Stereoelectronic Control on the Kinetic Stability of β-Acetoxy-Substituted (η^3-Allyl)palladium Complexes in a Mild Acidic Medium

Kálmán J. Szabó,* Eike Hupe, and Anna L. E. Larsson

University of Uppsala, Department of Organic Chemistry, Box 531, S-751 21 Uppsala, Sweden

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Deuteromethanolysis of *trans*- and *cis*-β-acetoxy-substituted (η^3-cyclohexylallyl)palladium complexes (**1** and **2**) were studied under mild acidic conditions. The *trans*-β-acetoxy-substituted complex (**1**) reacted about 200 times faster than its *cis*-substituted counterpart (**2**). A theoretical analysis of the structure and stability of slightly simplified model compounds (**4**−**7**) was performed employing density functional theory at the B3PW91 level in order to elucidate the relationship between the rate of deuteromethanolysis and the electronic interactions between the β-acetoxy substituent and the palladium atom. In the *trans* complex, the stereoelectronic requirements of the conjugative interactions between the palladium atom and the C−O(Ac) bond are fulfilled, which facilitates the C−O(Ac) bond cleavage in the deuteromethanolysis reaction. Since the substituent geometry in the *cis* complex is different, these conjugative interactions are suppressed, providing a greater kinetic stability for the *cis* complex under the reaction conditions applied. Since the (η^3-allyl)-palladium complexes studied and their derivatives are key intermediates of important palladium catalyzed transformations, the implications of the β-substituent effects for the regio- and chemoselectivity of the nucleophilic attack have also been discussed.

Introduction

The application of allylpalladium chemistry to organic synthesis has made remarkable progress in recent decades.[1−5] One of the most intriguing aspects of this type of chemistry is the possibility of controlling the selectivity of the nucleophilic attack on the allyl moiety through the choice of reaction conditions and the ancillary ligands on palladium. Accordingly, there is considerable interest at the present time in investigating those electronic and steric interactions that govern the selectivity in catalytic transformations proceeding through (η^3-allyl)palladium intermediates.[6−11]

It is well-known that nucleophilic attack on the allyl moiety proceeds with a very high regioselectivity in the presence of polar β-substituents.[2,3,12,13] It has been shown by a recent theoretical study that these β-substituents induce an asymmetric electron distribution on the allylic fragment, which enhances the regioselectivity of the nucleophilic attack and increases the chemoselectivity in the nucleophilic addition to conjugated dienes.[9] The theoretical calculations have also shown that the β-substituent effects have strict stereoelectronic requirements: the most intensive β-substituent effects occur when the Pd−C3 and C4−X bonds are in an antiperiplanar conformation. These effects are of particular importance for reactions proceeding through cyclic allyl−palladium intermediates in which the Pd−C3−C4−X dihedral angle is locked. Thus, strong β-substituent effects and, therefore, high regioselectivity is expected when a nucleophile attacks a *trans*-β-substituted complex, such as **1** (Figure 1), and weak β-substituent effects and, hence, low regioselectivity would result when the reaction proceeds through a *cis*-β-substituted complex, such as **2**. Such an interesting variation of the regioselectivity has recently been observed in catalytic transformations proceeding through β-acetoxy-substituted η^3-cyclohexenyl complexes.[14]

In this combined experimental and theoretical study, we report our results concerning the intensity of the β-substituent effects observed for *trans*- and *cis*-β-acetoxy-substituted (η^3-allyl)palladium complexes **1** and **2**. Since these complexes, particularly **1**, and their analogs are frequently occurring intermediates of allylic substitutions[13−15] and of 1,4-oxidation of conjugated dienes,[16−18] quantitative data on the intensity of these effects is very useful for the development of regio- and chemoselective catalytic procedures.

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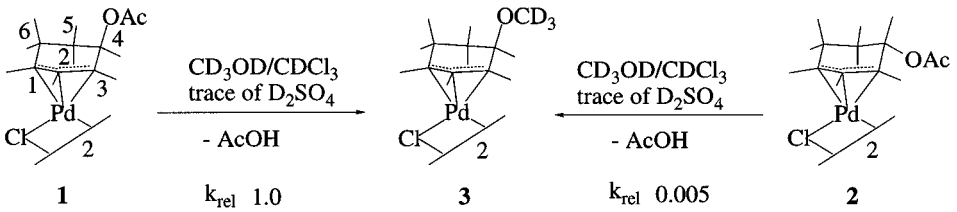
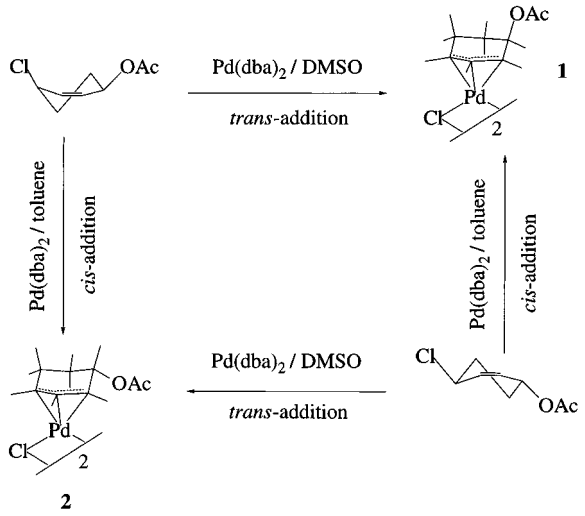


Figure 1. Relative deuteromethanolysis rates (k_{rel}) of bis(4-*trans*-acetoxy-1,3-η^3-cyclohexenyl)palladium chloride (**1**) and bis(4-*cis*-acetoxy-1,3-η^3-cyclohexenyl)palladium chloride (**2**).

Scheme 1



Experimental Results

Considering that the β-substituent effects are expected to weaken the C4−O bond,[9,19] the exchange rate of the β-acetoxy group will be proportional to the intensity of these effects. Recently, the β-substituent effects between the palladium atom and the methoxy functionality have been studied using deuteromethanolysis of various β-methoxy-substituted (η^3-allyl)palladium complexes.[19] Similarly, in the present study, deuteromethanolysis was employed under mild acidic conditions to determine the strength of the β-substituent effects in **1** and **2** (Figure 1).

The preparation of **1** is given in the literature,[20] however, we have used two alternative procedures to obtain it (Scheme 1). The *cis* complex **2** was also prepared by two different procedures: In toluene, *cis*-1-acetoxy-4-chloro-2-cyclohexene[18] reacts with $Pd(dba)_2$ by a *cis*-addition mechanism[21] providing the desired product, **2**. On the other hand, in DMSO, the reaction follows a *trans*-addition mechanism suitable for obtaining **2** starting from *trans*-1-acetoxy-4-chloro-2-cyclohexene.[14] Similarly, a *cis*-addition of $Pd(dba)_2$ to *trans*-1-acetoxy-4-chloro-2-cyclohexene provides **1**, as does a *trans*-addition of $Pd(dba)_2$ to *cis*-1-acetoxy-4-chloro-2-cyclohexene. The *cis* and *trans* mechanism of adding $Pd(dba)_2$ to allylic chlorides as a function of the solvent polarity was first studied by Kurosawa and co-workers.[21] The observations made by these authors are in complete agreement with our results.

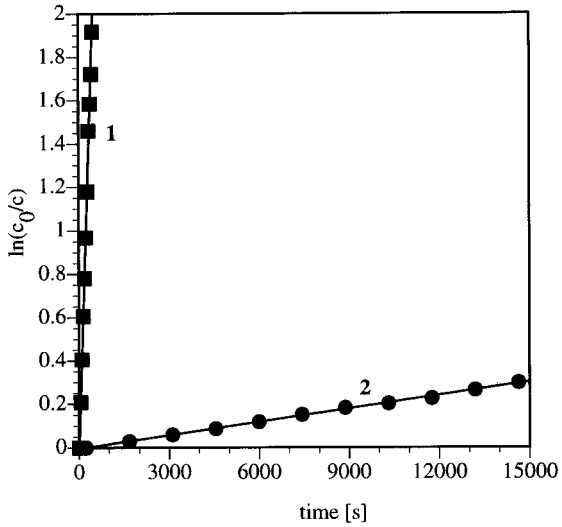


Figure 2. Plot of $\ln(c_0/c)$ against t for deuteromethanolysis of **1** and **2** under the same reaction conditions. The k_{obs} values and reaction conditions are provided in the Experimental Section.

The deuteromethanolysis of **1** and **2** was carried out in a mixture of $CDCl_3$ and CD_3OD in the presence of a small amount of D_2SO_4 at 25 °C (as described in the Experimental Section). The progress of the reactions could be followed conveniently by monitoring one of the ^1H signals of **1** and **2** using NMR spectroscopy (Figure 2). The *trans* complex **1** reacted very quickly and was completely converted to its deuteromethoxy analog **3**.[12,19,22] It is interesting to note that the deuteromethanolysis of the methoxy analog of **3** takes place about six times slower than that of **1** under exactly the same reaction conditions.[19] Retention of the configuration of C4 is a direct consequence of the anchimeric assistance of palladium,[22] which is, in fact, a manifestation of the β-substituent effects (*vide infra*). The *cis* complex **2** was significantly more stable than **1** under the reaction conditions of the deuteromethanolysis. It was converted, predominantly to **3**, about 200 times slower than the *trans* complex **1**.

Theoretical Results and Discussion

Computational Methods. The geometries of **4**−**7** were optimized employing a Becke-type[23] three-parameter density functional model, B3PW91. This so-called hybrid functional includes the exact (Hartree−Fock) exchange based on Kohn−Sham orbitals,[24] as well as

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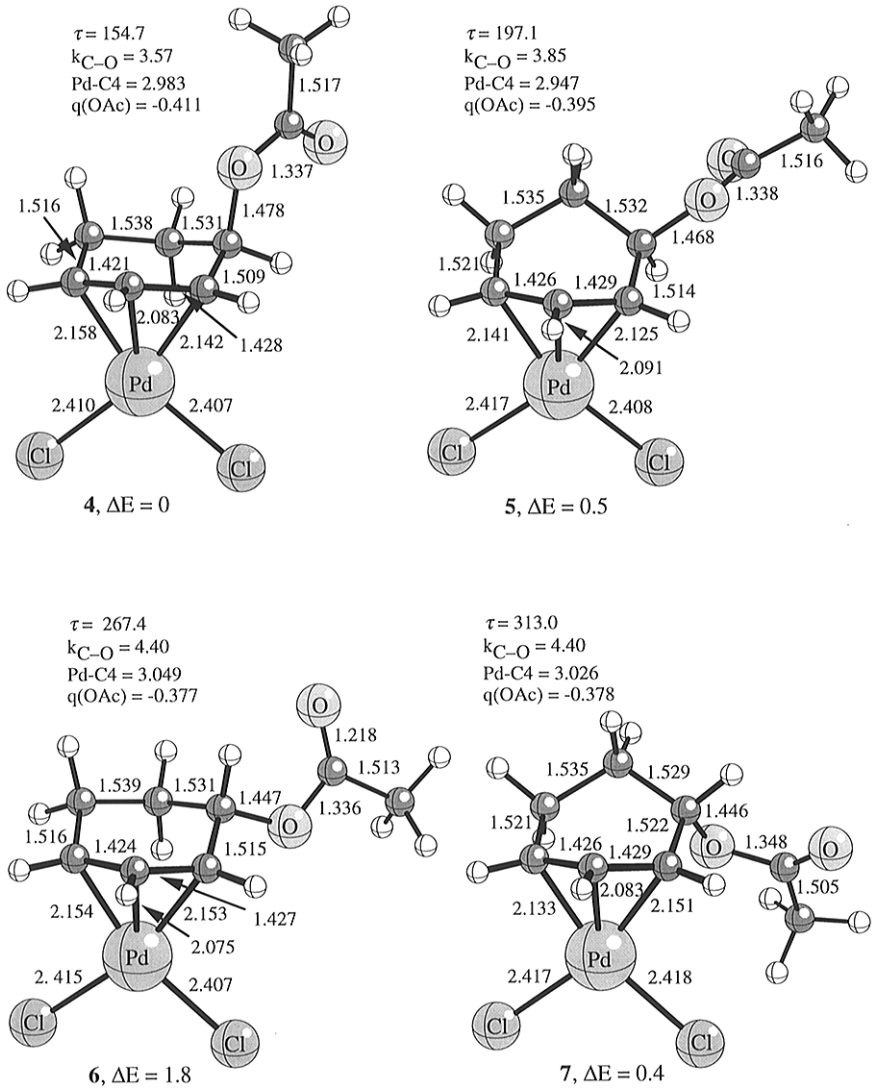

Figure 3. B3PW91/LANL2DZ+P energies, geometries, C−O force constants, and NBO charges of **4**−**7** (energies in kcal/mol, bond lengths in Å, angles in deg force constants in mdyn/Å); τ denotes the Pd−C3−C4−O dihedral angle; k_{C-O} values are calculated at the B3PW91/LANDZ2+P level and scaled by 0.96; all complexes bear one negative charge.

the gradient-corrected exchange functional of Becke[25] and the more recent correlation functional of Perdew and Wang.[26] All calculations were carried out using a double-ζ(DZ) + P basis set constructed from the LANL2DZ basis set,[27−29] which includes relativistic effective core-potentials for palladium, by adding one set of d polarization functions to the heavy atoms and a diffuse d function to palladium.[30,31] The charges were calculated by the natural bond orbital (NBO) analysis of Weinhold and co-workers.[32,33] The theoretical calculations were performed using the Gaussian94 program package.[34]

The calculations were carried out for monomers **4**−**7** (Figure 3) instead of chloro dimers **1**−**2**. However, this is not a serious simplification since it has been shown that the structures and properties of monomeric and Cl dimeric (η^3-allyl)palladium complexes are very similar.[35,36]

Dependence of the β-Substituent−Palladium Interactions on the Conformation of the Acetoxy Functionality. In order to analyze the stereoelectronic aspects of the interactions between the acetoxy functionality and palladium atom, we calculated the rotational potential for the acyclic model system **8** (Figure 4) as a function of the Pd−C3−C4−O dihedral angle τ (Figure 5). The antiperiplanar conformation ($\tau = 172.2°$) represents the absolute minima in the region of 120° <

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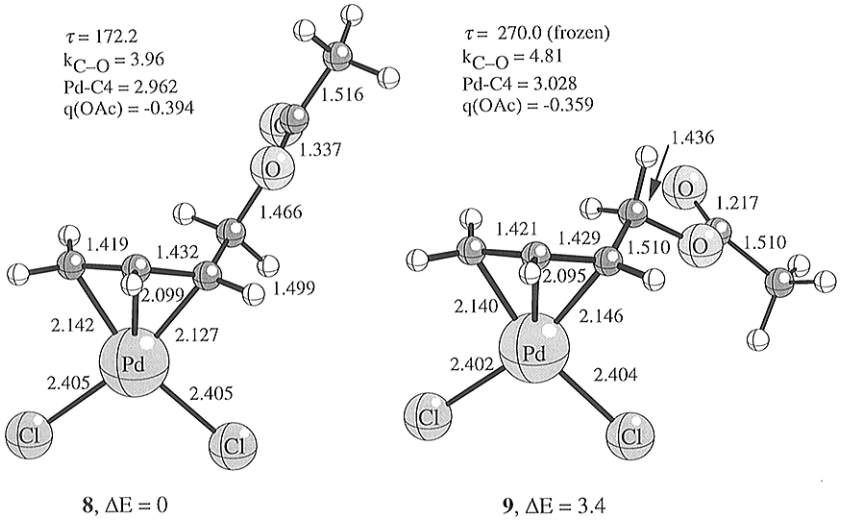

8, ΔE = 0 **9**, ΔE = 3.4

Figure 4. B3PW91/LANL2DZ+P energies, geometries, C−O force constants, and NBO charges of model systems **8** and **9** (for computational details see the caption for Figure 3).

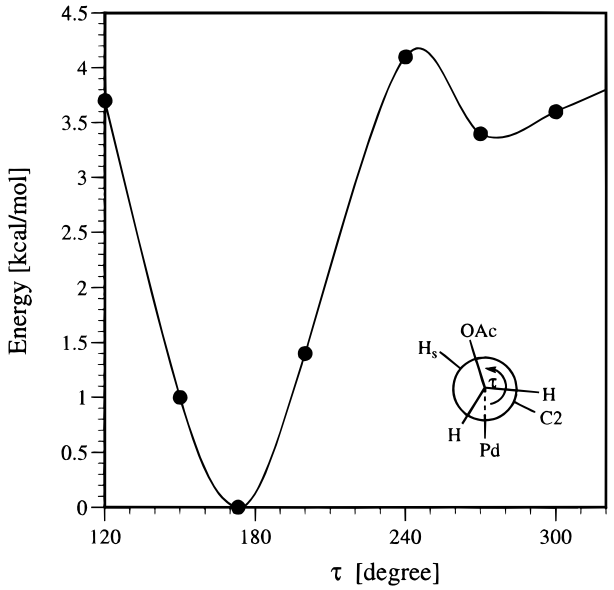

Figure 5. Rotation potential of **8**. Energy values are obtained by freezing the Pd−C3−C4−O dihedral angle (τ) to different values and reoptimizing all the other geometrical parameters at the B3PW91/LANL2DZ+P level.

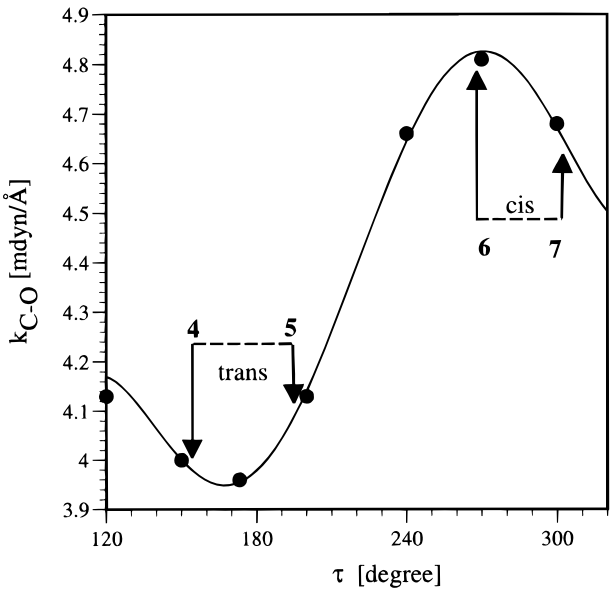

Figure 6. Stretching force constant (k_{C-O}) of **8** as a function of τ. The τ dihedral angles of the corresponding cyclic complexes are indicated by arrows.

τ < 320°, which is allowed for the β-acetoxy substituents in cyclic systems. The thermodynamic stabilization is 3−4 kcal/mol, which is lower than that in the case of β-chloro[9] or β-methoxy substituents[19] (6−8 kcal/mol). The C4−O bond strength is also a function of τ (Figure 6). In the antiperiplanar conformation the C−O stretching force constant is considerably smaller than in case of τ = 270° (−90°), which is a characteristic feature of the β-substituent effects.[9,19]

Weakening of the C−O bond in the antiperiplanar conformation **8** can be ascribed to charge transfer from a high-lying palladium−allyl bonding orbital (d_π) and a properly positioned lone pair orbital of palladium (n_d) into the σ^*(C−O) orbital (Scheme 2).[9,19] These conjugative interactions are shut off upon rotation to the **9** conformer (τ = 270.0°), in which the interacting MOs are orthogonal. The electron density transfer to the σ^*(C−O) MO in the antiperiplanar conformation is also indicated by accumlation of the negative charge on the β-substituent. As one goes from **9** to **8** the negative charge increases on the acetoxy functionality (Figure 4), and a similar trend has been observed for the corresponding β-chloro and β-methoxy complexes.[9,19]

Variation of the substituent conformation (τ) leads to systematic changes of several geometrical parameters. The change of the Pd−C distances relative to the corresponding parameters in the equilibrium form **8** is given in Figure 7. The Pd−C3 and Pd−C4 distances are shortest in **8**, and the difference between Pd−C3 and Pd−C1 is also quite large in this form. Interestingly, the more substituted allylic terminus (C3) is closer to the metal atom than the less substituted one (C1), which is suprising in view of the fact that in allyl−metal complexes there is a considerable repulsion between the metal atom and the *anti* functionality.[10,37] This geometrical feature can be attributed to a partial coordina-

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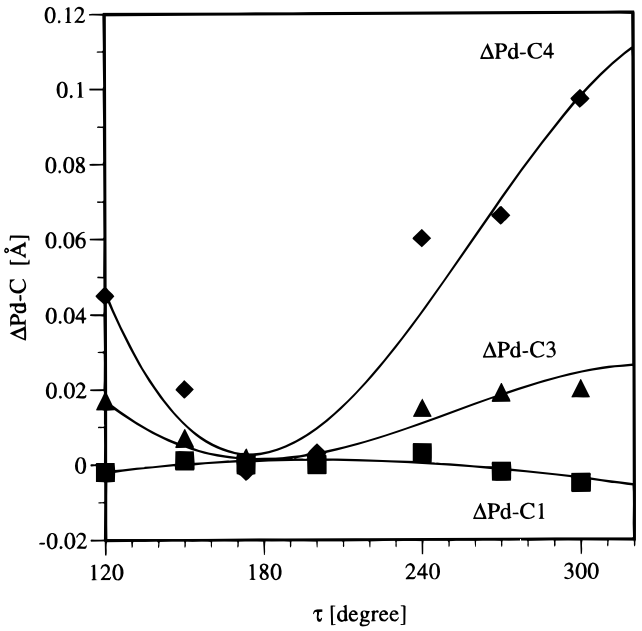
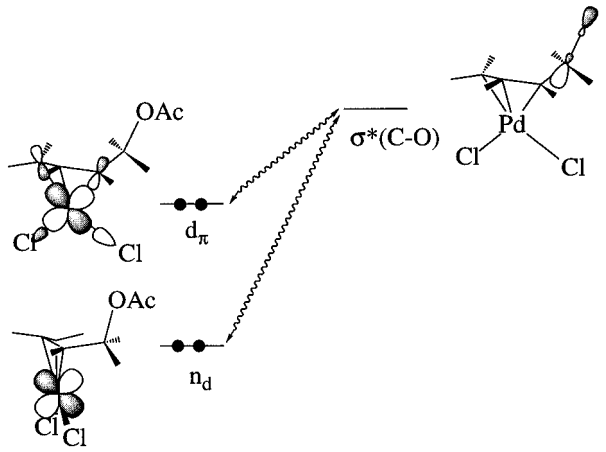


Figure 7. Deviation of the Pd−C bond lengths from the equilibrium values in **8** as a function of τ. ΔPd−C = Pd−C(τ) − Pd−C(**8**).

Scheme 2



tion of C4 to the palladium atom. The Pd−C4 distance rapidly decreases when τ approaches the value of the antiperiplanar conformation, which is encountered in the equilibrium form **8**. The partial coordination between Pd and C4 arises from the electronic interaction between a properly positioned lone pair orbital of palladium (n_d) and the σ*(C−O) MO of the acetoxy substituent (Scheme 2). This interaction is also a typical feature of the β-substituent effects, as it has been shown for β-chloro and β-methoxy substituted (η^3-allyl)-palladium complexes.[9,19]

Structure and Stability of Complexes 4−7. In accordance with the previous X-ray studies of cyclohexylallyl complexes,[38] two conformers were found for the *trans*- and *cis*-acetoxy-substituted species (Figure 3). The chair conformer of the *trans* complex (**4**) is slightly more stable than the boat form (**5**), suggesting that **4** is somewhat more populated. In contrast to the *trans* complex, in the case of the *cis* complex, the boat form (**7**) is thermodynamically more stable than the chair conformer. The slight difference in the stability of the *cis*- and *trans*-substituted species is the result of conflicting steric and electronic interactions. Since the Pd−H5(*cis*) distance in **4** is 2.7 Å, which is considerably shorter than the sum of the van der Wals radii of the palladium and hydrogen atoms (3.5 Å),[39,40] the repulsive interaction between the metal and the *cis*-H atom is quite strong. On the other hand, the β-substituent effects, which are rather strong in **4** and **5**, thermodynamically stabilize the complexes by about 3−4 kcal/mol (Figure 5).

In *trans* complexes **4** and **5**, the acetoxy functionalities are locked in such conformations, which are favored by the β-substituent effects. These effects are particularly strong in **4**, in which the Pd−C3−C4−O angle (τ = 155°) closely approaches the value of the antiperiplanar arrangement (cf. Figure 6). Due to the presence of strong β-substituent effects in the *trans* complexes, the C4−O4 bonds in **4** and **5** are longer and weaker than in the *cis* complexes **6** and **7**. Weakening of the C4−O4 bond is also reflected by the low stretching force constant in **4** being smaller than that in **6** and **7** by 23%. This tendency is the same as that found for the acyclic model system **8** (Figure 6), for which k_{C-O} is also weaker by about 1 mdyn/Å in the antiperiplanar conformation ($\tau \approx 172°$) than in the orthogonal conformation ($\tau \approx 270°$).

There are some other interesting structural features of **4**−**7** that are of relevance for the selectivity of the nucleophilic attack of β-acetoxy-substituted cyclic allylpalladium complexes. Because of the partial coordination of C4 to palladium, the Pd−C4 bond lengths are shorter by 0.07−0.08 Å in the *trans* complexes than in the *cis* complexes. This partial coordination also leads to asymmetric Pd−allyl bonding in **4** and **5**: the Pd−C bond to the more substituted terminus (C3) is somewhat shorter than the Pd−C bond to the less substituted one (C1). Such a "hinging" of the more substituted allylic terminus toward palladium has been observed for other allylpalladium complexes bearing polar β-substituents[41,42] and is also a typical structural feature of model system **8**. Since the nucleophilic attack on the allyl moiety involves Pd−C bond breaking, the asymmetric bonding also facilitates the attack at the less substituted terminus, for which the Pd−C bond is relatively long and, therefore, weak. In contrast to the *trans* complexes, in the *cis* complexes the Pd−allyl bonding is either symmetric (**6**) or the more substituted allyl terminus is hinged away from the metal (**7**). In the absence of partial Pd−C4 coordination, the allyl−palladium bonds, in particular the Pd−C3 bond, can be more easily deformed by steric interactions from the β-substituents, which weaken the Pd−C3 bond and, hence, facilitate the nucleophilic attack at the more substituted allylic terminus. Such types of steric effects were assumed by Gatti, Larsson, and Bäckvall[14] to rationalize the regioselectivity in catalytic reactions proceeding through *cis*-acetoxy-substituted allylpalladium intermediates, such as **2**.

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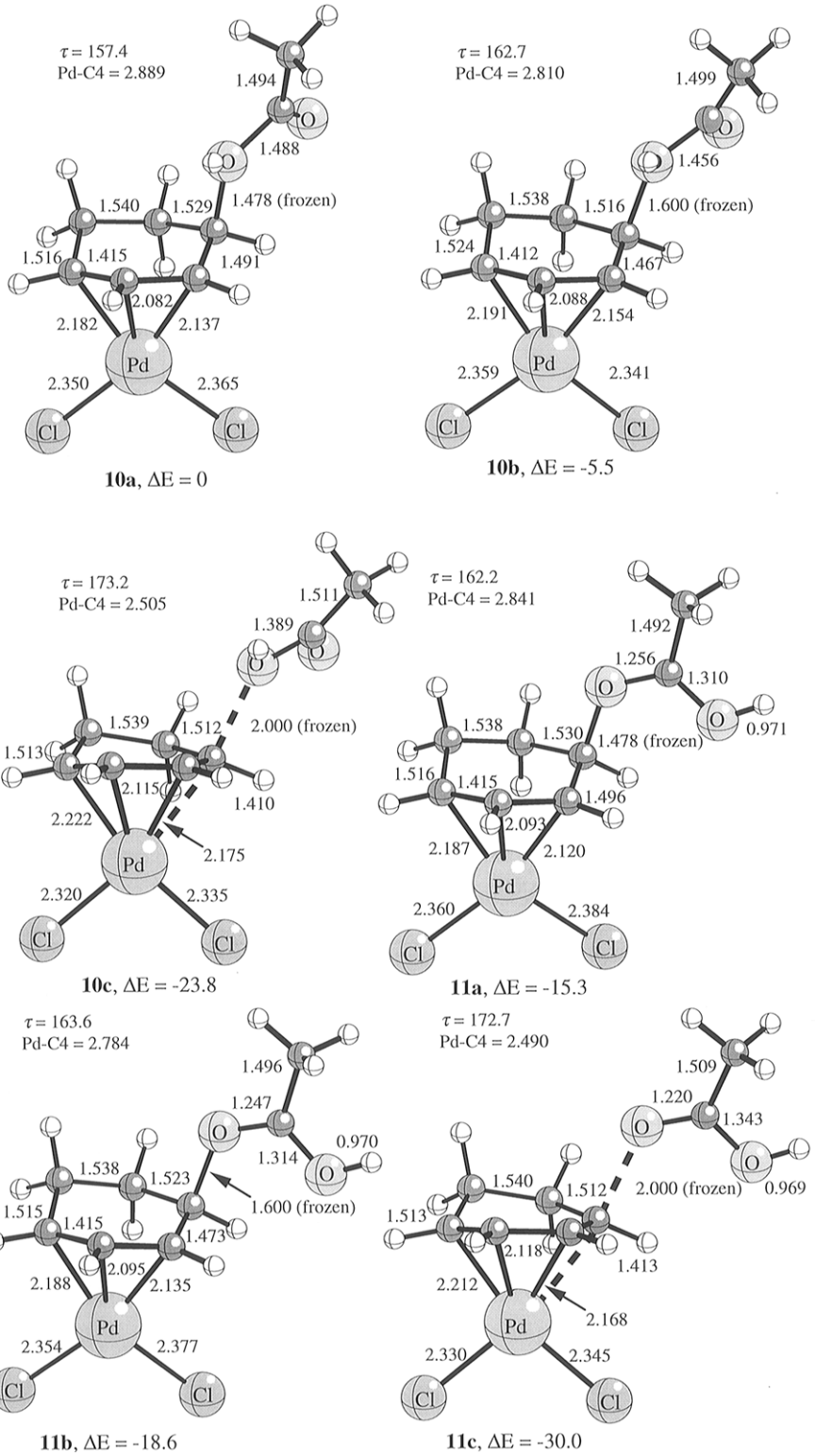

Figure 8. B3PW91/LANL2DZ+P energies and geometries for the protonated forms of **4**. Structures **10**−**11** are obtained by freezing the C4−O distances to different values (1.478 Å **10a**, **11a**; 1.600 Å **10b**, **11b**; 2.000 Å **10c**, **11c**) and reoptimizing all the other geometrical parameters at the B3PW91/LANL2DZ+P level.

Effects of Protonation of the Acetoxy Functionality. Replacement of the OAc functionality with an OCD_3 group in **1** and **2** requires acid catalysis. Protonation of the O4 atom or the carbonyl oxygen decreases the energy of the σ^*(C−O) MO, thereby amplifying the β-substituent effects in the *trans* complex **1** (Scheme 2). In fact, the β-substituent effects in the protonated *trans* complexes become so strong that these complexes decompose without an activation barrier to (η^4-cyclohexadiene)palladium dichloride and AcOH, encumbering the observation and theoretical investigation of these species.

Although stationary points cannot be obtained for the protonated forms of **4**, some interesting transient points of the potential energy surface have been determined in the vicinty of these species (**10** and **11**, Figure 8). Protonated complexes **10a** and **11a** were obtained by freezing the C−O bond at 1.478 Å, which is the C−O bond distance in **4**. Although the carbonyl protonated form (**11a**) is thermodynamically more stable than the

O4 protonated form (**10a**), the protonation affects the structure of the cyclohexyl−allyl−palladium unit in a similar way. Comparision of the geometry of **4** with **10a** and **11a** reveals some typical structural effects of the enchanced β-substituent interactions: (a) increased asymmetry in allyl−palladium bonding; (b) shortening of the Pd−C4 distance by 0.1−0.14 Å, due to increased coordination of C4 to Pd; (c) shortening of the C3−C4 bond, indicating the enchanced π-character of the C3−C4 bond. When the C−O distance is constrained at 1.6 Å (**10b**, **11b**), which would be conceivable for the equilibrium bond length in an O-protonated C−O(H)−C structure,[19,43] these structural changes are even more pronounced. In structures **10c** and **11c**, the C−O distance is frozen at 2 Å, which would be expected for the transition state of the C−O bond cleavege. These complexes are considerably more stable than **10a** or **11a**, and the η^4-cyclohexadiene−palladium structure is clearly developed: (a) the Pd−C4 distance is shorter by 0.5 Å than that in **4**, approching the lengths of the other three Pd−C bonds; (b) the C3−C4 bond is shorter by 0.1 Å than that in **4**, indicating the formation of a metal-coordinated double bond.

Variation of the allyl−palladium bonding in **10** and **11** also illustrates the mechanism of the anchimeric assistance of palladium in the acid-catalyzed dissociation of the acetoxy group. The heterolytic cleavage of the C4−O bond takes place synchronously with the Pd−C4 coordination. The intensity of the anchimeric assistance is a function of the polarity of the C−O bond. Accordingly, a less polar C4−O bond gives a kinetically stable complex, while a rapid, eventually barrierless, decomposition of the complex occurs when the C4−O bond becomes polar, due to, for example, protonation of the acetoxy group. As discussed above, another important factor determining the kinetic stability of a β-substituted (η^3-allyl)palladium complex is the substituent conformation with respect to the Pd−C3 bond: in an antiperiplanar conformation ($\tau \approx 172°$) the interactions between palladium and a polar C−O bond are strong, which weakens the C−O bond and lowers the kinetic stability of the complex; however, in an orthogonal conformation ($\tau \approx 270°$) the interactions are weakened leading to a kinetically stable complex (Figure 6).

Conclusions

The first time β-acetoxy-substituted (η^3-allyl)palladium complexes were subjected to deuteromethanolysis to measure the intensity of the β-substituent effects between the palladium atom and the acetoxy functionality. The rapid exchange of the β-substituent in the *trans* complex (**1**) arises from the acetoxy substituent being locked in a conformation that is favored by the β-substituent effects. On the other hand, the *cis* complex is more stable kinetically under the same reaction conditions, indicating the absence of the conjugative interactions between the palladium atom and the acetoxy functionality.

The low regioselectivity encountered for allylic substitution reactions proceeding through a *cis*-β-acetoxy-substituted allyl−palladium complex can be ascribed to the absence of the β-substituent effects, which would otherwise govern the regiochemistry, similar to, for example, when the reaction involves a *trans*-β-acetoxy-substituted allyl−palladium intermediate.[14] Accordingly, the presence of a polar β-substituent in an allylpalladium complex does *not* guarantee a high regioselectivity in the nucleophilic attack, unless the steroelectronic requirements of the β-substituent effects are fulfilled.

Another important implication of the present study is that relatively small structural differences in the β-substituents lead to significant changes in the intensity of the effects they induce. For example, under mild acidic conditions, the β-acetoxy group in **1** can be exchanged to a methoxy group six times faster than the β-methoxy group of **3**, which can be utilized to control the chemoselectivity in the 1,4-oxidation of conjugated dienes.

Experimental Section

Preparation of Bis(*cis*-4-acetoxy-1,3-η^3-cyclohexenyl)-palladium Chloride (2). *cis*-1-Acetoxy-4-chloro-2-cyclohexene[18] (0.2 g, 1.15 mmol) was added to a stirred solution of $Pd(dba)_2$[44] (0.6 g, 1.04 mmol) in toluene (5 mL) at room temperature. The resultant dark red mixture was then stirred for a further 18 h. After the evaporation of toluene, the reaction mixture was separated by silica gel chromatography using CH_2Cl_2/ether 97:3 as the eluent, yielding **2** (0.22 g, 76%). Alternatively, $Pd(dba)_2$ was reacted with *trans*-1-acetoxy-4-chloro-2-cyclohexene[14] in DMSO, giving a similar yield. ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 5.55 (t, 1H, H2), 5.18 (br m, 2H, H1 and H3), 4.56 (dd, 1H, H4), 2.15 (s, 3H, −OCOCH_3), 2.06 (m, 1H, $H6_{cis}$), 1.95 (m, 1H, $H5_{cis}$), 1.7 (m, 1H, $H6_{trans}$), 1.44 (m, 1H, $H5_{trans}$). ^{13}C NMR (δ, 100.6 MHz, $CDCl_3$): 170.9 (C═O), 102.3 (C2), 79.5 (C3), 68.4 (C4), 26.6 (C5), 25.8 (C6), 21.5 (OCOCH_3). The assignment of the ^{13}C NMR signals is based on HETCOR measurements.

Kinetic Measurements. The appropriate complex (0.02 mmol) was dissolved in a mixture of $CDCl_3$ (0.4 mL) and CD_3OD (0.2 mL) in an NMR tube. To this mixture, 0.100 mL of stock solution, prepared from CD_3OD (5 mL) and 98% D_2SO_4 in D_2O (0.092 g), was added with a syringe. At appropriate intervals, ^{1}H NMR spectra were recorded in the arrayed-experiment mode at 25.0 °C. The k_{obs} values for the disappearance of the substrates were calculated from integrals of the H3 (**1**) and H4 (**2**) peaks as a function of time by means of regression analysis. The measured absolute k_{obs} values are 4.31×10^{-3} s^{-1} (**1**) and 2.13×10^{-5} s^{-1} (**2**).

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