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Research Article

Real-time monitoring of tritium gas reactions using Raman spectroscopy

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Summary

The utility of Raman spectroscopy for noninvasive, real-time monitoring of a range of tritium gas labeling reactions has been investigated, using deuterium gas as a model in most cases. Reaction types include organoiridium-catalyzed heteroatom-directed exchange (HDE), olefin hydrogenation and catalytic aryl dehalogenation. Five examples of HDE reactions with several different substrate types were monitored by observation of Raman vibrational bands sensitive to the isotopic substitutions. Changes in peak intensities and/or frequencies associated with the course of labeling are clearly observable at concentrations and reaction scales typical of tritium gas reactions. Similarly, Raman bands sensitive to the chemical changes that occur during catalytic deuterogenation of an olefin and to catalytic deuterium–bromine exchange of an aryl bromide were successfully monitored. This methodology can provide unprecedented real-time information, otherwise difficult to obtain, over the course of such reactions. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: Raman spectroscopy; reaction monitoring; heteroatom-directed exchange; tritium–halogen replacement; deuteration; tritiation

Introduction

A major impediment to rapid development and optimization of tritium gas reactions stems from the limited options available for monitoring their progress. Such reactions generally use small quantities (20–200 μmol) of tritium gas at subatmospheric pressure, in small vessels with the minimum practical headspace. Investigators rarely monitor ongoing reactions by physical sampling of the reaction mixture because of radiation safety issues

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and the risk of perturbing the reaction's atmosphere. In addition, incorporation of a septum sidearm into the design of a reaction vessel inevitably increases the reaction headspace, leading to the need to use either larger amounts of tritium or lower pressures. To date, there has been no published method for noninvasive monitoring of such reactions to provide real-time functional group selectivity. In lieu of real-time monitoring, it is common practice either to conduct deuterium model reactions before embarking on a tritiation, or to run tritiations for extended periods of time against the possibility of slow reaction rates. Such practices require multiple experiments, increase the risk of failed tritiations, and/or generate excessive byproducts or radiation-induced decomposition from unnecessarily long reaction times.

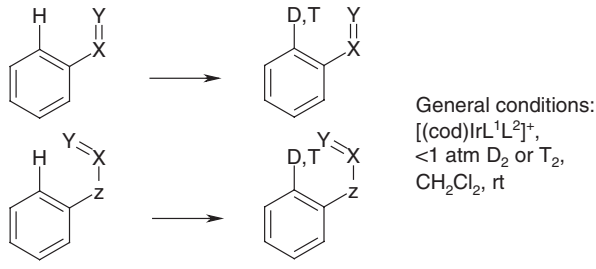
It would be desirable to monitor pathways and progress for these kinds of reactions without the need to physically contact the reaction mixtures. Raman spectroscopy provides one method by which functionally specific data can be obtained from a reaction mixture without the need for invasive sampling.[1] The ability to conveniently obtain spectra by aiming a small portable laser device at a reaction vessel and detecting the scattered radiation renders *in situ* reaction analysis practical in a tritium gas handling facility. A number of functional groups often involved with tritium gas reactions are known to have sufficiently sensitive Raman bands[2] to enable observation of the spectral features in relatively low concentration solutions commonly associated with tritium based reactions. Olefin, acetylene, conjugated carbonyl, aromatic ring, aliphatic C–H, C–D and C–T vibrations are examples of those suited to investigation by Raman analysis.[3]

The present work demonstrates the successful application of Raman spectroscopy for the noninvasive, real-time analysis of several common types of tritium gas reactions, and the use of various modes of data presentation and analysis. For reasons of cost and safety, most of the described reactions were conducted using deuterium as a surrogate; however, several tritium reactions were conducted to demonstrate that the methodology applies also to this isotope.

Results and discussion

Raman monitoring of heteroatom directed exchange

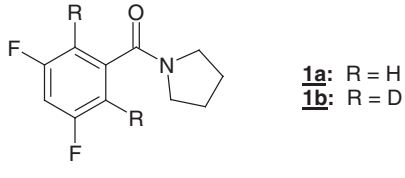
The catalytic exchange of hydrogen in unactivated C–H bonds[4] with isotopic hydrogen gas has proven to be an important addition to the repertoire of tritium (and deuterium) labeling methods. Typical of this class of reactions is the conversion shown in Scheme 1. Under suitable organoiridium catalysis, one or more aryl hydrogens *ortho* to an activating function are replaced by tritium or deuterium, leaving the gross chemical structure unchanged.



Scheme 1.

Published literature detailing the effects of deuterium substitution on the Raman spectra of arenes is limited yet consistant with theory by illustrating that the additional mass of the deuterium vs hydrogen atom results in an attenuation of the observed vibrational frequency. For example, the 1002 cm^{-1} aryl ring band of benzophenone is shifted to 960 cm^{-1} in perdeuterobenzophenone, and the 1599 cm^{-1} peak to 1568 cm^{-1};[5] the imidazole ring vibration of 9-β-D-arabinofuranosyladenine at 1518 cm^{-1} is shifted to 1488 cm^{-1} upon deuteration of the purine at C8.[6]

As a preliminary feasibility study, Raman spectra of 3,5-difluorobenzoyl pyrrolidine (**1a**) and 2,6-dideutero-3,5-difluorobenzoyl pyrrolidine (**1b**) were collected from methylene chloride solutions. An aromatic ring band of compound **1a** was observed at 1000 cm^{-1}. For compound **1b** this band was shifted to 973 cm^{-1}. At an instrumental resolution of 4 cm^{-1}, these peaks were baseline resolved and exhibited no interfering bands from either solvent or other vibrational modes of the compound itself. Results of this experiment further reinforced the potential utility of Raman spectroscopy for monitoring the course of an *ortho*-deuteration or tritiation reaction of **1a** to **1b**.



An HDE reaction of **1a** (12.5 mg in 0.5 ml CH_2Cl_2, 3.9 mol% of $[(cod)Ir(PPh_3)_2]BF_4$, 3.5 equiv of D_2) was run in a cylindrical reaction vessel (5 mm ID × 7 cm). The vessel was attached to the gas manifold by a Swagelok fitting and equipped with a small magnetic spinvane for stirring. The charged reaction vessel contained a residual headspace volume of approximately 5 ml. The laser was focused through the vessel wall into the solution about 5 mm above the spinvane, to avoid disturbance of the beam as the solution was stirred.

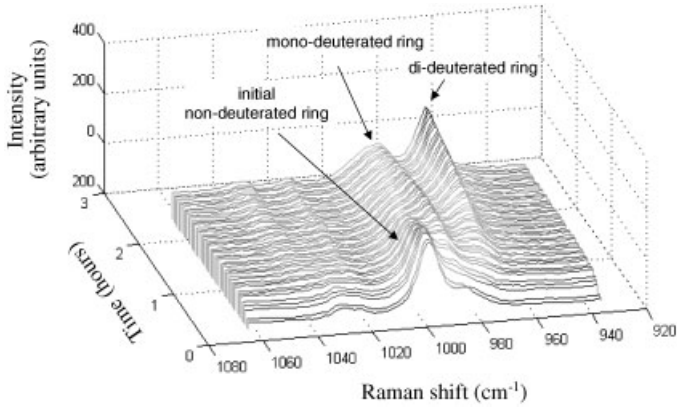
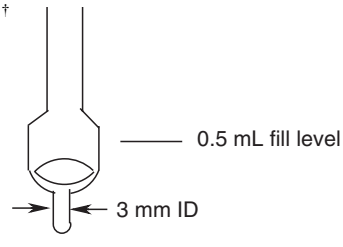


Figure 1. Waterfall view of the deuteration of 3,5-difluorobenzoylpyrrolidine

Spectra were collected at 3 min intervals throughout the reaction to provide the real-time feedback illustrated in the 1070-940 cm^{-1} waterfall plot of Figure 1. The progress of the reaction is clearly apparent, as the 1000 cm^{-1} peak of **1a** diminished and was replaced by that of **1b** at 973 cm^{-1} over the course of about 2.5 h. A peak at 990 cm^{-1} was observed to appear and then diminish through the course of the reaction. This peak has been assigned to the monodeutero intermediate. The reaction was worked up after about 2.5 h. LCMS analysis of the product showed the isotopic distribution to be 4%d_0, 32%d_1, 64%d_2, consistent with the extent of reaction indicated by the spectral record.

A tritiation of **1a** at much lower substrate concentration (2 mg **1a** in 0.5 ml CH_2Cl_2, 15 mol% $[(cod)Ir(PPh_3)_2]BF_4$, 2.3 equiv. T_2 at partial pressure of about 100 mbar) was conducted using a vessel† designed for more efficient gas/liquid exchange; the laser was focused on the solution inside the lower projection. Analogous to the deuterium experiment, diminution of the1000 cm^{-1} peak was observed throughout the reaction (Figure 2, shown in overlay mode). Growth of peaks at 968 cm^{-1} and 946 cm^{-1} was attributed to 2-tritio-**1a** and 2,6-ditritio-**1a**, respectively. The faster kinetics of the tritiation compared to the previous reaction are attributed to the higher catalyst loading and the more efficient gas/liquid exchange in this reaction

† 

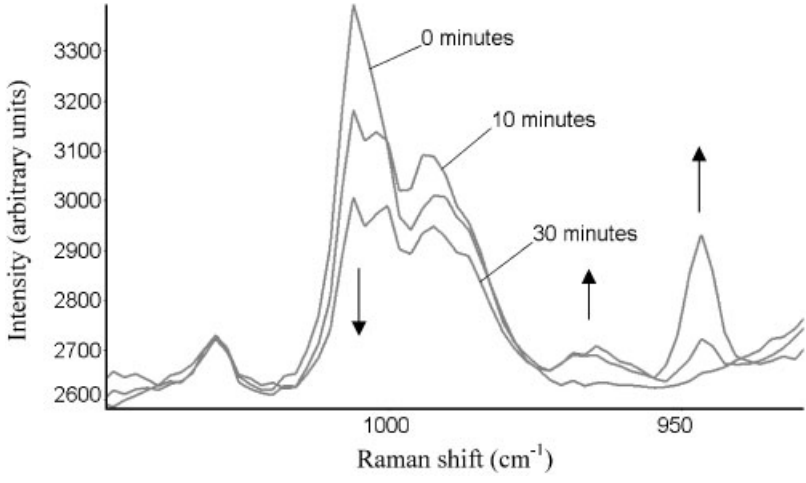


Figure 2. Overlay view of the tritiation of 3,5-difluorobenzoylpyrrolidine

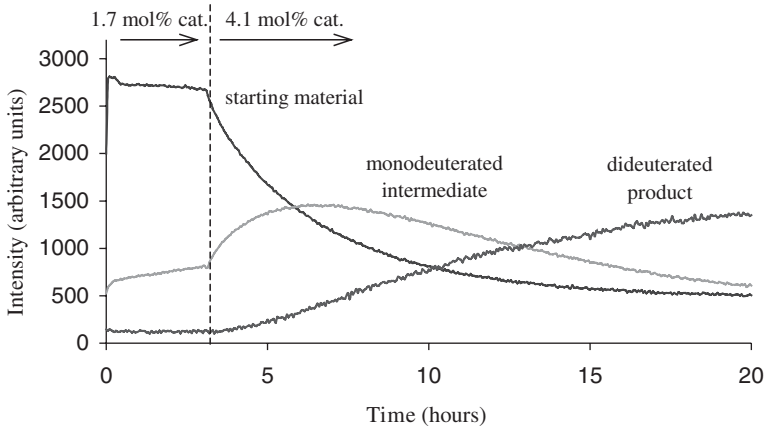


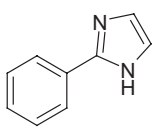
Figure 3. Graphic view of the deuteration of 2-phenylimidazole

vessel. Spectral changes had come to a stop within 30 min, indicating cessation of the reaction. Consistent with the Raman data, the isotope distribution of [^{3}H]**1** as measured by LCMS was 6% t_0, 37% t_1 and 57% t_2.

The deuteration reactions of several other model compounds were monitored by Raman, with similar results. Deuteration of 2-phenylimidazole (**2**) with $[(cod)Ir(PPh_3)_2]BF_4$ resulted in consumption of a 1001 cm^{-1} aromatic band and generation of new peaks at 986 and 974 cm^{-1} which were attributed to 2-(2-deuterophenyl)imidazole and 2-(2,6-dideuterophenyl)imidazole, respectively. The reaction, initiated with 1.7 mol% catalyst, progressed slowly, with no detectable dideuterated product observed after 3 h as illustrated in Figure 3 (shown in graphic mode). Addition of 2.4 mol% of catalyst at 3.1 h

significantly accelerated the reaction, which asymptotically approached equilibrium over the next 17 h.

Deuteration of 2-phenylpyridine was monitored by observation of the peaks at 1001 cm^{-1} (starting material), 990 cm^{-1} (2′-deutero) and 972 cm^{-1} (2′,6′-dideutero). Likewise, labeling of **3** in the benzoyl ring using [(cod)$Ir(PPh_3)_2$]BF_4 or [(cod)$Ir(PCy_3)$(py)]PF_6 could be monitored (unlabeled, 1001 cm^{-1}; 2-deutero, 988 cm^{-1}; 2,6-dideutero, 975 cm^{-1}).



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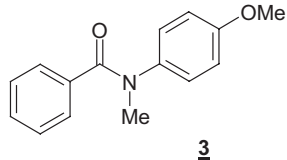

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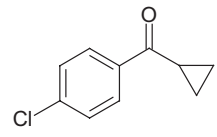


4

The Raman spectrum of 4-chlorophenyl cyclopropyl ketone (**4**) includes a peak at 1592 cm^{-1} which is sensitive to deuteration in the ring. As illustrated in Figure 4, the *ortho*-deuteration of this substrate is indicated by diminution of the 1592 peak and development of signals at 1585 cm^{-1} (monodeutero) and 1577 cm^{-1} (dideutero).

Raman monitoring of heterogeneously catalyzed tritiations

Many tritiation reactions utilize heterogeneous catalysts, such as palladium on carbon, in stirred solutions of substrates in organic solvents. Typical of such reactions are tritium–halogen exchange reactions of aryl halides and tritiogenation of olefins and acetylenes. The experiments described below show that the presence of suspended Pd/C does not seriously impede the

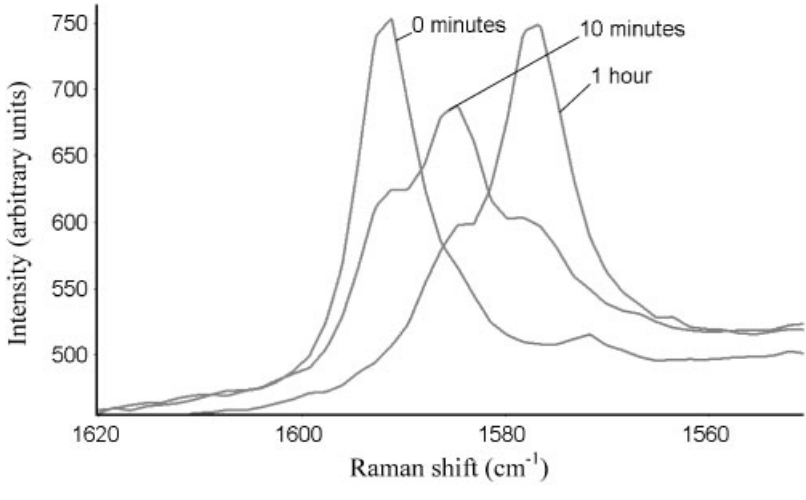


Figure 4. Overlay view of the deuteration of 4-chlorophenyl cyclopropyl ketone

ability to acquire a Raman signal, so that Raman spectroscopy can be used to follow the course of such reactions.

The first reaction investigated under heterogeneous catalyst conditions was the catalytic deuterogenation of methyl cinnamate. The Raman spectrum of methyl cinnamate includes two pairs of peaks, one pair at 1640 cm^{-1} (s) and 1602 cm^{-1} (m) and the other pair at 1205 cm^{-1} (s) and 1183 cm^{-1} (m). These peaks are absent in the spectrum methyl 3-phenylpropionate. As illustrated in Figure 5, the deuterogenation of methyl cinnamate could be monitored by observing the disappearance of the two pairs of peaks. All other peaks in the spectrum remained unchanged, indicating that the disappearance of these peaks correlated with a chemical change in the substrate. Figure 5 data indicate that the reaction was complete within 30 min. Analysis of the product showed clean conversion to methyl phenyl[2,3-$^2H_2$]propionate.

The catalytic reduction of *N*-acetyl-4-bromophenylalanine with deuterium gas was investigated as a representative of the tritium–halogen replacement class of reactions. The Raman spectrum of acetylphenylalanine includes an important peak at 1003 cm^{-1} which is absent in *N*-acetyl-4′-bromophenylalanine. Raman monitoring of the deuterium-bromine exchange reaction (Figure 6) shows the progress from starting material to product, as a peak emerges in the region of interest. Significantly, the product peak is at 987 cm^{-1} rather than at 1003 cm^{-1}, the frequency of unlabeled *N*-acetylphenylalanine. This shift is attributed to the presence of deuterium at C4 of the ring. NMR and mass spectrometric analyses were consistent with the expected product, *N*-acetyl-4′-deuterophenylalanine.

Mechanistic investigation

HDE of unsymmetrically substituted substrates offers the possibility that two different monodeutero isomers may be produced. Although this may be of little interest in a tritiation where the goal is to maximize tritium incorporation, the ability to measure the relative rates of exchange at different

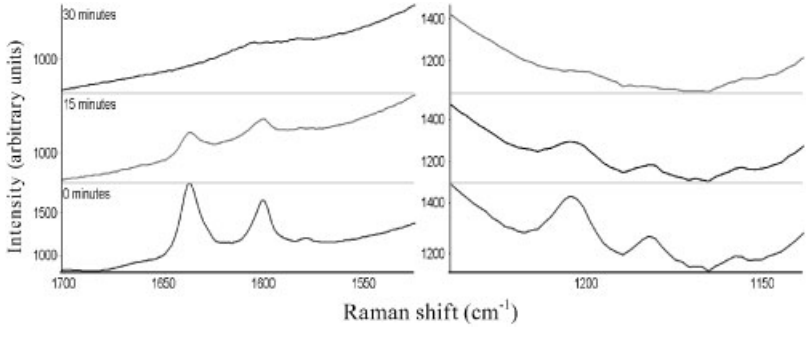


Figure 5. Staggered overlay views of methyl cinnamate deuterogenation

sites could provide mechanistic information about the labeling process. In order to investigate the consequences of this for Raman monitoring of HDE, we selected 3-methoxybenzoyl pyrrolidine (**5**). Authentic samples of 2-deutero-3-methoxybenzoyl pyrrolidine (**5a**) (85% deuterated), 6-deutero-3-methoxybenzoyl pyrrolidine (**5b**) (82% C6-d, 12% d_2) and 2,6-dideutero-3-methoxybenzoyl pyrrolidine (**5c**) (75% d_2, 19% d_1), were separately prepared as aids to spectral assignment. Relevant regions of their Raman spectra are shown in Figure 7. Monodeutero and dideutero isotopomers of **5** are easily differentiated from unlabeled **5** in the $\sim 1000\,cm^{-1}$ region, but the two monodeutero isomers **5a** and **5b** are indistinguishable in this region, as their peak maxima differ only by about $1\,cm^{-1}$. As shown in Figure 7, the spectra of **5a** and **5b** do differ enough at lower wave numbers that they could be

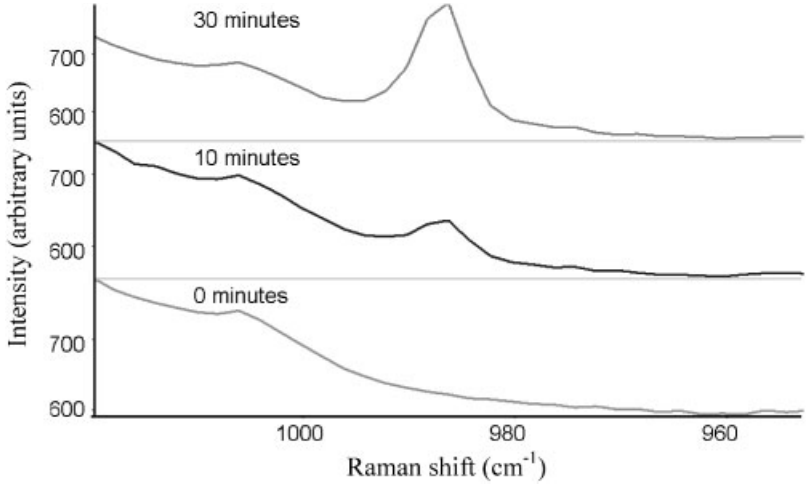


Figure 6. Staggered overlay view of *N*-acetyl-4′-bromophenylalanine deuterodebromination

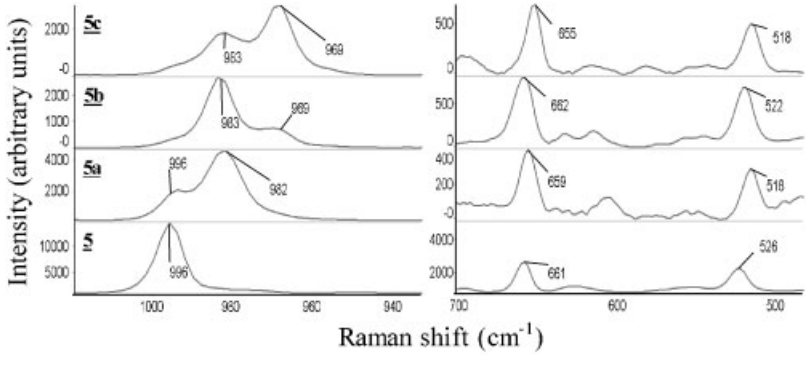
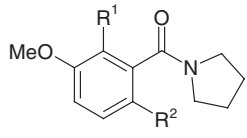


Figure 7. Isotope-sensitive bands of 3-methoxybenzoylpyrrolidine isotopomers

distinguished under favorable conditions. Unfortunately, these peaks were not very distinct from solvent background, so we were not able to distinguish during an actual labeling experiment between the rates of deuteration at C2 and at C6 in this substrate. Nevertheless, the principle has been demonstrated.



5: $R^1 = R^2 = H$
5a: $R^1 = D$; $R^2 = H$
5b: $R^1 = H$; $R^2 = D$
5c: $R^1 = R^2 = D$

Catalysts

In control experiments, Raman observations were made during the treatment of HDE catalysts with hydrogen or deuterium in the absence of substrate, in order to investigate the potential for interfering Raman spectral activity. This knowledge is important because high HDE catalyst loadings are sometimes used. Stirred solutions of $[(cod)Ir(PPh_3)_2]BF_4$ and $[(cod)Ir(PCy_3)(py)]PF_6$ were exposed with stirring to hydrogen or deuterium gas, and their Raman spectra were monitored for at least 12 h, over which period the organometallic complexes are first converted to active catalytic species, then to catalyst decomposition products analogous to those likely formed during actual labeling experiments. The spectrum of $[(cod)Ir(PCy_3)(py)]PF_6$ includes a weak peak at $1015\,cm^{-1}$. During the experiments, new peaks grew in at 990 and $1020\,cm^{-1}$ with hydrogen treatment, and at 996 and $1019\,cm^{-1}$ with deuterium treatment. Different changes may be produced upon treatment with tritium. Such changes could make it difficult to distinguish spectral changes associated with substrate, especially in those cases when high catalyst loadings are used. The spectrum of $[(cod)Ir(PPh_3)_2]BF_4$ includes a moderate-intensity peak at $1002\,cm^{-1}$ but it remained unchanged throughout the experiment, so that with this catalyst any spectral changes observed in this region can more safely be attributed to substrate.

Raman monitoring of experiments using (cod)Ir(1,1,1,5,5,5-hexafluoropentane-2,4-dionate)[7] to catalyze the deuterium exchange labeling of benzylamine and of 3-methoxy-5-trifluoromethylaniline (DMF, D_2) were unsuccessful because the Raman signal weakened drastically as the reactions turned black with precipitated or colloidal iridium. These results contrasted with the ability to obtain good signals throughout the course of reactions containing Pd/C.

Solvents

Several solvents were profiled for their utility in Raman-monitoring of isotopic labeling reactions. Methylene chloride is a highly suitable solvent since it lacks peaks in the regions 900–1100 and $1500–1700\,cm^{-1}$, where important substrate

signals often appear. Ethanol has interference-free windows 905–1025 and above 1545 cm^{-1}. DMF displays peaks at 1011 cm^{-1} (weak) and 1660 cm^{-1} (moderate); DMA 960, 1020 and 1636 cm^{-1} (all weak-moderate). These bands did not interfere with observation of the aryl breathing mode vibrations of undeuterated (1002 cm^{-1}), 2-deutero (989 cm^{-1}) and 2,6-dideutero (975 cm^{-1}) isotopomers of benzylamine at concentrations of 24 mg/ml. The spectrum of ethyl acetate contains several peaks in the 900–1100 cm^{-1} region which might prevent such observations, but its carbonyl stretch at 1737 cm^{-1} (medium) provides an alternative to the preceding solvents for use with substrates which have peaks of interest in the 1600–1700 cm^{-1} range. Most solvents lack peaks in the alkyne region (2100–2250 cm^{-1}) where strong substrate Raman signals may be used to monitor reactions such as Lindlar reductions. C–D and C–T vibrations stretching vibrations also occur near this region.

Conclusion

The results of initial studies demonstrate the successful application of Raman spectroscopy to noninvasive, real-time analysis of several different classes of labeling reactions in which tritium gas is normally used as the isotope source. These results indicate that Raman can be a useful tool for observing the progress of reactions, including disappearance of starting materials, formation of products, and in suitable cases the formation and consumption of isotopomeric intermediates. Further investigations continue into the applications of Raman spectroscopy to isotope labeling chemistry.

Experimental

Raman spectra were obtained on a Kaiser Optical Systems RXN1 spectrometer operating at 785 nm. Spectra were acquired using the integral software package HoloGRAMS 4.0 and processed with HoloReact in Matlab 6.5. Further software analysis of spectra was carried out using Nicolet OMNIC 6.0. Ambient room light was reduced and reactions shielded with a drape in order to minimize the appearance of spurious peaks in the spectra. Data collection parameters typically included 3-s acquisitions with 20 acquisitions averaged/spectrum. Deuterium exchange reactions were conducted using standard glassware attached to a glass vacuum manifold for manipulation of the reaction atmosphere. Tritiations and reactions modeling tritiations were conducted in specially fabricated glass vessels attached, via a Swagelok fitting, to a stainless steel manifold system (RC TRITEC AG, Teufen, Switzerland). Unless otherwise specified, all solvents were commercially available anhydrous reagent grade and all chemicals were ACS reagent grade or better from Aldrich.

3,5-Difluorobenzoyl pyrrolidine (**1a**). Pyrrolidine (2.83 ml, 34 mmol) was dissolved in diethyl ether (50 ml) with stirring in a round bottom flask under argon. 2,5-Difluorobenzoyl chloride (2.0 ml, 16 mmol) was added dropwise via

syringe, resulting in the formation of a white precipitate. The reaction mixture was stirred for 5 h then filtered to remove the white precipitate. The filtrate was washed with water (1×25 ml), 1N HCl (2×25 ml), H_2O (1×25 ml), and saturated $NaHCO_3$ (2×25 ml) and then was dried with $MgSO_4$. The solvent was evaporated by rotary evaporation and the residue dried *in vacuo* (1 Torr, rt, 30 min) to give 2.85 g (80% yield) of **1a** as a colorless oil. ^{1}H NMR (300.132 MHz, DMSO-d_6) δ 7.34 (dt, $J = 10.4$, 2.3 Hz, 1 H), 7.25 (dd, $J = 4.8$, 2.1 Hz, 2 H), 3.43 (m, 4 H), 1.84 (m, 4 H); MS (ES+) m/Z 212.

3,5-Difluoro[2,6-$^2H_2$]benzoyl pyrrolidine (**1b**). A 100 mg portion of **1a** and 10 mg of [(cod) $Ir(PPh_3)_2$]BF_4 were dissolved in 10 ml CH_2Cl_2 in a 50 ml round bottom flask containing a magnetic stir bar. The solution was frozen using a liquid nitrogen cooling bath, the flask was evacuated, and 1 atm of D_2 was introduced. The flask was allowed to warm to room temperature as expansion gases were allowed to escape through a bubbler, and the mixture was stirred for 16 h. The solvent was evaporated *in vacuo* and the residue was triturated with diethyl ether (2×5 ml), the supernatant was filtered through a syringetip PFTE membrane filter, and the filtrate evaporated *in vacuo* to provide 85 mg of colorless oil. ^{1}H NMR (300.132 MHz, DMSO-d_6) δ 7.34 (t, $J = 9.3$ Hz, 1 H), 7.25 (m, trace), 3.43 (m, 4 H), 1.84 (m, 4 H); MS (ES+, uncorr) m/Z 213 (9%), 214 (100%), 215 (14%).

N-(4-Methoxyphenyl)-N-methyl-benzamide (**3**). (4-Methoxyphenyl)methylamine (1 g, 7.3 mmol) was dissolved in anhydrous ether under argon in a 50 ml round bottom flask equipped with a stir bar. Benzoyl chloride (0.43 ml, 3.6 mmol) was added dropwise via a syringe, resulting in the formation of a white precipitate. The reaction mixture was stirred for 1 h and then filtered to remove the white precipitate. The filtrate was washed with 1N HCl (3×20 ml), H_2O (2×20 ml), and saturated $NaHCO_3$ (3×20 ml) and was dried with $MgSO_4$. The solvent was evaporated to give 0.83 g of solid. ^{1}H NMR (300.132 MHz, $CDCl_3$) δ 7.22 (m, 5 H), 6.95 (d, $J = 8.7$ Hz, 2 H), 6.73 (d, $J = 8.7$ Hz, 2 H), 3.74 (s, 3 H), 3.45 (s, 3 H); MS (ES+) m/Z 242.

3-Methoxybenzoyl pyrrolidine (**5**). Pyrrolidine (1.07 ml, 12.9 mmol) was dissolved in diethyl ether (50 ml) with stirring in a round bottom flask under argon. 3-Methoxylbenzoyl chloride (1.0 g, 5.8 mmol) was added dropwise via syringe, resulting in the formation of a white precipitate. The reaction mixture was stirred for 1 h and then filtered to remove the white precipitate. The filtrate was washed with water (1×20 ml), 1 N HCl (2×20 ml), H_2O (1×20 ml), and saturated $NaHCO_3$ (2×20 ml) and was dried with $MgSO_4$. The solvent was evaporated. The product was purified by flash chromatography (0–5% methanol in dichloromethane over 15 min) to give 0.38 g of colorless oil. ^{1}H NMR (300.132 MHz, C_6D_6) δ 7.36 (d, $J = 0.9$ Hz, 1 H), 7.16 (t, $J = 7.8$ Hz, 1 H), 7.25 (t, $J = 7.8$ Hz, 1 H), 6.91 (dt, $J = 7.8$, 0.9 Hz, 1 H), 3.66 (m, 2 H), 3.39 (s, 3 H), 3.05 (m, 2 H), 1.33 (m, 4 H); MS (ES+) m/Z 206.

2-Deutero-3-methoxylbenzoyl pyrrolidine (**5a**). A round bottom flask equipped with a stir bar was charged with **5** (0.1 g, 0.488 mmol), THF (2.5 ml), and TMEDA (81 µl, 0.536 mmol) under argon. This solution was cooled to –78°C. *Sec*-butyllithium (0.38 ml, 0.536 mmol) was added dropwise via syringe and the solution turned bright yellow. The reaction mixture was stirred 30 min, EtOD (287 µl, 0.488 mmol) was added dropwise, and the yellow color disappeared. The reaction was allowed to warm to room temperature. The solution was evaporated and the resulting residue was dissolved in ether, washed with H_2O (3 × 5 ml), and dried with $MgSO_4$. The ether was evaporated and the product purified by flash chromatography (0–5% methanol in dichloromethane over 15 min) to give 0.07 g of colorless oil. ^{1}H NMR (300.132 MHz, C_6D_6) δ 7.24 (dd, J = 7.5, 0.8 Hz, 1 H), 7.16 (t, J = 7.8 Hz, 1 H), 6.92 (dd, J = 7.5, 0.8 Hz, 1 H), 3.66 (m, 2 H), 3.39 (s, 3 H), 3.05 (m, 2 H), 1.33 (m, 4 H); MS (ES+, uncorr) m/Z 206 (15%), 207 (100%), 208 (12%).

6-Deutero-3-methoxylbenzoyl pyrrolidine (**5b**). A round bottom flask equipped with a stir bar was charged with **5c** (0.1 g, 0.488 mmol), THF (2.5 ml), and TMEDA (81 µl, 0.536 mmol) under argon. This solution was cooled to –78°C. *Sec*-butyllithium (0.38 ml, 0.536 mmol) was added dropwise via syringe and the solution turned bright yellow. The reaction mixture was stirred 30 min, EtOH (287 µl, 0.488 mmol) was added dropwise, and the yellow color disappeared. The reaction was allowed to warm to room temperature. The solution was evaporated and the resulting residue was dissolved in ether, washed with H_2O (3 × 5 ml), and dried with $MgSO_4$. After removing the ether, the product was purified by flash chromatography (0–5% methanol in dichloromethane over 15 min) to give 0.06 g of colorless oil. ^{1}H NMR (300.132 MHz, C_6D_6) δ 7.37 (d, J = 2.6 Hz, 1 H), 7.16 (d, J = 8.2 Hz, 1 H), 6.92 (dd, J = 8.2, 2.6 Hz, 1 H), 3.66 (m, 2 H), 3.39 (s, 3 H), 3.05 (m, 2 H), 1.33 (m, 4 H); MS (ES+, uncorr) m/Z 206 (7%), 207 (100%), 208 (28%).

2,6-Dideutero-3-methoxybenzoyl pyrrolidine (**5c**). A 250 ml round bottom flask equipped with a stir bar was charged with **5** (0.5 g, 2.44 mmol), Crabtree's catalyst (39 mg, 0.0488 mmol), and dichloromethane (49 ml). The reaction mixture was stirred under an atmosphere of D_2 for 4 h at which time additional catalyst (20 mg) in dichloromethane (3 ml) was added. This solution was stirred overnight under D_2. The solvent was evaporated and the resulting yellow oil was triturated with ether to precipitate the catalyst. The solid was filtered and the solvent was removed from the filtrate. The resulting oil was triturated and filtered again to leave a yellow oil. The product was purified by flash chromatography (0–5% methanol in dichloromethane over 15 min) to give 0.38 g of colorless oil. ^{1}H NMR (300.132 MHz, C_6D_6) δ 7.37 (0.2 H residual), 7.23 (0.2 H residual), 7.16 (d, J = 8.2 Hz, 1 H), 6.92 (d, J = 8.2 Hz, 1 H), 3.66 (m, 2 H), 3.39 (s, 3 H), 3.05 (m, 2 H), 1.33 (m, 4 H); MS (ES+, uncorr) m/Z 206 (0%), 207 (32%), 208 (100%), 209 (12%).

N-acetyl-4-bromophenylalanine deuterium-halogen replacement. *N*-acetyl-4-bromophenylalanine (0.05 g, 0.17 mmol), triethylamine (0.15 ml, 1 mmol), 5% Pd/C (10 wt%, 5 mg), and absolute ethanol (2.5 ml) were combined in a 25 ml pear-shaped flask equipped with a stir bar. Three cycles of evacuation and deuterium filling were performed. A Raman spectrum was acquired before stirring was started. After 50 min, the reaction mixture was filtered through a syringetip PTFE membrane to remove the catalyst. The solvent was removed to leave a white solid. ^{1}H NMR (300.132 MHz, C_6D_6) δ 8.15 (d, $J = 8.0$ Hz, 1 H), 7.32 (m, 4 H), 4.40 (td, $J = 8.7$, 4.8 Hz, 1 H), 2.91 (m, 2 H), 1.78 (s, 3 H); MS (ES+) m/Z 209; <2% content of m/Z 208.

Deuterogenation of methyl cinnamate. A 64 mg portion of methyl cinnamate was dissolved in 5 ml of absolute ethanol in a 25 ml pear-shaped flask equipped with a magnetic stir bar. A 7 mg portion of 5% Pd/C was added and the flask was attached to the glass manifold. Stirring was initiated, and Raman acquisition was begun in order to record a starting spectrum. Then in quick succession three cycles of partial evacuation and deuterium gas introduction were conducted; reaction stirring and spectra acquisition then continued for the next 30 min. At this time the catalyst was removed by passage of the reaction mixture through a syringetip PTFE membrane, and the filtrate was evaporated to give 58 mg of colorless oil. ^{1}H NMR (CD_2Cl_2) was consistent with clean deuterogenation: δ 7.58–6.96 (m, 5 H, aryl H), 3.68 (s, 3 H, $COOCH_3$), 2.94 (br s, 1.0 H, PhCDH-), 2.64 (br s, 1.0 H, -CDHCOOR); MS (ES+) m/Z 107 (base peak, PhCDHCDH), 135 (40%, PhCDHCDHCO).

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