

Reaction Mixture Analysis by Fast Atom Bombardment Mass Spectrometry: Palladium-Mediated Reactions of Organomercurials with Glycols

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Abstract: Analysis of organometallic reaction mixtures by fast atom bombardment (FAB) mass spectrometry in glycerol-acetic acid or triethanolamine matrices has permitted direct observation of previously undetected reaction intermediates. Thus, in FAB mass spectra of aliquots of reaction mixtures, formulated by addition of equimolar portions of an aryl or heterocyclic mercuric acetate, a glycol (enol ether), and palladium(II) acetate in acetonitrile, ions were observed which correspond to the aryl (heterocyclic) palladium transmetalation product, previously undetected but postulated on the basis of strong indirect evidence. Similarly, FAB mass spectra of such reaction mixtures exhibited ions assignable to adducts formed by addition of aryl (heterocyclic) palladium across the enol ether carbon-carbon double bond. The principal ions observed in FAB mass spectra of these organometallic reaction mixtures accord closely with species postulated on the basis of product isolation and reaction mechanism studies. This study demonstrates the effectiveness of direct reaction mixture analysis by FAB mass spectrometry for study of solution dynamics in complex organometallic reactions.

Characterization of liquid-phase systems remains a challenging analytical problem. The recent development of mass spectrometric techniques which use liquid matrices (summarized by Chan and Cook^{2,3}) has provided powerful new tools for study of solution dynamics. Fast atom bombardment (FAB) mass spectrometry,^{4,5} the most widely used of the mass spectrometric techniques for analysis of ions derived from solution, has already yielded impressive results. Caprioli was able to determine dissociation constants of weak acids in solution⁶ and to monitor the progress of an enzyme-catalyzed reaction⁷ by measurement of the relative abundances of selected ions present in FAB mass spectra of reaction solutions. Saito and Kato⁸ detected short-lived glutathione conjugates of an aryl nitroso carcinogen by carrying out the conjugation reaction in a glycerol matrix within a mass spectrometer ion source and periodically recording FAB mass spectra of reaction mixture components. Johnstone and co-workers⁹⁻¹¹ have correlated ion abundances in FAB mass spectra with changes in solution concentrations of metal cation-crown ether complexes.

Of particular relevance to the present study, in which FAB mass spectrometry is used to analyze organometallic reaction mixture solutions, are applications of FAB mass spectrometry in organometallic chemistry.¹² Currently, the critical test compound used to evaluate the capability of a mass spectrometric technique for polar, involatile molecules seems to be the organometallic natural product, cyanocobalamin (vitamin B-12, MW 1354).¹³ Barber and co-workers¹⁴ produced FAB mass spectra of vitamin B-12 and related compounds in 1981. FAB mass spectra of other

corrins,¹⁵ siderophores,¹⁶ technetium salts,¹⁷ and other organometallics,¹⁸⁻²⁶ have been reported. The interaction of the anti-cancer drug cisplatin with nucleosides has been studied using FAB mass spectrometry.²⁷ A relationship has been noted^{5,18} between processes observed by FAB mass spectrometry (e.g., ligand loss selectivity) and known solution chemistry of the organometallic species studied.

FAB mass spectrometry, which efficiently samples preformed ions present in a liquid matrix,^{6,7,28} can provide information regarding condensed-phase reactions.^{2-7,9,18,28-30} In the present study, we have employed mass spectrometry in conjunction with ongoing synthetic efforts to elucidate complex organometallic processes involving palladium(II)-mediated reactions of aryl and heterocyclic mercuric acetates with chiral furanoid³¹ and pyranoid³² glycols (cyclic enol ethers). These reactions present attractive opportunities for correlating solution species observed by FAB mass

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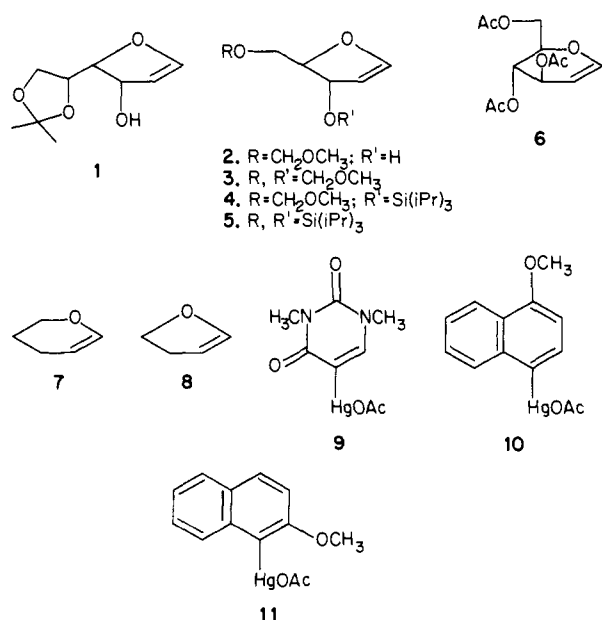
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spectrometry with data derived from synthetic and mechanistic studies. The reactions, which occur regio- and stereospecifically and lead to C-glycosides,³³ are complex, and postulated mechanisms^{31,32,34} involve a number of (usually) undetected metal-containing complexes.³⁵

The specific goal of this study was the direct detection of organometallic reaction intermediates within the reaction mixture by mass spectrometry. The results are encouraging; a number of metal-containing species have been identified by direct addition of reaction mixture aliquots to a liquid matrix of low volatility followed by FAB mass spectrometric analysis. FAB mass spectrometric analysis of reaction mixtures, in concert with product characterization studies, has contributed to an understanding of these complex, organometallic, reaction systems.

Experimental Section

Solvents and Reagents. Acetonitrile, used to prepare reaction mixtures, was spectral grade and used as received. Glycerol and triethanolamine, used as matrix materials, were of reagent grade and used without pretreatment. Palladium(II) acetate, triphenylphosphine 3,4,6-tri-*O*-acetyl-D-glucal³⁶ (6), 3,4-dihydro-2*H*-pyran (7), and 2,3-dihydrofuran (8)



were commercial samples used as received. Furanoid glycols 1–5³¹ and organomercurials 9–11^{37,38} were prepared as described.

Reaction Mixture Preparation. Reaction mixtures were prepared by combining 0.05 mmol of palladium(II) acetate, 3,4-dihydro-2*H*-pyran (7), 2,3-dihydrofuran (8), or a glycol (1–6), and an organomercury compound (9–11) in 2 mL of acetonitrile. Reaction mixtures were stirred at room temperature for the duration of the experiment.

Mixtures containing two reactants were prepared by combining 0.05 mmol of each reactant in 2 mL of acetonitrile; mass spectra of pure compounds were obtained from solutions containing 0.05 mmol of compound in 2 mL of acetonitrile. When triphenylphosphine was used, 2 equiv (0.10 mmol, 26 mg) was added to the reaction mixture 5 min after addition of other reactants.

Preparation of the Target. Three microliters of matrix material (glycerol or triethanolamine) was applied as a thin film to a 20-mm²

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Table I. Principal Ions in FAB Mass Spectra of Glycols 2, 4–6^a

| glycol | ion (<i>m/z</i>) | rel abund | ion composition |
|--------|--------------------|-----------|--|
| 2 | 161 | 20 | MH ⁺ |
| | 159 | 13 | [MH ⁺ – H ₂] ⁺ |
| | 115 | 100 | [MH ⁺ – C ₂ H ₆ O] ⁺ |
| 4 | 317 | 6 | MH ⁺ |
| | 315 | 12 | [MH ⁺ – H ₂] ⁺ |
| | 273 | 100 | [MH ⁺ – C ₃ H ₈] ⁺ |
| 5 | 429 | 3 | MH ⁺ |
| | 427 | 16 | [MH ⁺ – H ₂] ⁺ |
| | 385 | 100 | [MH ⁺ – C ₃ H ₈] ⁺ |
| 6 | 273 | 5 | MH ⁺ |
| | 271 | 8 | [MH ⁺ – H ₂] ⁺ |
| | 213 | 100 | [MH ⁺ – HOAc] ⁺ |

^a Obtained from acetonitrile solutions using a glycerol–acetic acid matrix.

Table II. Principal Ions in FAB Mass Spectra of Organomercuric Acetates

| RHgOAc | matrix ^a | ion (<i>m/z</i>) ^b | rel abund | ion composition |
|--------|---------------------|---------------------------------|-----------|---|
| 9 | A | 525 | 24 | [RHg ⁺ + 2 glycerols] ⁺ |
| | | 481 | 44 | [RHgR + H ⁺] ⁺ |
| | | 433 | 100 | [RHg ⁺ + glycerol] ⁺ |
| | | 341 | 54 | RHg ⁺ |
| | | 141 | 67 | [RH + H ⁺] ⁺ |
| | | 490 | 100 | [RHg ⁺ + triethanolamine] ⁺ |
| 10 | A | 517 | 18 | [RHgR + H ⁺] ⁺ |
| | B | 157 | 100 | R ⁺ |
| | | 508 | 100 | [RHg ⁺ + triethanolamine] ⁺ |
| 11 | B | 464 | 17 | [RHg ⁺ + diethanolamine] ⁺ ^c |
| | | 508 | 100 | [RHg ⁺ + triethanolamine] ⁺ |
| | | 464 | 19 | [RHg ⁺ + diethanolamine] ⁺ ^c |

^a Matrix A is glycerol–acetic acid; matrix B is triethanolamine. ^b Based on ²⁰²Hg. ^c Reference 49.

molybdenum target using a clean glass rod. One microliter of acetic acid, 1% solution in water, was added to the glycerol film prior to the addition of the sample.^{28,39–42} A 3- μ L aliquot of a reaction mixture was combined with the matrix material by injection into the matrix film using a microliter syringe (~ 75 μ mol of each reactant was present on the target). Samples were inserted into the mass spectrometer ion source through a vacuum lock using a direct insertion probe. The probe was rotated to obtain optimum secondary ion flux.⁴³ The minimum time required to remove a sample from the reaction vial and record a spectrum was about 3 min.

Mass Spectrometry. Mass spectra were obtained using a DuPont (CEC) 21-110B mass spectrometer modified to operate in the fast atom bombardment (FAB) mode. Argon fast atom beams were produced with an Ion Tech, Model B11NF, saddle-field neutral beam source with primary atom beam energy variable between 5 and 8 keV. Varying atom beam energy within this range did not affect the appearance of the resulting spectra. Spectra reported in this study were obtained using atom beam energies of 5.8 to 6.4 keV. The primary beam source was mounted perpendicular to the direct insertion probe, pumped differentially to enhance pumping speed in the mass spectrometer ion source, and water cooled to improve its lifetime. The primary source was mounted on an X–Y platform so that the atom beam could be optimally aimed at the target. The angle of incidence of the primary beam on the sample target was approximately 70°.

Acceleration voltages of either 6 kV (1200 dalton mass range) or 8 kV (800 dalton mass range) were employed and the sample target was held at a slightly positive potential (<100 V) relative to the accelerating

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Table III. Principal Ions in FAB Mass Spectra of Reaction Mixtures Containing Palladium(II) Acetate and an Organomercuric Acetate^{a,b}

| organo-mercuric acetate | triphenyl-phosphine ^c | FAB matrix ^d | ion (<i>m/z</i>) ^e | ion composition |
|-------------------------|----------------------------------|-------------------------|---------------------------------|--|
| 9 | A | A | 106 | Pd ⁺ |
| | | | 198 | [Pd ⁺ + glycerol] ⁺ |
| | | | 279 | R ₂ H ⁺ |
| | | | 290 | [Pd ⁺ + 2 glycerols] ⁺ |
| | | | 341 | RHg ⁺ |
| | | | 255 | [Pd ⁺ + triethanolamine] ⁺ |
| | B | A | 490 | [RHg ⁺ + triethanolamine] ⁺ |
| | | | 279 | R ₂ H ⁺ |
| | | | 341 | RHg ⁺ |
| | | | 507 | [RPdPPh ₃] ⁺ |
| | | | 630 | [Pd(PPh ₃) ₂] ⁺ |
| | | | 507 | [RPdPPh ₃] ⁺ |
| 10 | A | A | 630 | [Pd(PPh ₃) ₂] ⁺ |
| | | | 106 | Pd ⁺ |
| | | | 198 | [Pd ⁺ + glycerol] ⁺ |
| | | | 315 | R ₂ H ⁺ |
| | | | 255 | [Pd ⁺ + triethanolamine] ⁺ |
| | | | 508 | [RHg ⁺ + triethanolamine] ⁺ |
| | B | A | 315 | R ₂ H ⁺ |
| | | | 525 | [RPdPPh ₃] ⁺ |
| | | | 630 | [Pd(PPh ₃) ₂] ⁺ |
| | | | 508 | [RHg ⁺ + triethanolamine] ⁺ |
| | | | 525 | [RPdPPh ₃] ⁺ |
| | | | 630 | [Pd(PPh ₃) ₂] ⁺ |
| 11 | B | B | 508 | [RHg ⁺ + triethanolamine] ⁺ |
| | | | 525 | [RPdPPh ₃] ⁺ |
| | | | 630 | [Pd(PPh ₃) ₂] ⁺ |
| | | | 508 | [RHg ⁺ + triethanolamine] ⁺ |
| | | | 525 | [RPdPPh ₃] ⁺ |
| | | | 630 | [Pd(PPh ₃) ₂] ⁺ |

^aEquimolar amounts of RHgOAc and Pd(OAc)₂ were mixed in acetonitrile (see Experimental Section). ^bOther ions (*m/z* 359 and 403) corresponding to Pd²⁺ triethanolamine complexes were observed (see Figure 1b). ^cAdded 5 min after mixing of other reagents. ^dMatrix A is glycerol-acetic acid; matrix B is triethanolamine. ^eBased on ¹⁰⁶Pd and ²⁰²Hg.

electrode to aid in extracting sample ions.

Electronic ion detection, utilizing a channeltron electron multiplier and oscillographic recording, was employed. Ions of the matrix compound were used to assign masses, which were counted by hand. In cases where matrix ions were not observed, the palladium(I) ion cluster was used as a reference. Values of mass to charge ratio (*m/z*) for metal containing ions are reported using the value of the most abundant metal isotope, ¹⁰⁶Pd or ²⁰²Hg. Comparison of experimental isotope ratios with known abundances showed positive deviations in intensities of 2 to 35% relative to ¹⁰⁶Pd and ²⁰²Hg (av 10.5%) owing to FAB background ions at every mass. In no instance did the deviations from theory in the isotope ratios observed preclude unambiguous distinction between Pd and Hg.

Results

Fast atom bombardment (FAB) mass spectrometric data for reactants and two- and three-component reaction mixtures are summarized in Figures 1 and 2 and Tables I-V. In Figure 1 are FAB mass spectra of palladium(II) acetate and mercury(II) acetate. Table I contains the principal ions observed in the mass spectra of reactant glycols (2, 4-6) obtained using glycerol-acetic acid as the FAB matrix. Similar data for organomercurials (9-11) are in Table II. In Table III are mass spectrometric data for mixtures of palladium(II) acetate and organomercurials 9-11. In Tables IV and V are FAB mass spectrometric data for three-component reaction mixtures composed of palladium(II) acetate, organomercurials 9 or 10, and a glycol (enol ether, 1-8). Palladium-containing ions present in the FAB mass spectra are summarized in Table IV and ions related to the C-nucleoside products of the palladium-mediated reactions are listed in Table V. A typical FAB mass spectrum obtained in this study—that of a reaction mixture containing palladium(II) acetate, organomercurial 9, and glycol 6—is shown in Figure 2.

Table IV. Palladium-Containing Ions Detected in FAB Mass Spectra of Reaction Mixtures Involving Equimolar Palladium(II) Acetate, an Organomercuric Acetate, and a Glycol (Enol Ether)

| glycol | RHgOAc | FAB matrix ^a | ion (<i>m/z</i>) ^b | ion composition |
|--------|----------------------------|-------------------------|---------------------------------|--|
| 1 | 9 | A | 472 | [RPd(glycol)(MeCN)] ⁺ |
| | | | 413 | [<i>m/z</i> 472 - MeCN - H ₂ O] ⁺ |
| | | | 383 | [(R ₂ - H ⁺) ⁻ + Pd ²⁺] ⁺ |
| | | | 245 | RPd ⁺ |
| | | | 446 | [RPd(glycol)(MeCN)] ⁺ |
| | | | 405 | [RPd(glycol)] ⁺ |
| | | | 387 | [<i>m/z</i> 405 - H ₂ O] ⁺ |
| | | | 245 | RPd ⁺ |
| | | | 449 | [RPd(glycol)] ⁺ |
| | | | 387 | [<i>m/z</i> 449 - HOCH ₂ OCH ₃] ⁺ |
| | | | 751 | ^c |
| | | | 4 | 10 |
| 673 | [RPd(glycol)] ⁺ | | | |
| 5 | 9 | B | 691 | [RPd(glycol)] ⁺ |
| | | | 304 ^d | [RPd(MeCN)] ⁺ |
| 6 | 9 | A | 575 ^e | [PdOAc(glycol + R - H)] ⁺ |
| | | | 517 | [RPd(glycol)] ⁺ |
| | | | 457 | [<i>m/z</i> 517 - HOAc] ⁺ |
| | | | 397 | [<i>m/z</i> 517 - 2HOAc] ⁺ |
| | | | 245 | RPd ⁺ |
| | | | 535 | [RPd(glycol)] ⁺ |
| | | | 304 ^d | [RPd(MeCN)] ⁺ |
| | | | 467 | [RPd(pyran + R - H)] ⁺ |
| | | | 387 ^e | [PdOAc(dihydropyran + R - H)] ⁺ |
| | | | 383 ^d | [(R ₂ - H ⁺) ⁻ + Pd ²⁺] ⁺ |
| | | | 329 | [RPd(dihydropyran)] ⁺ |
| | | | 245 | RPd ⁺ |
| 8 | 9 ^f | A | 453 | [RPd(dihydrofuran + R - H)] ⁺ |
| | | | 315 ^d | [RPd(dihydrofuran)] ⁺ |
| | | | 209 | [dihydrofuranyl + R + H] ⁺ |

^aMatrix A is glycerol-acetic acid; matrix B is triethanolamine. ^bBased on ¹⁰⁶Pd. ^cCorresponds to [RPd(glycol)(MeCN)(triethanolamine)]⁺. ^dObserved only at short (<1 min) reaction times. ^eObserved only at long (<60 min) reaction times or with excess Pd(OAc)₂. When the reaction mixture contained 2 equiv of glycol, the ion was not detected. ^fIons related to RHgOAc (Table II) were also detected.


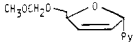
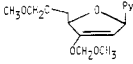
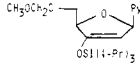
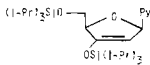
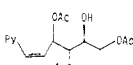
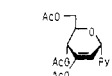

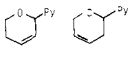
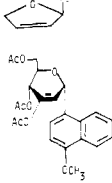
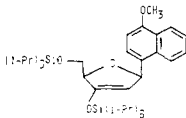
Mass spectra were recorded using aliquots taken from reaction mixtures at various time intervals after mixing. Except as noted (see below and Table IV), spectra of reaction mixture aliquots recorded 5 min following reactant mixing differed little from spectra of aliquots removed after 1 h. At longer reaction time (>12 h) organometallic species were not observed and only ions derived from the product C-nucleosides were present in the mass spectra.

Matrix Selection. Glycerol, the most widely used matrix material for FAB mass spectrometry,⁴³ is miscible with the reaction solvent used (acetonitrile), and no evidence of separation was noted when reaction mixture aliquots were combined with glycerol. Subjection of such mixtures to FAB mass spectrometric analysis yielded spectra; however, ions observed were of relatively low abundance and ion emission was often of short (<5 min) duration. Such "fading" of FAB mass spectra has been noted,^{39,44} and addition of acid to a glycerol matrix has been used successfully to overcome spectral "fading" and to increase ion emission.^{28,41,45} Addition of a small amount (1%) of acetic acid (chosen because acetate ions were already present in the reaction mixtures) resulted in increased ion currents which persisted for up to 45 min. Triethanolamine, introduced as a matrix for FAB mass spec-

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Table V. Ions Related to C-Nucleoside Products of Palladium-Mediated Reactions of Organomercurials with Glycals Observed in FAB Mass Spectra of Reaction Mixtures

| reactants | C-nucleoside product(s) ^f | mol wt | FAB matrix ^a | ion (<i>m/z</i>) | ion composition | |
|--------------------|---|--------|-------------------------|---|--|--|
| 9 + 1 ^b |  | 324 | A | 325 | MH ⁺ | |
| | | | | 323 | [MH ⁺ - H ₂] ⁺ | |
| 9 + 2 ^b |  | 282 | A | 283 | MH ⁺ | |
| 9 + 3 ^b |  | 342 | A | 343 | MH ⁺ | |
| | | | | 341 | [MH ⁺ - H ₂] ⁺ | |
| 9 + 4 ^b |  | 454 | A, B | 455 | MH ⁺ | |
| | | | | 453 | [MH ⁺ - H ₂] ⁺ | |
| 9 + 5 ^b |  | 564 | B | 565 | MH ⁺ | |
| | | | | 563 | [MH ⁺ - H ₂] ⁺ | |
| 9 + 6 ^c |  | 412 | A | 413 | MH ⁺ | |
| | | | |  | 410 | MH ⁺ |
| | | | | | 409 | [MH ⁺ - H ₂] ⁺ |
| 9 + 7 ^d |  | 352 | A | 353 | MH ⁺ | |
| | | | | 351 | [MH ⁺ - H ₂] ⁺ | |
| | | | | 222 | MH ⁺ | |
| 9 + 8 ^e |  | 208 | A | 221 | [MH ⁺ - H ₂] ⁺ | |
| | | | | 209 | MH ⁺ | |
| 10 + 6 |  | 428 | A | 207 | [MH ⁺ - H ₂] ⁺ | |
| | | | | 427 | [MH ⁺ - H ₂] ⁺ | |
| 10 + 5 |  | 584 | B | 583 | [MH ⁺ - H ₂] ⁺ | |

^a Matrix A is glycerol-acetic acid; matrix B is triethanolamine. ^b Reference 31. ^c Reference 32. ^d Reference 55. ^e Reference 38. ^f Py = 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedion-5-yl.

trometry by Harada and co-workers,⁴⁶ was also used and proved effective in a number of instances (Tables II-IV).

Addition of a reaction mixture aliquot to either glycerol-acetic acid or triethanolamine quenched the reaction. This was demonstrated most convincingly in a study of reaction mixtures involving 2,3-dihydrofuran (**8**) and 3,4(2*H*)-dihydropyran (**7**) which proceed rapidly to product.⁴⁷ For example, removal of an aliquot of a reaction mixture containing **8**, 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedion-5-ylmercuric acetate³⁷ (**9**), and palladium(II) acetate (Table IV) and addition to glycerol-acetic acid within 1 min of reactant mixing yielded FAB mass spectra which exhibit an ion at *m/z* 315 corresponding to an adduct formed by insertion of the enol ether double bond of **8** into the Pd-C bond of an organopalladium reagent formed from **9**. The ion at *m/z* 315 was not observed when aliquots of reaction mixtures were taken following more than 1 min of reaction time. FAB mass spectra of these reaction mixture aliquots exhibited prominent ions assignable to a protonated molecular ion of the coupled product at

m/z 209 (Table IV). By combining the reactants in a 1:1 mixture of acetonitrile and glycerol and placing the reaction mixture directly on the FAB target, mass spectra exhibiting the ion at *m/z* 315 were detected up to 15 min after reactant mixing.

FAB Mass Spectra of Palladium(II) Acetate and Mercury(II) Acetate. FAB mass spectra of compounds (salts) which contain a (formal) dicationic center exhibit ions of two types: (a) ions resulting from one-electron reduction of the dication [C²⁺ + e⁻ → C⁺] and (b) cation-anion clusters (e.g., [C²⁺A⁻]).⁴⁸ The spectrum of palladium(II) acetate obtained using a glycerol-acetic acid matrix (Figure 1a) exhibits only ions involving metal reduction, i.e., Pd⁺ at *m/z* 106, (Pd⁺ + glycerol)⁺ at *m/z* 198, and (Pd⁺ + 2 glycerols)⁺ at *m/z* 290. However, when a triethanolamine matrix was used, the resulting spectrum was significantly different (Figure 1b). Under these conditions, ions involving both palladium reduction (*m/z* 255) and cluster formation (*m/z* 359 and 403) are present. The anions incorporated in these cluster ions are derived from triethanolamine (or diethanolamine⁴⁹) by

(46) Harada, K.; Suzuki, M.; Kambara, H. *Org. Mass Spectrom.* **1982**, *17*, 386-391.

(47) Product isolation studies indicate that while product appears within minutes, maximum yields are obtained after several hours reaction time.³⁸

(48) Barofsky, D. F.; Giessmann, U. *Int. J. Mass Spectrom. Ion Phys.* **1983**, *46*, 359-362.

(49) Whether diethanolamine was present as an impurity or is formed in a FAB-mediated process had not been determined.

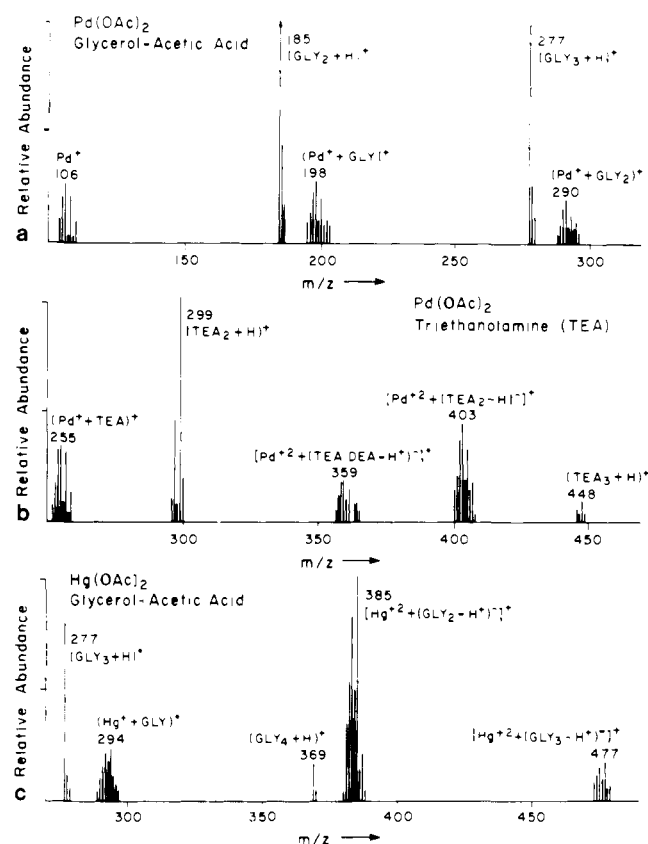


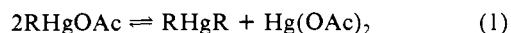
Figure 1. Fast atom bombardment mass spectra of palladium(II) acetate obtained using glycerol-acetic acid (a) and triethanolamine (b) as matrix materials and of mercury(II) acetate using a glycerol-acetic acid matrix (c).

loss of a proton. It seems likely that the deprotonated ethanolamine unit serves as a bidentate ligand for palladium in these ions. The failure to observe ions incorporating acetate is indicative of the very weak association of palladium with this anion.⁵⁰

The FAB mass spectrum of mercury(II) acetate produced using the glycerol-acetic acid matrix (Figure 1c) exhibits an ion involving metal reduction ($\text{Hg}^+ + \text{glycerol}$)⁺ at m/z 294 and cluster ions incorporating deprotonated glycerol [$\text{Hg}^{2+} + 2 \text{ glycerols} - \text{H}^+$]⁺ at m/z 385 and [$\text{Hg}^{2+} + 3 \text{ glycerols} - \text{H}^+$]⁺ at m/z 477. Again, no ions incorporating an acetate anion were observed.

FAB Mass Spectra of Glycols. A protonated molecular ion, MH^+ , was observed for each of four representative glycols (**2**, **4**–**6**) when FAB mass spectra were recorded using a glycerol-acetic acid matrix (Table I). The protonated molecular ion was of relatively low abundance; in each spectrum, more abundant ions resulted from loss of a small neutral molecule from MH^+ . An ion corresponding to loss of H_2 from MH^+ is relatively prominent in each of the spectra.

FAB Mass Spectra of Organomercuric Acetates. When triethanolamine was used as a matrix for organomercuric acetates **9**–**11**, the FAB mass spectra (Table II) were dominated by ions (m/z 490 for **9**, m/z 508 for **10** and **11**) corresponding to [$\text{RHg}^+ + \text{triethanolamine}$]⁺ formed by association of triethanolamine with the metal center and loss of acetate anion. The ion types observed in FAB mass spectra obtained using the glycerol-acetic acid matrix indicate that, in this matrix, a number of reactions occur. Thus, in the spectrum of **9**, in addition to ions indicative of the free organomercuric cation RHg^+ (m/z 341) and RHg^+ complexed with glycerol solvent (m/z 433 and 525), an ion (m/z 481) is present which corresponds to a protonated diorganomercurial [R_2HgH]⁺ indicative of disproportionation (eq 1).



Also present in the spectrum of **9** is an ion at m/z 141 which corresponds to protonated 1,3-dimethyl-2,4-pyrimidinedione. Formation of this ion involves two protonations: replacement of the mercuric ion (eq 2) and a second protonation to form a cation.



The FAB mass spectrum of **10**, obtained using the glycerol-acetic acid matrix, also exhibits an ion (m/z 517) indicative of organomercurial disproportionation (eq 1). No ion corresponding to protonolysis of the R–Hg bond is present; instead, an intense ion is present at m/z 157 assignable to a methoxynaphthalenyl cation (R^+). Ions derived from mercury(II) acetate are not seen in these spectra although mercury(II) acetate formation (via the reactions shown in eq 1 and 2) is probable.

FAB Mass Spectra of Reaction Mixtures Containing Equimolar Palladium(II) Acetate and an Organomercuric Acetate. Admixture of palladium(II) acetate and an organomercuric acetate (**9**–**11**) in acetonitrile followed by FAB mass spectrometric analysis using either glycerol-acetic acid or triethanolamine as the matrix yielded spectra in which the few organometallic ions present (Table III) are derived from the organomercuric acetate reactants. In each spectrum, ions were observed (i.e., R_2H^+) which indicate that the organic moieties bonded to mercury had undergone dimerization. Although this dimerization is palladium-catalyzed,^{51,52} in no instance was an ion corresponding to an organopalladium species observed. If triphenylphosphine was added to the reaction mixtures to stabilize organopalladium intermediates, ions corresponding to [RPdPPh_3]⁺ were present in spectra obtained using either glycerol-acetic acid or triethanolamine as matrix.

FAB Mass Spectra of Reaction Mixtures Containing Equimolar Palladium(II) Acetate, a Glycol, and an Organomercurial. Palladium-mediated reaction of 3,4,6-tri-*O*-acetyl-D-glucal³⁶ (**6**) with 1,3-dimethyl-2,4-(1*H*,3*H*)-pyrimidinedion-5-ylmercuric acetate³⁷ (**9**) leads to an intermediate palladium-containing adduct which, following stabilization by provision of a triphenylphosphine ligand, can be isolated and characterized.^{19,32} The FAB mass spectrum of this isolated organopalladium adduct¹⁹ exhibits prominent ions at m/z 779 and 517 characteristic of the intact adduct minus chloride ion⁵³ (m/z 779) and the adduct minus triphenylphosphine and chloride ion⁵³ (m/z 517). A FAB mass spectrum of a reaction mixture of glycol **6**, organomercurial **9**, and palladium(II) acetate without added triphenylphosphine (Figure 2) also exhibits an ion at m/z 517 indicative of the presence in solution of an intact organopalladium adduct.^{19,32} Other palladium-containing ions are observed at m/z 473, 457, 397, and 245, and an ion at m/z 341 arising from the pyrimidinylmercuric derivative **9** is present. Noteworthy in this spectrum (Figure 2) are ions (m/z 413, 411, and 353) corresponding to the three organopalladium adduct decomposition products which have been isolated and characterized.³²

Tables IV and V contain FAB mass spectrometric data for other three-component reaction mixtures. In each spectrum (Table IV), evidence was present for the transmetalation step (eq 3) which precedes glycol adduct formation.³² When pyrimidinylmercuric acetate **9** was used, an ion at m/z 245 corresponding to RPd^+ was sometimes observed. In contrast, spectra of reaction mixtures containing 4-methoxynaphthylmercuric acetate³⁸ (**10**) exhibited no ions corresponding to RPd^+ ; in every instance ions incorporating the 4-methoxynaphthyl residue and a palladium also include a molecule of acetonitrile solvent or a glycol moiety.

Also present in these spectra (Table IV) are ions which incorporate all three reactants (i.e., the organic moiety (R) of the organomercurial, a Pd(II) center, and a glycol) and are indicative of organopalladium-glycol adducts^{19,31,32,54} in the reaction mixtures. Ions observed in which Pd(II) is associated with two organomercurial derived aryl groups are suggestive that the palladium

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(53) The actual process is probably protonation by glycerol and loss of HCl (see ref 18).

(54) Hacksell, U.; Daves, G. D., Jr. *Organometallics* **1983**, *2*, 772–775.

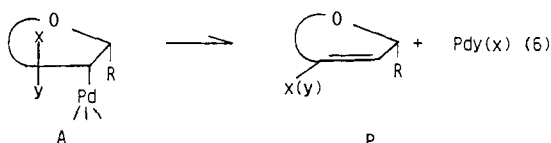
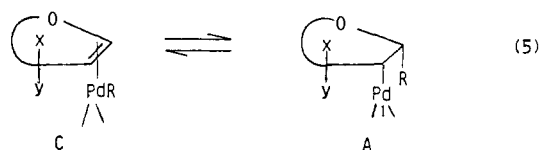
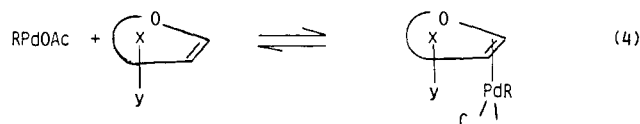
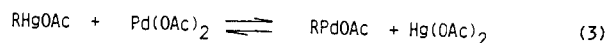
(50) Dehand, J.; Mauro, A.; Ossor, H.; Pfeffer, M.; Santos, R. H. DeA; Lechat, J. R. *J. Organometal. Chem.* **1983**, *250*, 537–550.

transmetalation product (RPdOAc) disproportionates as does the organomercuric acetate precursor (eq 1).

These FAB mass spectra also exhibited ions corresponding to the known C-nucleoside products of each of the reactions (Table V). As was observed in the FAB mass spectra of glycals (Table I), the C-nucleosides exhibit both MH^+ and $[MH^+ - H_2]^+$ ions.

Discussion

The reactions selected for this initial study involve the palladium(II) mediated coupling of an aryl or heterocyclic mercuric derivative with a cyclic enol ether (glycal) to form a C-nucleoside.³³ These reactions are well described by detailed product characterization studies.^{19,31,32,37,38,54,55} The overall process leading to the coupled organic product, as usually formulated, involves four discrete organometallic reactions^{31,32,34} (eq 3–6).⁵⁶



Transmetalation. A large body of data^{32,57–61} provides compelling, but indirect, evidence for the transmetalation process in palladium-mediated reactions of organomercurials (eq 3). However, to our knowledge, the arylpalladium product of this reaction has not been observed directly prior to the present study.

Initial attempts to observe transmetalation by FAB mass spectrometric analysis of reaction mixtures prepared by dissolving equimolar portions of an organomercuric acetate and palladium(II) acetate in acetonitrile were unsuccessful (Table III). Ions related to dimerization of the aryl (heterocyclic) group⁵¹ (R_2H^+) were detected. Also present in these mass spectra were ions related to the organomercurial and palladium(II) acetate reactants. However, ions related to an arylpalladium species were not observed in FAB mass spectra of these reaction mixtures which contained only palladium(II) acetate and an organomercurial reagent (Table III). When triphenylphosphine was added to the reaction mixtures (after 5 min reaction time), ions corresponding to the triphenylphosphine complexed transmetalation products $[RPdPPh_3]^+$ were observed. If the addition of triphenylphosphine was delayed beyond 5 min, FAB mass spectra dominated by an ion at m/z 630, $[Pd(PPh_3)_2]^+$, resulted.

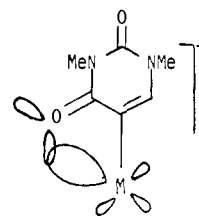
The transmetalation process was also evident in FAB mass spectra of ternary reaction mixtures involving equimolar palladium(II) acetate, an organomercuric acetate, and a glycal (Table IV, Figure 2). In FAB mass spectra of ternary reaction mixtures

involving 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedion-5-ylmercuric acetate (**9**), an ion corresponding to RPd^+ was observed at m/z 245; in spectra of reaction mixtures involving 4-methoxynaphthylmercuric acetate (**10**) an ion was observed at m/z 304 corresponding to $[RPd(MeCN)]^+$.

The results of FAB mass spectrometric analysis of the binary (Table III) and ternary (Table IV) reaction mixtures, taken together, point strongly to a role for the glycal in formation of the observed RPd^+ ions. The RPd^+ species observed may result from arylpalladium-glycal complex C (eq 4) in a gas-phase process involving loss of the π -bonded glycal ligand since, when glycal or another stabilizing ligand (PPh_3) was not present, no arylpalladium ion was observed.

Metal and Organometallic Ion Types. In these studies only divalent metal ions, Pd(II) and Hg(II), were used. However, the FAB mass spectra obtained (Figures 1 and 2, Tables II–IV) exhibit ions involving Pd(I) and Hg(I) as well as dicationic metal centers. In many spectra of reaction mixtures incorporating Pd(II) acetate, an uncomplexed Pd(I) ion (m/z 106) was observed. No corresponding uncomplexed Hg(I) ion was observed although such an ion (m/z 202) is routinely seen in electron ionization mass spectra of mercury-containing compounds.⁶² Similarly, uncomplexed Pd(II) or Hg(II) ions were not present.^{63,64}

The Pd(II) and Hg(II) ions observed (Figures 1 and 2, Tables II–IV) possess one anionic and one or more neutral ligands bound to the metal. The possible exceptions to this generalization are RPd^+ (m/z 245) and RHg^+ (m/z 341) where R, derived from **9**, is 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedion-5-yl. However, it



M = Pd, m/z 245; M = Hg, m/z 341

is likely that the pyrimidinyl group serves as a bidentate ligand with the C-4 carbonyl group functioning as a neutral donor ligand. Apparently, similar ion stabilization is not available from the *o*-methoxy group when R is 2-methoxynaphthyl; when **11** was used, no ions corresponding to RM^+ were observed (Table III).

Organometallic Complex and Adduct Ions. The progression of the palladium-mediated coupling reaction between a glycal (**1–8**) and an organomercuric acetate (**9–11**) involves two organopalladium intermediates, each of which incorporates glycal, the aryl (heterocyclic) group of the organomercury reactant, and Pd(II). These two intermediates, complex C (eq 4 and 5) and adduct A (eq 5 and 6), differ fundamentally in the nature of the bonding between the reactant partners. However, complex C and adduct A are not readily distinguished by mass spectrometry because they are of identical mass (if solvent, matrix, and/or anion ligands present in an observed ion which may differ in kind and/or number are ignored).⁶⁵ No experimental data are available concerning the stability or solution lifetimes of complexes C in the coupling reaction. In two instances relatively stable adducts A have been encountered;^{19,32,54} in most cases observation of the progress of a coupling reaction using thin layer chromatography has revealed rapid (<15 min) disappearance of glycal with product (P, eq 6) formation beginning within minutes but often requiring hours for completion.³¹ Reactions involving 3,4-dihydro-2*H*-pyran

(55) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1978**, *43*, 4110–4112.

(56) Bäckvall, J. E.; Björkman, E. E.; Pettersson, L.; Siegbahn, P. *J. Am. Chem. Soc.* **1984**, *106*, 4369–4373.

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(64) Ryan, T. M.; Day, R. J.; Cooks, R. G. *J. Anal. Chem.* **1980**, *52*, 2054–2057.

(65) Presumably, Pd(II) is tetradentate in the reaction mixture and in the FAB matrix; neutral and anionic ligands necessary to fill Pd binding sites may be derived from acetate, acetonitrile (solvent), glycerol, or triethanolamine. Complex equilibria may exist precluding precise specification of Pd ligands.

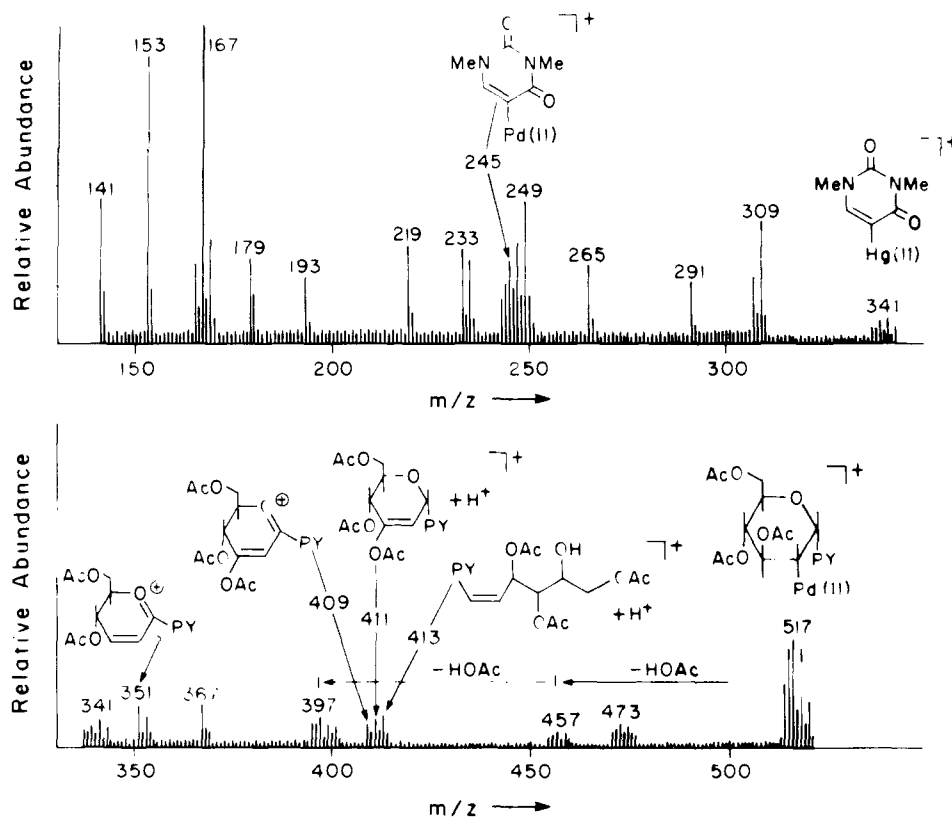


Figure 2. Fast atom bombardment mass spectrum obtained using a glycerol-acetic acid matrix to which was added an aliquot of a reaction mixture formulated by dissolving equimolar portions of palladium(II) acetate, 3,4,6-tri-*O*-acetyl-D-glucal (**6**) and 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedion-5-ylmercuric acetates (**9**) in acetonitrile. Unassigned prominent ions at m/z 309, 291, 265, 249, and <240 are fragment ions derived from the C-nucleoside products formed in the reaction mixture.

(**7**) or 2,3-dihydrofuran (**8**) appear to be faster,³⁸ and we find it particularly noteworthy that organopalladium ions were detected in reaction mixtures utilizing these enol ethers (Table IV). It is likely that the ions observed (Table IV) derive from adducts (A) and not complexes (C), although as noted (see above) the observation of RPd^+ ions in FAB mass spectra of ternary reaction mixtures containing glycal and not in binary reaction mixtures containing only Pd(II) and an organomercurial is suggestive that RPd^+ ions derive from complex C in the reaction mixture solution.

Other Organometallic Ions. Table IV includes a number of ions which do not represent intermediates of the primary palladium-mediated coupling reaction (eq 3-6). For example, an ion at m/z 383 in the reaction of glycal **1** or **7** with organomercurial **9** accords with a palladium derivative of the known pyrimidinyl dimer by-product of the glycal coupling reaction.⁵¹

Ions at m/z 575 (in the reaction of glycal **6** with organomercurial **9**) and 387 (in the reaction of glycal **7** with **9**) accord with adducts formed by acetoxy-palladium of C-nucleoside products (P, eq 6) resulting from decomposition of adduct A via palladium hydride elimination. It is noteworthy that electron ionization mass spectra of crude product resulting from the Pd(II) mediated coupling of glycal **6** with **9** (unpublished) exhibit an ion at m/z 470 corresponding to such an acetoxy-palladium product although it was not isolated owing to the very small amounts produced.

More difficult to account for are ions at m/z 467 (in the reaction of **7** with **9**) and 453 (in the reaction of **8** with **9**). These ions accord with a palladium adduct involving two pyrimidinyl moieties associated with an enol ether (glycal); no other evidence for such species has been observed.

Conclusions

This study has demonstrated that FAB mass spectrometry can be an effective tool for study of the solution dynamics of complex

organometallic reactions through its use in direct reaction mixture analysis. The principal ions present in FAB mass spectra of the organometallic reaction mixtures studied accord closely with the species postulated on the basis of product isolation studies and mechanistic considerations.

We were able, for the first time, to observe, directly in reaction mixtures, the transmetalation process (eq 3) which is central to palladium-mediated reactions of organomercurials. The necessity for the presence in the reaction mixture of glycal reactant, or a stabilizing triphenylphosphine ligand, for the transmetalation RPd^+ product to be observed is noteworthy and unexpected.

In every reaction studied, ions corresponding to the intermediate organopalladium adduct (A, eq 5 and 6) were observed. This is particularly impressive for reactions involving 3,4-dihydro-2*H*-pyran (**7**) and 2,3-dihydrofuran (**8**) where the adducts are very unstable and decompose by palladium hydride loss rapidly.³⁸

The elegant studies of Halpern^{66,67} provide ample warning that the presence of a species in a reaction mixture is not sufficient evidence that it is an intermediate in a sequence leading to the reaction product isolated. Nonetheless, detailed understanding of reaction dynamics requires knowledge of the species present in reaction mixture solutions. FAB mass spectrometric analysis of organometallic reaction mixtures promises to be an effective tool in the elucidation of these complex reaction mechanisms.

Acknowledgment. Support for this study was provided by grants from the National Institutes of Health (AM20937, GM30310), from S. Söderlundhs Minnesfond, and from Thuns fond.

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