constant concentration lines of maleic acid with respect to PIR$_2$,

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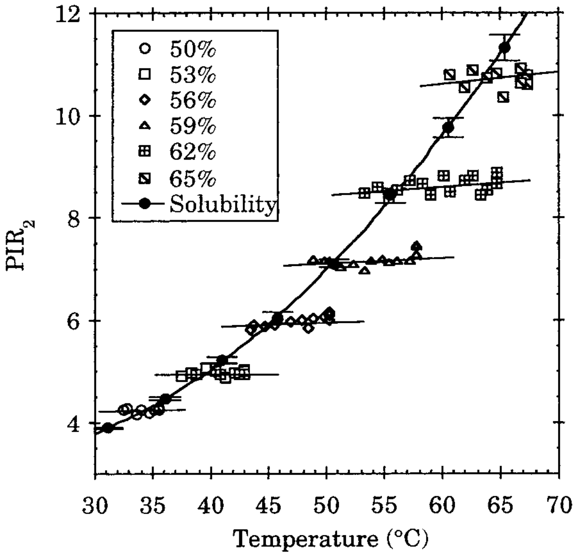

Figure 4. **Solubility and concentration lines of maleic acid with respect to PIR$_2$ measured *in situ*. In addition, solubility was measured in a slurry. PIR$_2$ = (DA at 1740 cm^{-1} − BL2)/(DA at 1692 cm^{-1} − BL2). DA = derivative absorbance.**

measured *in situ*, are given in Figure 4. PIR$_2$, unlike PIR$_1$, is a function of concentration and only slightly dependent on temperature as demonstrated by slightly sloping concentration lines. The fact that PIR$_2$ is a strong function of concentration renders it a highly suitable candidate for measurement of supersaturation as demonstrated in Figure 4. The extension of the constant concentration lines into the supersaturated region across the solubility line is indicative of measurement of supersaturation.

Previously, it has been established that band ratioing techniques such as PIRs or area intensity ratios are appropriate for measurement of system variables of crystallization processes.[1,2] This is because ratioing gives rise to an internal standard that effectively eliminates errors due to instrumental drifts. Instrumental drifts usually occur due to energy fluctuations that arise as a result of radiation source instabilities and alignment problems of optical coupling attachments. In many systems, it may be difficult to identify features that can be used for ratioing in the original spectra. Features of infrared spectra of crystallization systems can be masked by the presence of various species such as impurities, byproducts, and additives that have strongly absorbing vibrational modes making the identification of features suitable for ratioing difficult. In addition, most solvents have characteristic IR spectra that may complicate the issue further. Derivative spectroscopy is one analytical tool, among many, that can be used to enhance features that may be well suited for ratioing, as demonstrated above. The ν(C=O) peak used for demonstration is devoid of any identifiable feature in the original spectra. Nevertheless, the features that the first-derivative profile reveals are quite remarkable. This is convincing evidence for the productiveness of derivative spectroscopy and in general for the far-reaching utility of *in situ* ATR FTIR spectroscopy for use in measuring crystallization system variables, including supersaturation and solubility.

Parameters presented thus far that were suitable for quantitative measurements were based on ratioing features isolated by derivative profiles. Another parameter that is suitable for quantitative measurements is the peak shift of numerous vibrational modes. Derivative spectroscopy is a convenient method for extracting peak shift information. The same information can be obtained from the original spectra. However, the shifts are more discernible in derivative spectra (first and third derivative). Consider the δ(O−H) in-plane deformation vibration of maleic acid given in Figure 1. The red shift of the peak at higher temperatures is evident. The same shift is more convincingly depicted by the derivative profiles of the δ(O−H) vibrational mode in Figure 5. The parameter $\Delta\nu$ denotes the total shift of the peak in going from saturation at 30.75 °C to that at 65 °C. The derivative profiles render the facile identification of shifting peaks that may be suitable for measurements. The peak shift information was extracted using the user programmable OBEY programming utility available in the Perkin-Elmer IRDM software. To demonstrate the usefulness of peak shifts for measurements, supersaturation and solubility of maleic acid measured with respect to the shifts of two maleic acid vibrational modes are presented.

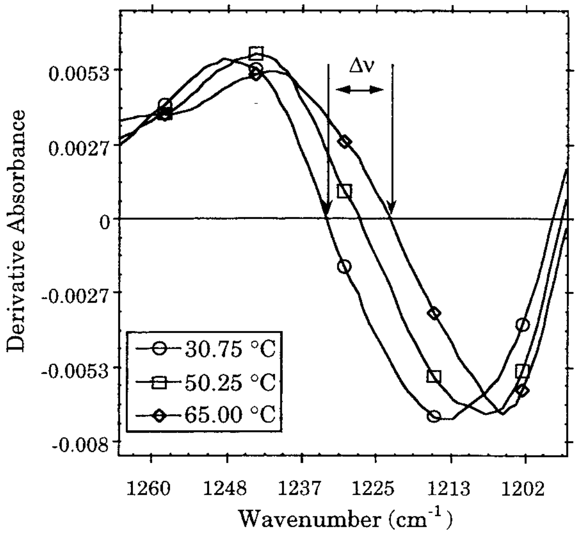

Figure 5. **First-derivative profiles of the δ(O−H) in-plane deformation vibrational mode from Figure 1.**

Solubility and constant concentration lines of aqueous maleic acid with respect to the peak shifts of the ν(C=O) and the δ(O−H) vibrations, measured *in situ*, are shown in Figures 6 and 7, respectively. Solubility, in addition to being measured *in situ*, was measured in a slurry. Clearly, the ν(C=O) vibrational mode is not suitable for the measurement of solubility and supersaturation, since it is independent of concentration. The δ(O−H) vibrational mode is sensitive to the maleic acid concentration and therefore is suitable for measurements. The extension of the constant concentration lines into the supersaturated region across the solubility line is indicative of measurement of supersaturation. The slope of the constant concentration lines from the two vibrational modes differs in sign and magnitude since each bond responds differently to the organization of the solute and the solvent in supersaturated solutions. A shift to higher wavenumbers indicates a gradual weakening of the bond and vice versa.

3.2. The Scope of *in Situ* ATR FTIR Spectroscopy. Between the band ratioing techniques used by Dunuwila et

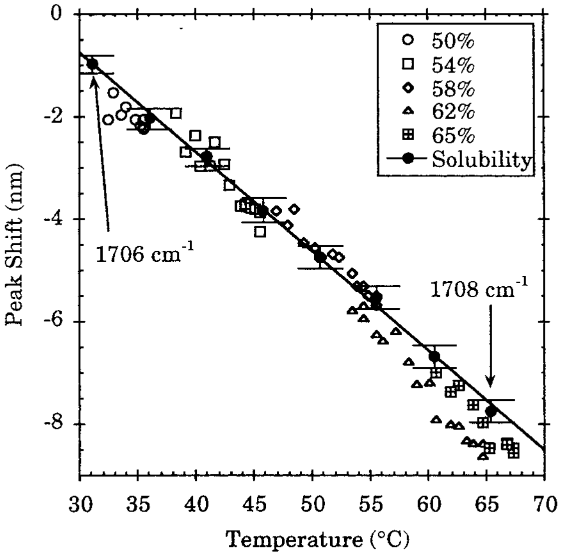

Figure 6. **Solubility and concentration lines of maleic acid measured with respect to the peak shift of the ν(C=O) vibrational mode, *in situ*. In addition, solubility was measured in a slurry. Absolute peak positions at two conditions are shown for reference purposes. The reference point for the peak shift was the peak position at 27 °C, at saturation.**

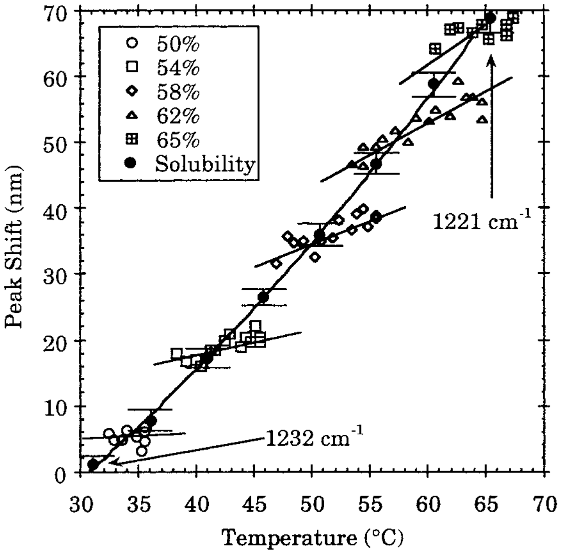

Figure 7. **Solubility and concentration lines of maleic acid measured with respect to the peak shift of the δ(O−H) vibrational mode, *in situ*. In addition, solubility was measured in a slurry. Absolute peak positions at two conditions are shown for reference purposes. The reference point for the peak shift was the peak position at 31 °C, at saturation.**

al.[1] and Dunuwila and Berglund[2,3] and discussed herein and the peak shifts of numerous vibrational modes, it is anticipated that it will not be a difficult task to identify a parameter appropriate for measurement of crystallization system variables of most inorganic and organic systems. As indicated above, features of IR spectra suitable for quantitative measurements of many other crystallization systems can be masked by the presence of various species such as impurities, byproducts, additives, and solvents that have strongly absorbing vibrational modes. When such a system is encountered, the multidimensionality of IR spectra with respect to features they offer for quantitative measurements, as demonstrated herein, can be exploited.

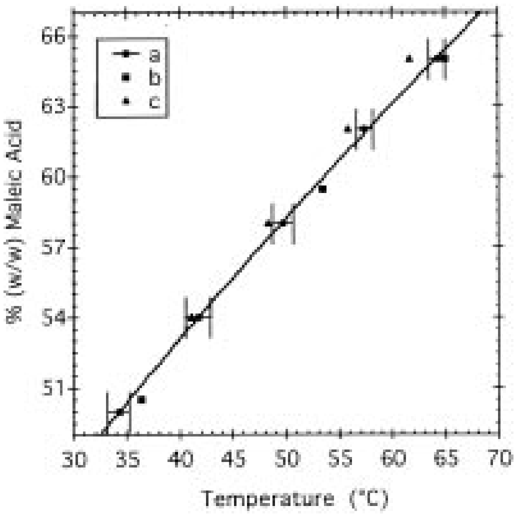

Figure 8. **Solubility of maleic acid in concentration units [% (w/w) maleic acid in water]: (a) solubility measured with respect to IR features including the ones presented in Figures 4 and 8 and the ones presented by Dunuwila and Berglund[2,3] (the procedure is given in the discussion); (b) solubility measured by determining the dissolved solute content; (c) solubility given in the literature.[13]**

In the case of maleic acid, many features that are equally effective for quantitative measurements are available as presented herein and by Dunuwila and Berglund.[2,3] The solubility measured with respect to each of the features discussed above and discussed by Dunuwila and Berglund,[2,3] in concentration units, is shown in Figure 8a. Each of the intersection points between constant concentration lines and the solubility line in Figures 4 and 7 represents the measured solubility in terms of the respective IR parameter and concentration. All of the other functional IR features (Dunuwila and Berglund[2,3]) provide similar measurements. The solubility data points (a) presented in Figure 8 are the averages of the measurements extracted from all the functional IR features including the ones presented in Figures 4 and 8 and the ones presented by Dunuwila and Berglund.[2,3] The solubility of aqueous maleic acid measured by determining the dissolved solute content and the solubility given in the literature[13] are given in Figure 8 for comparison. The precision and the accuracy of the solubility data extracted using IR features are quite reasonable considering the diversity of the parameters used to extract them. This indicates that many IR spectral features, including the ones enhanced by derivative profiles, can be used for measurement of solubility and supersaturation with consistency. Most chemicals and pharmaceuticals absorb IR radiation, giving rise to a characteristic IR spectrum. Considering that most of them are crystallized at some point in their manufacturing process, we contend that *in situ* ATR FTIR spectroscopy has a wide scope in crystallization research, development, and eventually control. *In situ* ATR FTIR spectroscopy provides a convenient and widely applicable technique suitable for measurement of crystallization phenomena such as solubility, supersaturation, and metastable limits in dense slurries. Such a technique has eluded the crystallization community to date.

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Previously,[1] an inconsistency between the solubility data extracted from two different peak intensity ratios, one defined by a longer wavelength peak and the other defined by a shorter wavelength peak, was attributed to the optical properties and the material of the ATR configuration of the micro CIRCLE open boat cell. It was postulated that the deeper penetration of the evanescent field into the sample at longer wavelengths may have been responsible for this anomaly. It was also pointed out that the depth of penetration can be reduced by using alternative ATR configurations and ATR elements that have higher refractive indices such as AMTIR-1 crystals. In the initial feasibility study,[1] the ATR element used was a cylindrical, ZnSe rod that has a low refractive index. In addition, the micro CIRCLE open boat cell used in that study is a sampling device that may allow settling of slurries over the ATR rod, leading to inconsistencies in accumulated data. In the study undertaken subsequently[2] and in the study presented here, the ATR element used was a conical, AMTIR-1 ATR crystal that has a higher refractive index configured for *in situ* measurements. It is very likely that the combination of *in situ* measurements, the conical ATR configuration, and the AMTIR-1 ATR element with a higher refractive index contributed to the consistency of the data extracted from the diverse set of IR parameters used in this study. It is quite apparent that the inconsistencies observed in the initial study[1] were due to the physical properties of the ATR element and the ATR configuration used in that study and not due to the technique itself.

Not all parameters considered were suitable for measurement of supersaturation as a result of some being independent of concentration. The existence of a clear distinction between parameters in terms of the dependence on concentration may be indicative of the unique structure of aqueous maleic acid in supersaturated solutions. Therefore, in addition to quantitative measurements, FTIR spectroscopy may provide valuable information that may help in the elucidation of solution structure in supersaturated solutions. However, such a study is beyond the scope of this investigation since other corroborative evidence by way of Raman and NMR spectroscopic data and experimental data using deuterated analogues of water and maleic acid is necessary to resolve structural information.

4. Conclusions

The primary focus of this paper was to demonstrate the multidimensionality of IR spectroscopy with respect to the wide array of features it offers for utilization in measurement of crystallization system variables such as solubility and supersaturation. This unique attribute of spectroscopic techniques, particularly that of vibrational spectroscopic techniques such as IR, was illustrated with the aid of several IR spectral features. The more straightforward feature used was the peak position shift of numerous vibrational modes. In addition, derivative profiles of the primary spectra were utilized to reveal useful features otherwise obscured by spectral artifacts. The utility of these select features for the measurement of solubility and supersaturation was demonstrated. The precision and the accuracy of the solubility measurements extracted from the numerous IR features used established the consistency of IR spectroscopy toward measurement of crystallization system variables. We contend that it will not be difficult to identify an IR spectral feature suitable for the measurement of solubility and supersaturation of many organic and inorganic systems, considering the multitude of available features. Thus, *in situ* ATR FTIR spectroscopy can be a powerful tool for utilization in research and development of bulk crystallization from solution.

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