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Four Criteria for Evaluating Pure Component Spectral Estimates and the Subsequent Identification of Intermediates in Homogeneous Catalysis

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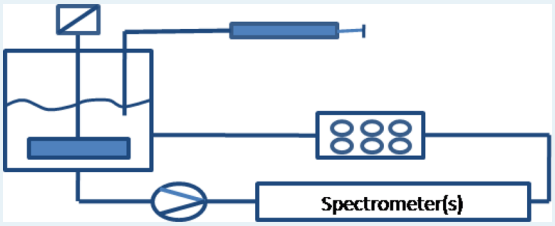
ABSTRACT: In situ spectroscopic studies are increasingly used to better understand mechanistic aspects of homogeneous catalytic systems. In many cases, the raw measured spectra are simply inspected to identify new bands that appear under catalytic conditions. However, various types of advanced signal processing techniques can often provide considerably more detail and can even provide the underlying pure component spectra. Since intermediates are rarely isolatable, the availability of new pure component spectral estimates suggests a need for internal consistency checks and other forms of validation. The present contribution surveys four recently developed criteria for assessing the accuracy of pure component spectral estimates and then their subsequent usefulness in confirming the identity of newly discovered and nonisolatable intermediates in complex metal-mediated syntheses. Criteria I and II address the consistency of spectral estimates within an experimental study and between different experimental studies, and criteria III and IV deal with establishing the stoichiometry and geometry of the nonisolatable complexes and their potential role as intermediates, respectively.



KEYWORDS: *homogeneous catalysis, in situ studies, band target entropy minimization (BTEM), spectral estimates, density functional theory (DFT), intermediates, turnover frequency, chemometrics*

1. INTRODUCTION

In recent years, catalytic research has benefited enormously from the introduction of appropriate in situ spectroscopic measurements. This is certainly true for studies in homogeneous metal-mediated organic syntheses in the liquid phase, where a very wide variety of spectroscopic techniques are often appropriate or applicable (i.e., FTIR, Raman, NMR, UV−vis, circular dichroism (VCD, ECD, ROA) etc.).[1,2] At one level, these techniques are often used to assess issues of substrate conversion, selectivity patterns, and yield. At another level, there is intense interest to understand the speciation of the organometallics formed under catalytic conditions and, hence, gain better mechanistic understanding. Excellent examples include elucidation of the Ir-catalyzed Cativa process[3] and the Pd-catalyzed Lucite process for methyl propanoate.[4] The goal of identifying intermediates is not always easy to achieve because (1) trace organometallics typically contribute only weak signals during the catalysis, (2) there is often a wide gap between the observation of new spectroscopic signals during the catalysis and subsequent definitive identification of new organometallics, and (3) only some of the observed time-dependent organometallics are actually associated with the catalytic transformations (e.g., are true intermediates).

Recently, a rather wide range of very advanced signal processing techniques have begun to be applied to the raw in situ spectroscopic homogeneous catalytic measurements.[5] Perhaps the most important techniques are those associated with pure component spectral estimation. In such situations, the entire set of raw in situ spectroscopic measurements are subjected to analysis to estimate the full underlying pure component spectra of the constituents present. Such pure component spectral estimates clearly represent very valuable information because they afford a window into better understanding of time-dependent speciation during catalysis.

Of course, there are a number of potential hurdles and pitfalls in this approach. Indeed, (a) the process of obtaining accurate pure component spectra is potentially fraught with complications, and (b) even when accurate pure component spectra are attainable, there is a big step between these spectral estimations and the ultimate unambiguous identification of intermediates.

In situ spectroscopic studies of homogeneous catalytic metal-mediated syntheses have reached a sufficient state of development that it is now possible to review some of the most useful criteria for assessing the accuracy and quality of the spectroscopic results in a systematic manner. In the present contribution, issues a and b above are addressed in considerable detail. These criteria have been tested on real systems, are relatively straightforward to implement, and appear to provide

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quite rigorous internal consistency checks. It is hoped that these criteria will become more widely understood and used in the future.

2. EXPERIMENTAL, SPECTROSCOPIC AND COMPUTATIONAL CONSIDERATIONS

2.1. Experimental Section. Three of the most common experimental situations for in situ spectroscopic experiments in homogeneous catalysis are shown in Figure 1. Figure 1a shows

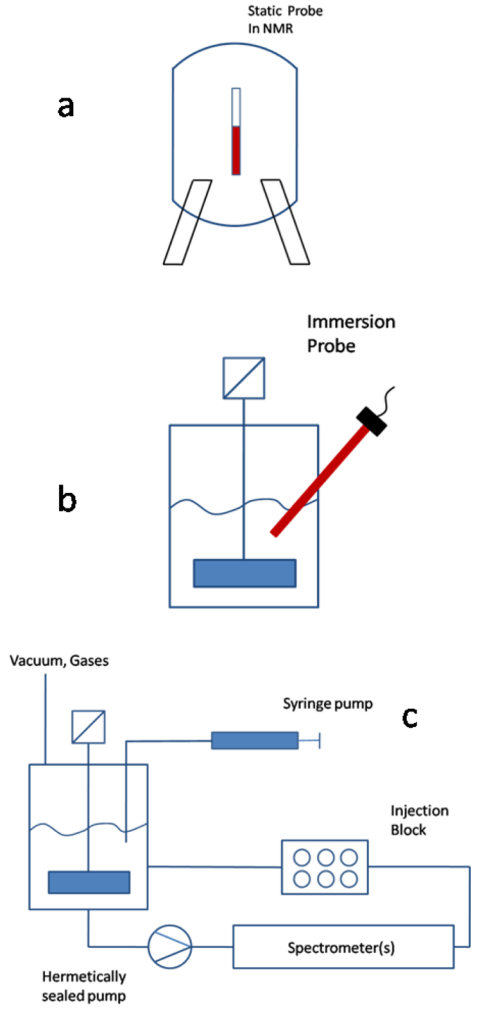

Figure 1. Schematics of various contacting patterns for in situ homogeneous catalytic measurements: (a) static spectroscopic cell, that is, an NMR tube in an NMR spectrometer; (b) immersion probe in a vessel, that is, Raman probe in a round-bottom flask; (c) flow-through recycle system, that is, stirred tank, hermetically sealed pump, FTIR spectrometer.

a nonagitated reacting liquid in a spectrometer. This is frequently encountered when a liquid is measured in the interior of a NMR spectrometer, although quite similar situations can arise with other spectroscopic measurements (cuvettes in UV−vis spectrometers, etc.). Figure 1b shows a well agitated reacting liquid system with an immersion spectroscopic probe. Common immersion probes are available for FTIR, Raman, and UV−vis. Figure 1c shows a well agitated reacting liquid in a recycle configuration. Numerous spectrometers can be conveniently placed in series when accompanied by appropriate flow-through cells, and frequently, such flow-through measurements afford far better signal-to-noise levels compared with immersion probes. Such a configuration also easily accommodates multiple perturbations experiments, that is, the introduction of various reagents at intervals via either syringe pumps or multiple-port injection valves. This issue of perturbing the catalytic system is often important in the design of experiments (vide infra). For completeness, it should be mentioned that two excellent examples of flow-through NMR systems have been developed and successfully applied to stoichiometric organometallic reactions and homogeneous catalysis.[5,6]

As with all experimental work, attention has to be given to prerequisites and details of the procedures used. In the present context, some of the more important issues are (1) mass transfer and mixedness of the measured liquid; (2) recycle rates (i.e., configuration in Figure 1c) and its impact on representative sampling; (3) the wavelengths of the radiation used and, hence, the possibility of radiation-induced changes (i.e., concurrent photochemical reactions); and (4) inadvertent introduction of stray light and, hence, irreproducibility of results (i.e., dark versus photoinduced reaction pathways). Because such prerequisites are not part of the present scope, the reader is referred to a recent review of such considerations.[7,8]

2.2. Design of Experiments (DoE) and Spectroscopic Implications. Experimental design can have an enormous impact on the ultimate usefulness of the in situ spectroscopic measurements.

In homogeneous catalysis, it is typical to start a reaction in some manner with some specific sequence of events and then let the reaction proceed uninterrupted to completion. Such procedures are typically called *batch experiments*, and batch experiments are widely used as the standard operating procedure in metal-mediated organic synthesis. For a well thought-out spectroscopic study, the researcher will often need to conduct a large number of batch reactions with different start-up procedures and with different reaction conditions (substrate, ligand/metal ratio, other reagents, auxiliaries).

Alternatively, a homogeneous catalytic reaction can be conducted in *semibatch mode*. In this procedure, the reaction is started in some manner with some specific sequence of events, but then many further additions (perturbations) to the system are performed at semiregular intervals throughout the duration. Thus, more starting complex, substrate, ligand, auxiliaries, or solvent may be added, either individually or occasionally in combinations. This semibatch approach affords the researcher the ability to survey a very wide range of reaction conditions in one experiment with comparable ease. Nevertheless, for a well thought-out spectroscopic study, the researcher will still need to conduct a number of semibatch reactions with different start-up procedures so that the composition and, hence, reaction space can be adequately surveyed.

Regardless of which approach is used, batch or semibatch, two more aspects of the design of experiments (DoE) should not be overlooked. These are (1) different sources of solvents, metal complexes, ligands, auxiliaries typically contain different impurities and/or different concentrations of impurities, and (2) it is convenient to make a list of impurities typically present in the reagents or the system, which can be deliberately added toward the end of an experimental run (these may include oxygen, water, etc.).

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Therefore, a well-planned spectroscopic study should consist of many experimental runs in which variations are made in (1) the start-up procedures, (2) the reaction conditions, and (3) the sources and purities of the materials used. In addition, (4) the deliberate addition of known impurities is strongly encouraged. By doing so, the experimentalist has done due diligence to surveying as wide a possible set of reaction conditions as possible and, hence, surveying the broadest possible set of observable speciation in the system. At this point, because we are discussing perturbations and design of experiment, it is convenient to define the set of all experiments in a study $\{exp_1, ..., exp_N\}$.

As an example of different approaches to experimental design, the unmodified rhodium-catalyzed hydroformylation of alkenes has been studied using both the batch reaction approach and the semibatch reaction approach, followed by spectroscopic analysis. The results, which have been reported elsewhere,[9,10] provide a concise overview and comparison of in situ studies conducted in batch and semibatch modes.

2.3. Spectroscopic Measurements. Although virtually any type of 1D, 2D, and 3D spectroscopic measurements can be considered, we will restrict the present discussion to 1D spectroscopic vibrational data, such as FTIR or Raman, because all the following experimental results will arise from vibrational measurements. Accordingly, let $\mathbf{A}_{1\times\nu}$ be a single 1D FTIR or Raman spectroscopic measurement where ν represents the number of channels of data. Furthermore, let us assume that k represents the total number of spectra taken in the entire spectroscopic study. Then it is convenient to acknowledge that the ensemble $\mathbf{A}_{k\times\nu}$ of all spectroscopic measurements is simply the matrix formed by augmentation over all N experiments. The individual sets of data (i.e., $\mathbf{A}_{exp1}$, ..., $\mathbf{A}_{expN}$) obtained from the individual experiments will be important for defining some of the self-consistency checks and criteria in the following sections.

$$\mathbf{A}_{k\times\nu} = [\mathbf{A}_{exp\ 1}, ..., \mathbf{A}_{exp\ N}] \tag{1}$$

2.4. Computational Aspects. Self-modeling curve resolution is the common term used in the chemometrics community for describing procedures aimed at estimating pure component spectra from sets of bulk mixture spectra. Numerous procedures have been developed. The common procedures, including SIMPLISMA,[11] IPCA,[12] and OPA-ALS,[13] have a variety of restrictions. The most notable restriction is probably the need for the experimentalist to accurately guess a priori the number of species present in the system before all s pure component spectra are estimated simultaneously. Another algorithm developed and used by our group, BTEM, does not have such a restriction and, instead, estimates pure component spectra one-by-one until the information in the data set is exhausted.[14,15]

Let us assume that a robust algorithm is available for the estimation of pure component spectra from mixture data. Then for *any* given spectroscopic data set $\mathbf{A}_i$ there is a corresponding set of pure component spectral estimates $\{\mathbf{a}_1, ..., \mathbf{a}_s\}_i$. Consequently, this procedure can be performed on individual sets of measurements or even the measurements from an entire study.

$$\mathbf{A}_i \rightarrow \{\mathbf{a}_1, ..., \mathbf{a}_s\}_i \tag{2}$$

Because the matrix of all mixture spectra can be expressed as $\mathbf{A}_{k\times\nu} = [c_{k\times s}\mathbf{D}_{s\times s}]\mathbf{a}_{s\times\nu}$ where c is concentration and $\mathbf{D}$ is a scaling matrix (calibration matrix), it is implicit that there is a concentration, c, or at least a relative concentration $c\mathbf{D}$ (signal weighting) associated with each measurement. In some algorithms, such as SIMPLICMA etc., c or $c\mathbf{D}$ is forced to be non-negative during the calculations. In other algorithms such as BTEM (See Appendix I for a brief overview), c or $c\mathbf{D}$ is not a built-in constraint (this can be very helpful when species have weak signals and severe baseline changes etc occur). Nevertheless, c or $c\mathbf{D}$ can always be calculated a posteriori. The essential issue is that associated with any set of spectra $\mathbf{A}$, there is a concentration c or at least a relative concentration $c\mathbf{D}$, and this information can be useful for internal consistency checks (eq 3). For further details concerning concentration calculations and calibrations, at least in the context of BTEM, the reader is referred to the original publication.[16]

$$\mathbf{A} \rightarrow c \tag{3}$$

3. RESULTS AND DISCUSSION

This section is divided into two specific criteria, I and II, for testing the quality and accuracy of pure component spectral estimates and then two specific criteria, III and IV, for using these verified pure component spectral estimates to establish the identity of the species present and assess their possible roles as intermediates.

3.1. Criterion I: Internal Consistency From One Experimental Study. It would be extremely useful if a robust internal consistency check for a single experimental study could be identified. Indeed, because exploratory studies target the identification of new species, assurance and certainty in the pure component spectral estimates is a must.

Such a test can be constructed. Since there are N experimental data sets in the study, it is possible to construct a series of N augmented spectroscopic matrices, $\mathbf{A}_1$, ..., $\mathbf{A}_N$, in which each matrix is larger than the previous matrix. These matrices represent the ensembles $A_1 = [\mathbf{A}_{exp1}]$, $A_2 = [\mathbf{A}_{exp1}, \mathbf{A}_{exp2}]$, ... $A_N = [\mathbf{A}_{exp1}, ..., \mathbf{A}_{expN}]$. As the size of the spectroscopic matrices $\mathbf{A}_1$, ..., $\mathbf{A}_N$ increases, the number of independent observations of the system increases. This has the rapid and advantageous effect of mitigating possible collinearities in the data (see Appendix II for further information). Accordingly, analyses of the N spectroscopic matrices $\mathbf{A}_1$, ..., $\mathbf{A}_N$ results in N sets of pure component spectral estimates $\{\mathbf{a}_1, ..., \mathbf{a}_s\}_1$, ..., $\{\mathbf{a}_1, ..., \mathbf{a}_s\}_N$. If a thorough and thoughtful design of experiments has been performed, the N sets of pure component spectral estimates $\{\mathbf{a}_1, ..., \mathbf{a}_s\}_1$, ..., $\{\mathbf{a}_1, ..., \mathbf{a}_s\}_N$ should converge to a consistent answer. Note that the dimension of the sets, s, may not be the same until convergence is achieved.

$$\{\mathbf{a}_1, ..., \mathbf{a}_s\}_1 \neq \{\mathbf{a}_1, ..., \mathbf{a}_s\}_2 ... \{\mathbf{a}_1, ..., \mathbf{a}_s\}_{N-1} \approx \{\mathbf{a}_1, ..., \mathbf{a}_s\}_N \tag{4}$$

Figure 2 illustrates this concept of converging spectral estimates from a single experimental study (emphasis is restricted to the organometallic species present). The experimental example is a rhodium-catalyzed hydroformylation of cyclopentene starting with $Rh_4(CO)_{12}$ and $HRe(CO)_5$ as catalyst precursor. Seven semibatch experiments were performed, and perturbations were made in $Rh_4(CO)_{12}$, $HRe(CO)_5$, cyclopentene, CO, hydrogen, and hexane. The detailed experimental design is reported elsewhere.[17]

A total of k = 1160 FTIR spectra were analyzed using the BTEM algorithm. As can be seen from the results shown in Figure 2, the first set of pure spectral estimates look somewhat

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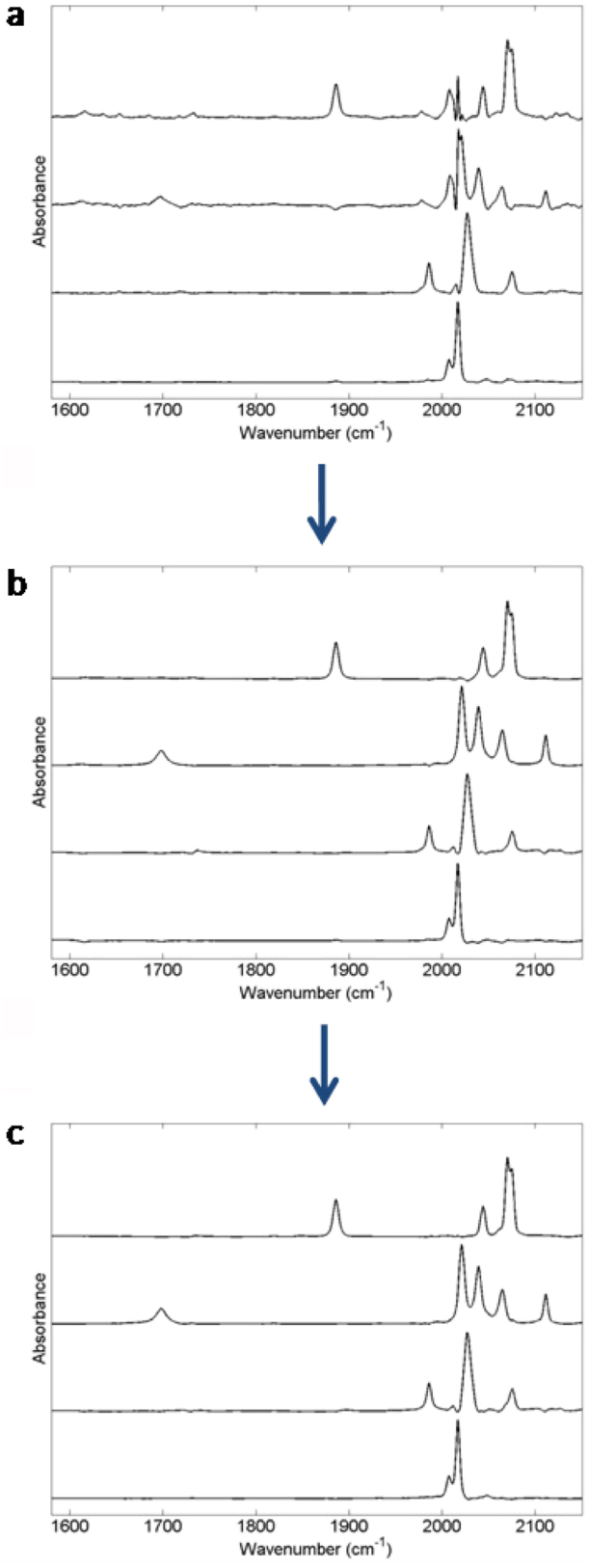

Figure 2. Criterion I: Convergence of spectral estimates within a single experimental study. (a) Results from analysis of data set no. 1 (experimental run). (b) Results from analysis of data sets nos. 1−5. (c) Results from analysis of data sets nos. 1−7 (emphasis is restricted to the organometallic species present). The species are (from top of each figure) $Rh_4(CO)_{12}$, $RCORh(CO)_4$, $RhRe(CO)_9$, and $HRe(CO)_5$.[17]

distorted, but this undesirable effect is quickly alleviated as more and more data are analyzed. The present procedure—namely, the analysis of larger and larger data sets within a single experimental study until consistence is achieved—has been used by our group in every homogeneous catalytic study that we have reported since 2002.

3.2. Criterion II: Internal Consistency between Related Studies. It is fairly common in homogeneous catalytic research to study related systems. This tendency to study related systems can, with proper considerations, provide an additional consistency check for pure component spectral estimates.

Consider a research program in which one metal (i.e., rhodium) is of primary interest. However, in some experimental studies, one or more additives are present, that is, other metal precursors. In such a situation, there should be overlap between the pure component organorhodium spectral estimates obtained in the pure rhodium experiments and the pure component organorhodium spectral estimates obtained in the modified experiments. Let $\mathbf{A}_{Rh}$, $\mathbf{A}_{Rh+Re}$, and $\mathbf{A}_{Rh+Mo}$ represent spectroscopic data sets obtained from (1) an unmodified rhodium-catalyzed hydroformylation; (2) a rhodium-catalyzed hydroformylation modified by addition of a rhenium precursor; and (3) a rhodium-catalyzed hydroformylation modified by addition of a molybdenum precursor, respectively. Figure 3 is a simple Venn diagram representation of this concept. Clearly, there should be some overlap in the results if proper spectral estimates have been achieved in each analysis.

Our group has performed rhodium catalyzed hydroformylations with only $Rh_4(CO)_{12}$ as precursor,[9,10,18−20] $Rh_4(CO)_{12}$ and $HRe(CO)_5$ as precursors,[17,21] $Rh_4(CO)_{12}$ and $HMn(CO)_5$ as precursors,[21−23] $Rh_4(CO)_{12}$ and $HMoCp(CO)_3$ as precursors,[24] and $Rh_4(CO)_{12}$ and $HWCp(CO)_3$ as precursors.[25] Although the set of species observed in each system is different, there is overlap between some spectral estimates. Indeed, the pure component spectra of the precursor $Rh_4(CO)_{12}$, the intermediate $RCORh(CO)_4$, and the occasional degradation product $Rh_6(CO)_{16}$ have been, for all practical purposes, identical among different studies. Figure 4 shows one example of this consistency check by comparing the results for a rhodium-catalyzed hydroformylation and a rhodium−molybdenum hydroformylation. In both cases, the pure component spectra of $Rh_4(CO)_{12}$ and $RCORh(CO)_4$ are extremely similar in both frequencies as well as relative intensities.

3.3. Criterion III: Comparisons of Pure Component Spectral Estimates with DFT. Vibrational spectra of molecules can be predicted with a high degree of accuracy using first principles.[26] Since this situation holds for organometallics, as well,[27] density functional theory (DFT) provides a powerful means of confirming the identity of nonisolatable intermediates. In other words, the pure component spectral estimates obtained from an experimental study can be compared with DFT spectral predictions until the stoichiometry as well as the geometry of the new nonisolatable organometallic is established.

Figure 5b shows a BTEM spectral estimate of a new organometallic observed during a rhodium−molybdenum-catalyzed hydroformylation.[24] Since there are considerably more than 3−4 metal carbonyl vibrations in the spectral estimate, the species is almost certainly not mononuclear. Accordingly, numerous Rh−Mo stoichiometries were considered, and numerous geometries were evaluated. After

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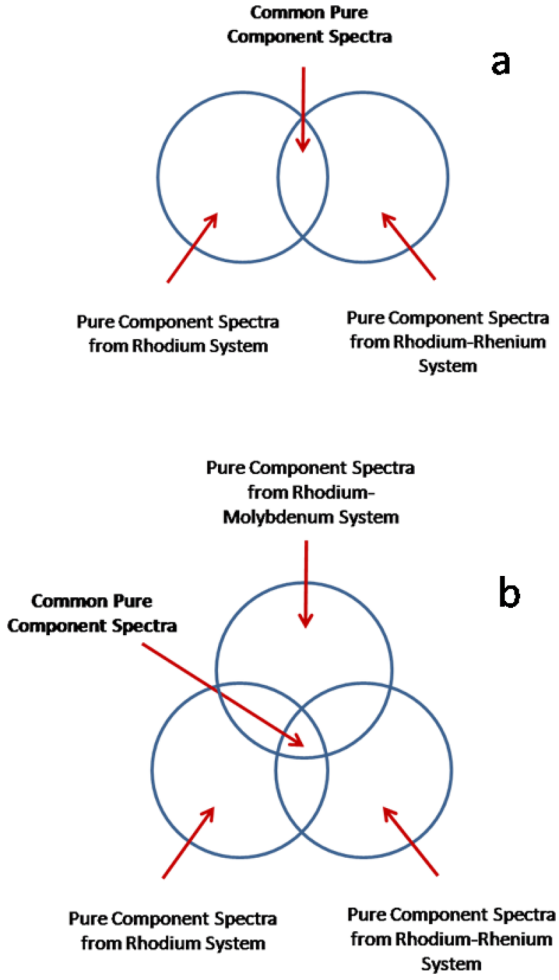

Figure 3. A conceptual representation for the consistency of spectral estimates between independent but related catalytic systems. (a) A Venn diagram for spectral estimates from (i) a rhodium-catalyzed hydroformylation and (ii) a rhodium−rhenium-catalyzed hydroformylation. (b) A Venn diagram for spectral estimates from (i) a rhodium-catalyzed hydroformylation, (ii) a rhodium−rhenium-catalyzed hydroformylation, and (ii) a rhodium−molybdenum hydroformylation.

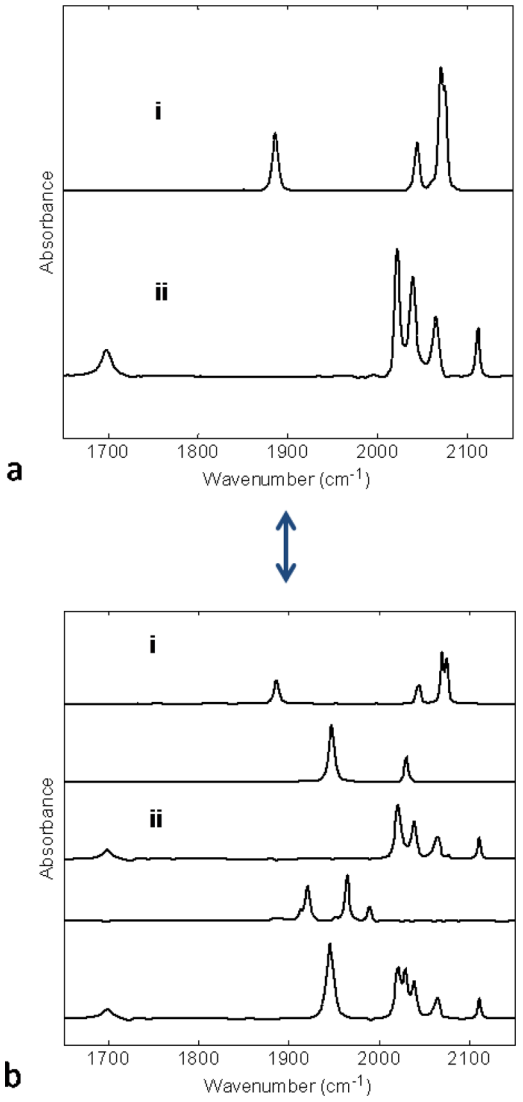

Figure 4. Criterion II: Comparison of BTEM spectral estimates from two independent but related catalytic systems: (a) the spectral estimates from a rhodium-catalyzed hydroformylation of cyclopentene showing $Rh_4(CO)_{12}$ and $RCORh(CO)_4$ and (b) the spectral estimates from a rhodium−molybdenum-catalyzed hydroformylation of cyclopentene.[24] (i) $Rh_4(CO)_{12}$ and (ii) $RCORh(CO)_4$.

optimizing the geometries for each of the postulated Rh−Mo organometallics using DFT, the corresponding FTIR spectra were predicted. One DFT predicted IR spectrum was nearly a perfect match for the BTEM spectral estimate of the new organometallic. Indeed, the number of bands and the relative intensities of the bands are in outstanding agreement. This approach of comparing BTEM spectral estimates with DFT spectral predictions has allowed the identification of numerous nonisolatable organometallics in various studies by our group.

Because the search space for comparisons of BTEM spectral estimates and the DFT predicted spectra is enormous, it is prudent that the experimentalist use some spectroscopic reasoning and knowledge to judiciously narrow the possible choices of structures to be considered. As the above example illustrates, the presence of many metal carbonyl vibrations in the spectra are inconsistent with a mononuclear stoichiometry.

3.4. Criterion IV: Turnover Frequencies and Identifying Intermediates. Even after the accuracy of a pure component spectral estimate has been validated, and even after the identity (stoichiometry and geometry) of the corresponding organometallic complex has been established, there are always questions about the role of the new organometallic in the metal-mediated synthesis. The most likely possibilities for a new organometallic are (A) it is an intermediate in the synthesis (either on the cycle or equilibrated exchange with the cycle) or (B) it is a side product or degradation product and has nothing to do with the catalysis as such.

For simple catalytic cycles, the time-dependent profiles of situations A and B are dramatically different. Following the seminal work of King and Altman[28] and then confirmed by many others,[29,30] it has been clearly shown that the instantaneous concentrations of intermediates (and equilibrated reservoirs) are strongly coupled to the instantaneous rates of product formation (Appendix III). This is most easily seen during the start-up of a catalytic system (induction period), when there is a dramatic change in the concentrations of the organometallics present and relatively low conversion of the substrate. In this situation, there is only proportionality

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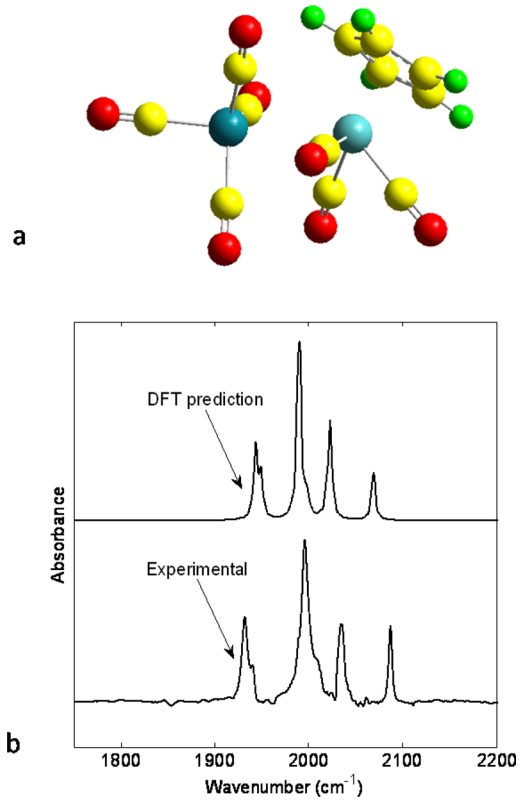

Figure 5. Criterion III: comparison of BTEM spectral estimate with DFT spectral prediction at the PBEPBE level of theory. (a) DFT optimized structure of binuclear intermediate $(CO)_4Rh\text{-}MoCp(CO)_3$ and (b) comparison of the corresponding BTEM spectral estimate and the DFT predicted spectrum.[24].

between the instantaneous rates of product formation and the concentrations of those organometallics directly involved in the catalysis (situation A). The organometallics that have nothing to do with the catalysis directly (i.e. precursor and degradation products) will not exhibit such a correlation.

Figure 6a shows the time-dependent concentrations of a number of solutes, obtained by in situ FTIR measurements, during a rhodium-catalyzed hydroformylation. As this figure shows, the concentrations of organometallics change rapidly during the induction period. However, as Figure 6b shows, the ratio of instantaneous reaction rate divided by instantaneous concentration is a constant in the case of acyl rhodium tetracarbonyl. This situation does not hold for the precursor $Rh_4(CO)_{12}$. Stated in other terms, Figure 6a,b together provides strong evidence that $RCORh(CO)_4$ is, indeed, an intermediate on the catalytic cycle or is an equilibrated reservoir connected to the cycle (situation A).

Although Figure 6 was constructed with fully calibrated data, in other words, the real instantaneous concentrations are known, criterion IV is much more flexible. As indicated in section 2.4, the experimentalist often has the choice to work with real concentrations or simply the relative concentrations (signal weightings). Thus, criterion IV works equally well with just the relative concentrations (signal weightings). Stated in other words, a researcher has the opportunity to postpone criterion III (determining the chemical identity of a new organometallic) and instead proceed directly to criteria IV to test the hypothesis that a particular signal (pure component spectrum) is actually consistent with the behavior of a true

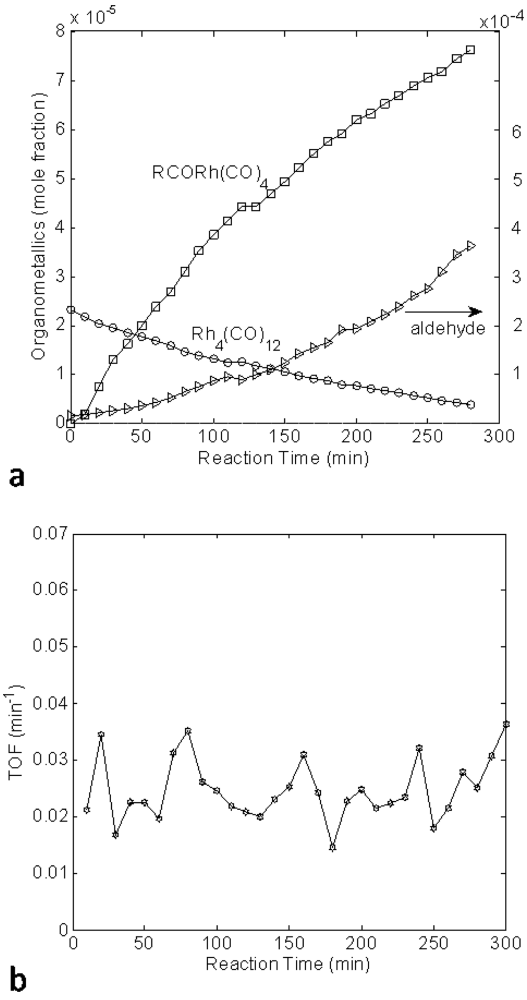

Figure 6. Criterion IV: confirming the role of an organometallic species as an intermediate in the catalysis. (a) A plot of concentrations versus time from a rhodium-catalyzed hydroformylation. (b) A plot of TOF (based on acyl) versus time.

intermediate. If the pure component spectrum of an organometallic passes that test, then the experimentalist has further incentive to perform the full DFT calculations to determine the stoichiometry and geometry of the new organometallic species.

4. CONCLUSIONS

Although the past decade has witnessed a dramatic increase in the use of in situ spectroscopic investigations of metal-mediated homogeneous catalyzed organic syntheses, it has not been entirely clear how to most effectively use this information. The present contribution has attempted to address the opportunities that exist when pure component spectral estimates can be obtained. Accordingly, four criteria have been described. Two of these criteria, I and II, deal with internal consistency checks of the pure component spectra: namely, internal consistency from one experimental study and internal consistency between related studies. The other two criteria, III and IV, deal with the consequence of accurate pure component spectral estimates: namely, comparisons of pure component spectral estimates with DFT (identification of the new and nonisolatable organometallics) and the use of turnover frequencies for identifying intermediates. It is hoped that the

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present effort will stimulate further work into developing rigorous tests for investigation homogeneous catalytic systems.

APPENDIX I

Given a spectroscopic data matrix formed from 1D spectra **A**, the basis vectors from these observations can be determined, for example, using singular value decomposition. The matrix of right singular vectors $\mathbf{V}^{\mathbf{T}}$ contains information on the features present in the spectra, and these are ranked in descending order with respect to their signal variance contribution. If a very large set of spectroscopic measurements are made, for example, $k > 1000$, it is quite typical that only the first 50−100 right singular vectors possess localized features indicative of real physical features. The remaining right singular vectors are basically randomly distributed noise. Let j be the index for the number of meaningful right singular vectors that are clearly not white noise, then the main equation in the BTEM algorithm takes the form of eq 5, where T is a transformation matrix.

$$a_{1\times\nu} = \mathbf{T}_{1\times j}\mathbf{V}^{\mathbf{T}}{}_{j\times\nu} \tag{5}$$

The BTEM algorithm searches for the simplest spectra, $a_{1\times\nu}$, one-at-a-time. Accordingly, during each search, the elements of the transformation matrix, **T**, are optimized to yield a simple spectral estimate. This is done repeatedly until all the information in the data set are exhausted. For a detailed review of BTEM analysis in catalysis, the reader is referred elsewhere.[31]

APPENDIX II

Collinearity is the term frequently used to describe a particular situation in which it is difficult or even impossible to untangle multivariate data. In spectroscopic terms, collinearities often arise when the concentrations of two or more species are nearly proportional over all observations. This makes it very difficult to untangle the true pure component spectra of the individual species.

Consider a metal-mediated regioselective synthesis in which there are two regioisomers formed. If the reaction is conducted at a fixed temperature, there is a high likelihood that the regioselectivity at, say, 30 min and the regioselectivity at 3 h are almost the same. Consequently, any "pure component" spectral estimate of the product is most likely a superposition of the two regioisomers and not a pure component. However, if during the experiment the reaction temperature is significantly changed, it is unlikely that the regioselectivity at 30 min and the regioselectivity at 3 h are the same. Analysis of the new data set should provide two distinct pure component spectral estimates, one for each regio-isomer. In other words, the potential collinearity in the data set has been broken.

APPENDIX III

Interpreted in the context of metal-mediated homogeneous catalysis, the work of King and Altman and others[28−30] shows that if the nuclearity of all the intermediates on a cycle is one and the same (in other words, intermediates do not react together and create more complicated reaction networks), then the simple catalytic cycle can be represented as a linear network in the intermediates, and hence, the rate of product formation is described by simple matrix algebra. In particular, they showed that the rate of instantaneous product formation is proportional to the sum total instantaneous concentration of all intermediates $\Sigma[\mathrm{I}]$ (eq 6) and proportional to the instantaneous concentration of each intermediate [I] (eq 7) at a pseudosteady state. In the first case, the coefficient of proportionality is the turnover frequency TOF, and in the second case, it is a scaled coefficient, here designated $\mathrm{TOF_I}$, where I represents an intermediate. In the case of a large excess of organic reactants with very low conversions (i.e., in the induction period), the two terms TOF and $\mathrm{TOF_I}$ are constants to a very good first approximation.

$$\mathrm{rate}_t = \mathrm{TOF}\cdot\Sigma[\mathrm{I}]_t \tag{6}$$

$$\mathrm{rate}_t = \mathrm{TOF_I}\cdot[\mathrm{I}]_t \tag{7}$$

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Notes

The authors declare no competing financial interest.

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