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Mechanism of Palladium(II)–Copper(II)-Mediated Demercuration of Cycloalkyl and Cycloalkylmethyl Systems

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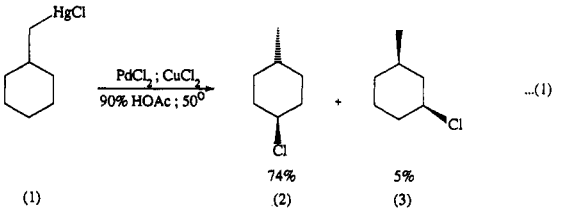
Summary: The palladium(II)–copper(II)-mediated demercuration of cycloalkyl- and cycloalkylmethylmercuric chlorides exhibit mechanistic changes as a function of ring size, with elimination–readdition of [HPdX] being important in cyclohexyl systems but direct carbocation formation dominating in cyclooctyl cases.

Palladium–carbon bond formation and subsequent cleavage are often central to palladium-mediated organic transformations.[1] Regarding oxidative cleavage of [RPdCl] by Cu(II), evidence for carbocation involvement has been provided in certain cases,[2-4] but for cyclohexylmethylpalladium chloride[2] ($C_6H_{11}CH_2PdCl$), a 1,5-H shift leading to a "palladabicyclooctane" and subsequent transannular functionalization were suggested. In view of the implications of this latter suggestion for C–H activation generally, we now report results that clarify some of the processes that operate in the oxidative cleavage of cycloalkyl- and cycloalkylmethylpalladium systems. Unfortunately, direct transannular insertion of Pd into a C–H bond is not one of them.

The reaction of cyclohexylmethylmercuric chloride (1) with $PdCl_2/CuCl_2$ in 90% acetic acid containing no added chloride ion has been reported[2] to provide mainly *trans*-4-methylcyclohexyl chloride (2), together with a minor amount of the *cis*-2-isomer 3 and other unidentified products (~20%) (eq 1).

The favored pathway[2] involved a transannular 1,5-H migration via a cyclic seven-membered transition state and



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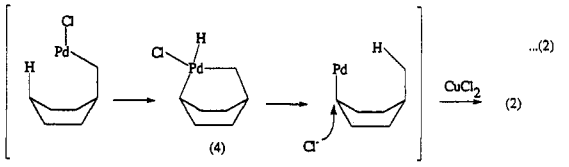
a palladabicyclooctane 4 (eq 2), and the general implications of this proposal for C–H activation were raised.



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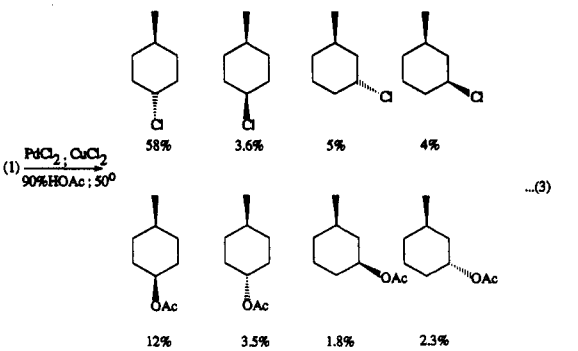
Repetition of this reaction with 1 under the described[2] conditions led to the product profile in eq 3, with ca 10% (six components) being unidentified. The major acetate



...(3)

is of *opposite* relative configuration to the major chloride.[5]

(1) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. Henry, P. M. *Adv. Organomet. Chem.* **1975**, *13*, 363.
(2) Heumann, A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 207.
(3) Bäckvall, J.-E., Nordberg, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 393.
(4) Baird, N. C. *J. Org. Chem.* **1966**, *31*, 2411.

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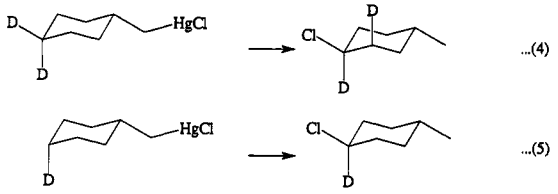
Use of 90% CD_3COOD–D_2O resulted in *no* ^2H incorporation into the products, on the basis of careful ^2H and ^{13}C NMR spectroscopic studies. Similarly, there was *no* loss of ^2H from any of the ^2H-labeled **1** to the solvent, 90% CH_3COOH–H_2O.

The palladabicyclooctane route (eq 2) envisages[2] the transfer of an H-4 ultimately into the CH_3 group, but this was not consistent with the outcome when [4,4-$^2H_2$]-**1** was employed,[6] as shown in eq 4. ^{13}C and ^2H NMR examination of the isolated chloride fraction that was predominantly **2** showed *no* ^2H incorporation into the CH_3 group, but it did demonstrate a stereospecific cis-transfer of ^2H from C-4 to C-3 (eq 4). This was confirmed by examination of *cis*-[4-^2H]cyclohexylmethylmercuric chloride,[7] which exhibited no ^2H migration (eq 5).



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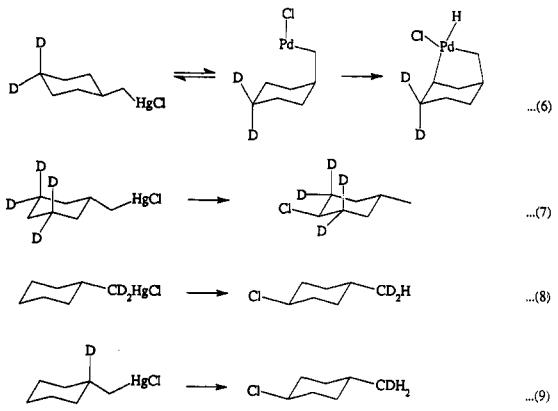
...(5)

We then considered palladacycle formation to C-3 as in eq 6 but this does not assist in accounting for the predominance of **2** and the labeling results shown in eq 4 and 5. In addition, the sequence in eq 6 would result in relocation of H from C-3 into the CH_3 group, but this was not the case as shown in eq 7,[8] although a stereospecific cis-1,2-H shift was observed, this time from C-3 to C-2. Use of the ^2H-labeled materials[9] shown in eqs 8 and 9 established that the CH_3 group was created by H-migration



...(6)

...(7)

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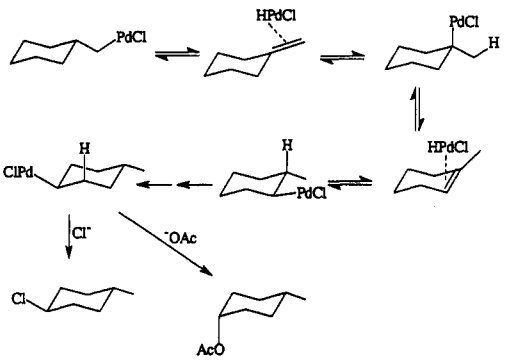
...(9)

from C-1 and that H did not migrate from CH_2HgCl to ring sites.

Scheme I



These stereospecific H-migrations and the lack of solvent involvement suggested a sequence initiated by Pd-for-Hg exchange, followed by reversible elimination–addition of [HPdX] and completed by the chloride or acetate displacement of [Pd], perhaps assisted by Cu(II) interaction at the C–Pd bond. Henry[10,11] has provided strong evidence for *cis*-palladium(II) hydride (or deuteride) eliminations (and cis-readditions) in cyclohexene systems and shown that these processes are faster than exchange of [HPdX] with solvent.[10] Scheme I, based on this chemistry, accounts for the results shown in eqs 4–9. The predominance of chloride **2** is attributed to retentive collapse of *trans*-4-methylcyclohexylpalladium chloride by an S_Ni-S_Ni type of process, with chloride capture from within the coordination sphere of Pd(II). Acetate, which is not significantly coordinated to Pd(II) in the presence of chloride ion,[13] is more likely to approach from without the coordination sphere, thus explaining the lower level of inverted (S_N2-type displacement) acetates.[10,11,14] In addition, in the series of presumed equilibria portrayed in Scheme I, the *trans*-2- and *trans*-4-methylcyclohexylpalladium chlorides would be anticipated to predominate and should be accessible directly from the corresponding trans-mercurials, which are known.[15] Indeed, treatment of these mercurials with Pd(II)/Cu(II) under the same reaction conditions provided product profiles essentially identical with that obtained when unlabeled mercurial **1** was employed. This correspondence requires that Pd-for-Hg substitution proceed with retention of configuration for which there is evidence.[16] Concordantly, use of *cis*-4-methylcyclohexylmercuric chloride[15] provided predominantly *cis*-3-methylcyclohexyl chloride and *trans*-3-methylcyclohexyl acetate, which are minor products from **1**. This is explicable on the basis that the putative *cis*-4-methylcyclohexylpalladium chloride (retentive Pd-for-Hg exchange) will rapidly revert (by cis elimination and readdition of [HPdX]) to the presumed more stable diequatorial *cis*-3-methylcyclohexylpalladium chloride and retentive collapse to the *cis*-3-methylcyclohexyl chloride (eq 10).[17]

(5) Authentic samples of the various methylcycloalkyl chlorides and acetates were obtained from the alcohols and were fully characterized by ^1H and ^{13}C NMR spectra, after purification by preparative gas chromatography. The reaction products were initially examined by capillary VPC and GC-MS and then separated into "chloride" and "acetate" fractions by preparative gas chromatography. High-quality, high-field ^{13}C and ^1H NMR spectra were then obtained and compared with those of the authentic samples. VPC monitoring of the reaction showed no product distribution change with time.

(6) This compound was obtained from 4-carbethoxycyclohexanone (Sanchez, I. H.; Ortega, A.; Garcia, G.; Larrazaal, M. I.; Flores, H. J. *Synth. Commun.* **1985**, *15*, 141–149) by reduction of the tosylhydrazone with acetic acid-*d* and $NaBD_4$. (Miller, V. P.; Yang, D.; Weigel, T. M.; Han, O.; Liu, H. **1989**, *54*, 4175–4188). Further reduction of the ester ($LiAlH_4$), followed by bromination of the alcohol and conversion to the mercurial provided [4,4-$^2H_2$]-**1**, together with ca. 30% of each of the cis and trans 4-$^2H_1$-analogues. The proportions of these components and the location of ^2H in the products was established by high-quality ^1H, ^2H, and ^{13}C NMR spectroscopy.

(7) Monodeuteration was achieved by adaptation of the procedure described above in ref 4.

(8) The [3,3,5,5-$^2H_4$]-**1** was acquired from ^2H exchange of the 4-carbethoxycyclohexanone and subsequent steps as detailed in ref 6.

(9) These ^2H-labeled mercurials were acquired by $LiAlD_4$ reduction of 4-carbethoxycyclohexanone and LDA treatment of this ester followed by D_2O quenching, respectively, before standard conversion to the mercurial.

(10) Henry, P. M.; Ward, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 1494–1497.

(11) Henry, P. M.; Ward, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 673–674. See also: Larock, R. C.; Lu, Y.; Bain, A. C. *J. Org. Chem.* **1991**, *56*, 4589–4590 and references cited therein.

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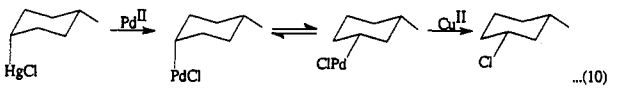
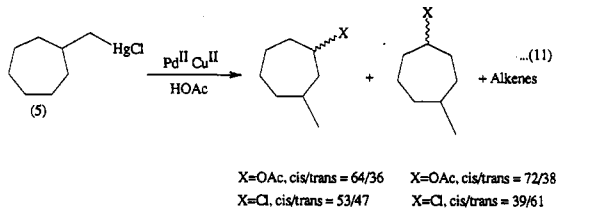
(16) (a) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 335. (b) Bäckvall, J.-E.; Akermark, B. *J. Chem. Soc., Chem. Commun.* **1975**, 82.



...(10)

Similar [HPdX]-mediated processes may operate with the cycloheptylmethyl system **5**, but a different blend of cleavage modes for the C–Pd bond is indicated by the increased acetate fraction (38% acetate, 38% chloride, 14% cycloalkenes) compared with the cyclohexyl case. No 2-methyl chlorides or acetates were detected[5,19] (eq 11).

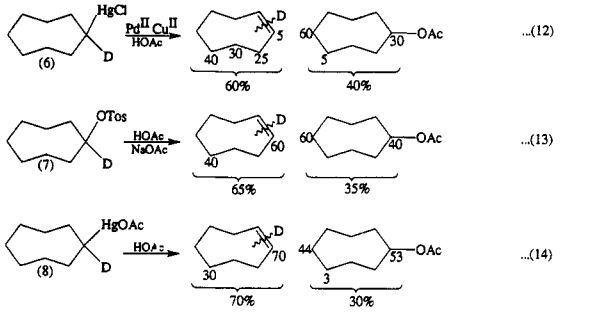


...(11)

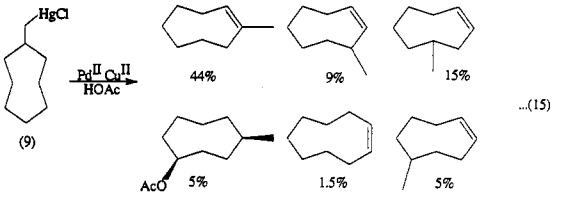
Cycloheptylmercuric chloride,[18] under the same conditions, provides predominantly cycloheptyl acetate (66%) and chloride (28%) and cycloheptene (6%).[5,19]

Extension to cyclooctylmercurials reveals that the [HPdX] mediated processes are now supplanted by direct C–Pd heterolysis and carbocation formation.[2-4] For example, treatment of [1-$^2H_1$]cyclooctylmercuric chloride[18] (**6**) with Pd(II)–Cu(II) in the normal way provided cyclooctene and cyclooctyl acetate, with a barely detectable level of cyclooctyl chloride (eq 12). This contrasts markedly with the product patterns in eqs 3 and 10.

The ^2H distribution in the product acetate (eq 12), with 60% located at C-5, reflects predominating 1,5-transannular hydride shifts, along with direct replacement (~ 30%). This result is inconsistent with Pd-migration of



the type outlined in Scheme I but is similar to that observed by us in tosylate solvolysis[20-22] (eq 13) or in carbocation-mediated demercuration[23] (eq 14). Cyclooctylmethylmercuric chloride[18] (**9**) provides largely methylcyclooctenes, some cyclononene, and *cis*-4-methylcyclooctyl acetate[24] (eq 15), such products being consistent with carbocation intermediacy. Cycloalkyl chlorides were present at very low levels.



...(15)

Therefore, a range of mechanistic possibilities for Pd(II)-promoted demercuration in the presence of Cu(II) appears to exist, with [HPdX]-mediated processes in the cyclohexyl system competing favorably with other routes, whereas the easily reached cyclooctyl cation results from direct oxidation of the C–Pd bond. A full report of this and related work will appear at a later date.

Acknowledgment. The authors are grateful to the Australian Research Council for support and for a scholarship to A.P.W.

Supplementary Material Available: ^1H, ^2H, and ^{13}C NMR spectra of compounds 1 and 8, ^1H and ^2H NMR spectra of compound 2 from eq 4, ^{13}C NMR spectra of cyclooctyl acetate and cyclooctene from acetolysis of compound 7 in eq 13, detailed description of the Pd(II)–Cu(II)-mediated reaction of mercurial 1, and a listing of the assigned ^{13}C NMR chemical shifts for the *cis*- and *trans*-3- and -4-methylcycloheptyl alcohols, acetates, and chlorides (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) Reaction of [1-$^2H_1$]cyclohexylmercuric chloride leads cleanly to a mixture of cyclohexyl chloride (88%) and cyclohexyl acetate (12%). The chloride consists of the 1-$^2H_1$ (36%), trans 2-$^2H_1$ (31%), and trans 3-$^2H_1$ (21%) isomers. This pattern is consistent with stereospecific [HPdX] eliminations and readditions and retentive chloride displacement of palladium.[10,11]

(18) Characterized by high-quality NMR spectra (^1H, ^2H, ^{13}C as applicable), elemental analyses, and/or high-resolution mass spectra.

(19) For a discussion of the ^{13}C NMR spectra of the regioisomeric methylcycloheptanols, see: Christl, M.; Roberts, J. D. *J. Org. Chem.* **1972**, *37*, 3443. Authentic samples of the corresponding acetates and chlorides were prepared as part of the present study, and their ^{13}C NMR spectra were assigned.

(20) [1-$^2H_1$]Cyclooctyltosylate was solvolyzed in acetic acid in the present study and the location of ^2H in the products, cyclooctene and cyclooctyl acetate, was determined by careful ^{13}C NMR spectroscopy. In this connection, see: Penman, K. G.; Kitching, W.; Wells, A. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2501–2507. See also: Cope, A. C.; Gale, D. M. *J. Am. Chem. Soc.* **1963**, *85*, 3747. Allinger, N. L.; Szbrybalo, N. *Tetrahedron* **1968**, *24*, 4699.

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(22) The ^2H distribution in the cyclooctene product is complicated by subsequent exchange and possible Pd(II)-induced double-bond migration. This latter effect may apply to eq 15 also.

(23) Jensen, F. R.; Ouellette, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 4477–4479.

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Ab Initio Investigation of Substituent Effects in 4-Substituted Bicyclo[2.2.2]oct-1-yl Cations. Computational Support for Through-Bond Stabilization via Double Hyperconjugation

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Summary: Ab initio calculations support the interpretation of experimental substituent and isotope effects in terms of double hyperconjugative stabilization of bicyclo[2.2.2]oct-1-yl cation.

