OH–Pd(0) interaction as a stabilizing factor in palladium-catalyzed allylic alkylations

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In palladium-catalyzed alkylations of allylic acetates with malonate as nucleophile, catalysts with oxazoline ligands bearing hydroxymethyl substituents in 4-position have been shown by density functional theory computations to undergo a conformational change on nucleophilic attack, which is accompanied by reduction of Pd(II) to Pd(0). The conformations of the Pd(0) complexes were shown to be governed by the presence of a hydrogen bond with the metal center acting as a hydrogen bond acceptor. The conformational change, which is absent in catalysts with O-alkylated analogs, largely affects the enantioselectivity of the catalytic process. This process is a previously uninvestigated example of where this type of weak hydrogen bond has been shown to influence the stereochemistry of a chemical reaction.

A symmetric metal catalysis constitutes a powerful method for the preparation of enantiopure chiral compounds (1–3). To achieve high selectivity in the catalytic reactions, proper design of chiral ligands having the ability to transfer the chiral information to the reacting substrates is required. Proper design is usually accomplished by consideration of the steric and electronic demands of the catalytic process under study. Secondary interactions between the chiral ligand and the reacting species may influence the conformation of the catalyst, thereby affecting the stereoselectivity (4). At the same time, such interactions may be used to tune the electronic properties, resulting in increased reactivity of the catalytic system. Several examples of increased stereoselectivity and/or acceleration of catalytic processes by ligands containing properly situated hydroxy groups have been reported. In rhodium-catalyzed hydrogenations of olefins, hydroxy substituents in the ligands have been shown to have remarkable effects. Thus, Knowles et al. (5) observed that a (R,R)-1,2-ethanediylbis[2-methoxyphenyl]-phenylphosphate derivative with the methoxy groups replaced by hydroxy groups provided high enantioselectivity, although it was at the expense of the high reactivity. Later, Börner (ref. 6 and references cited therein) noted similar effects for other types of ligands and provided evidence that properly situated hydroxy groups in the ligands coordinate to the cationic rhodium center by their oxygen lone pairs. Hayashi and coworkers (7–9) observed an accelerating effect by hydroxy groups in palladium-catalyzed allylic alkylations by using ferrocenylphosphine ligands. The effect was believed to be caused by an attractive interaction involving hydrogen bonding between a hydroxy group in the ligand and the nucleophile.

We recently found that use of 2-(1-hydroxyalkyl)- (1a) and 2-(1-alkoxyalkyl)pyridinoxazolines (1b) as ligands in palladium-catalyzed allylic alkylations with malonate resulted in profoundly different enantioselectivities, ligands with (R*′,R*)-configuration of the former type and those with (R*,S*)-configuration of the latter type, resulting in higher enantioselectivity than their diastereomers (10). This difference was shown to be due to a conformational change in the alcohol ligand 1a, absent in 1b (Scheme 1), involving rotation from an anti-periplanar structure in the Pd(II) allyl complex to a Pd(0) olefin product complex having an O—C—C—N dihedral angle of ≈57° (11). Our results suggested the existence of an interaction between the hydroxy group and the electron-rich metal center in the Pd(0) olefin complex, which affects the stereochemistry of the reaction.

To study whether this effect appears in suitably substituted oxazolines, we decided to prepare and investigate ligands 2a (12) and 2b and to undertake a theoretical study of the conformational preferences of the relevant reactive species. The results obtained suggest the presence of a hydrogen bond where the metal serves as the hydrogen bond acceptor and the hydroxy group serves as the hydrogen bond donor.

Experimental Procedures

Computational Details. Geometries and energies of all intermediates were optimized by using the gradient-corrected density functional method B3LYP (13). This popular and computationally relatively cheap method has been shown to predict reliable geometries and energies (14–17). A basis set of double-ζ valence quality-labeled “laur” was used in the JAGUAR program (JAGUAR 4.0, Schrödinger, Portland, OR). A relativistic electron core potential developed by Hay and Wadt replaced the palladium core electrons (18, 19). In the geometry optimizations we used the 6–31G* basis set except in the geometry optimizations of the transition state structures, where we used the 6–31+G* basis set for all nonmetal atoms. All energies are calculated by using the 6–31G* basis set.

Materials and Instruments. Methylene chloride was dried over CaH₂. 2,2-Bis[(4S,5S)-4-hydroxymethyl-5-phenyl-1,3-oxazolin-2-yl]propane (2a) was obtained as described (12). 1H and 13C NMR spectra were recorded at 400.13 and 100.62 MHz, respectively, in CDC13. Enantiomeric excesses were determined by HPLC with a chiral column (Chiralcel OD-H, hexane/propan-2-ol 99:1, 0.5 ml/min). Comparison of reaction rates was achieved by monitoring the progress of the reactions by HPLC.
Scheme 2.

2,2-Bis(45,55)-4-methoxymethyl-5-phenyl-1,3-oxazolin-2-yl)propane (2b). Compound 2a (78.8 mg, 0.20 mmol) was added to a suspension of NaH (17.6 mg, 60% in mineral oil, 0.44 mmol) in tetrahydrofuran (2 ml) under nitrogen. The reaction mixture was heated at 36°C for 2 h and, after cooling to room temperature, methyl iodide (28 µl, 0.44 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and Et2O (5 ml) was added. The organic phase was washed with brine (5 ml) and then with H2O (5 ml). The organic phase was dried over Na2SO4 and the solvent was removed under reduced pressure. The slightly yellow oil obtained was dissolved in a small amount of hexane. Cooling to −78°C yielded white crystals, which were isolated and dried under vacuum to give 2b (37 mg, 44%). [α]D20 = −24.0° (c 0.53, CH2Cl2). 1H NMR δ 1.06 (s, 6H), 2.39 (s, 6H), 3.00 (s, 6H), 3.67 (dd, 2H, J = 9.8 and 6.9 Hz), 3.67 (s, 6H), 3.67 (dd, 2H, J = 9.8 and 4.4 Hz), 4.14–4.20 (m, 2H), 5.35 (d, 2H, 6.9 Hz), 7.25–7.30 (m, 10H); 13C NMR δ 24.9, 39.2, 59.5, 74.5, 74.6, 84.5, 125.9, 128.2, 128.8, 140.9, 169.8; HRMS (EI) caled for C29H30N2O4: 422.2206; found 423.2301 (MH+).

General Procedure for the Catalytic Reaction. Ligand (0.029 mmol, 6 mol%) and [([η5-C5H5]PdCl)2, ligand] (3.5 mg, 0.0096 mmol, 2 mol%) were dissolved in CH2Cl2 (1 ml) under dry conditions. The reaction solution was degassed at −78°C and put under nitrogen atmosphere before the reaction vessel was sealed. The reaction mixture was stirred for 2 h at −50°C, then cooled to −78°C. 1,3-Diphenyl-2-propenyl acetate (121 mg, 0.480 mmol) was transferred to the reaction vessel with dichloromethane (1 ml). A suspension of NaH (17.6 mg, 60% in mineral oil, 0.44 mmol) in 1.68 (s, 6H), 3.39 (s, 6H), 3.48 (dd, 2H, J = 9.8 and 4.4 Hz), 4.14–4.20 (m, 2H), 5.35 (d, 2H, 6.9 Hz), 7.25–7.30 (m, 10H); 13C NMR δ 24.9, 39.2, 59.5, 74.5, 74.6, 84.5, 125.9, 128.2, 128.8, 140.9, 169.8; HRMS (EI) caled for C29H30N2O4: 422.2206; found 423.2301 (MH+).

Results

Catalytic Reaction. The palladium-catalyzed substitution of allylic acetates (Scheme 2) is known to proceed by initial coordination of Pd(0) to the olefinic bond of the allylic acetate. Oxidative addition yields a π-allylpalladium(II) complex, which is attacked by the nucleophile, in the present case dimethyl malonate.

Fig. 1. Calculated minima for complexes 4a (Left) and 5a (Right). All hydrogen atoms on nonheteroatoms have been omitted for clarity.

Nucleophilic attack may occur at either of the two terminal allylic carbon atoms, resulting in two different palladium olefin complexes. Final ligand exchange completes the catalytic cycle (20). With symmetrically substituted allylic units, the stereochemistry of the reaction is determined by the regioselectivity of the nucleophilic attack.

Catalytic reactions performed with 2a and 2b as ligands and dimethyl malonate as the nucleophile resulted in products with (S) absolute configuration with 96% and 89% enantiomeric excess (ee), respectively.

Density Functional Theory Calculations. First the structures of the palladium(II) diphenylallyl complexes of ligands 2a and 2b (3a and 3b; Scheme 3) were computed. Ignoring less abundant syn–anti and anti–anti complexes, only one major complex from each ligand needs to be considered because of the C2 symmetry of the ligands. It was found that in the π-allyl complexes the O—C—C—N dihedral angles were similar for the hydroxy- and methoxy-containing ligands, 180.0° and 64.7° in 3a and −175.3° and 64.9° in 3b. Essentially equal conformations of the complexes with the two types of ligands were thus found, which is in accordance with what was previously found for Pd(II) π-allyl complexes of 1a and 1b.

Next the structures of the Pd(0) olefin complexes were calculated. NH2 was chosen as a suitable model nucleophile for the calculations of the olefin complexes (4–5) resulting from nucleophilic attack at the two diastereotopic allylic positions. The energy difference between the lowest energy conformations of complexes 4a and 5a was calculated to be 8.6 kcal/mol (Fig. 1 and Scheme 4). The complex leading to the (R)-product (which, because of the priority rules, corresponds to (S) absolute configuration when malonate is the nucleophile) (4a) was found to be lowest in energy, in agreement with the experimental results using dimethyl malonate as nucleophile [96% ee of the (S)-enantiomer]. The O—C—C—N dihedral angles in the lowest energy complex were −66.5° and 54.6°. What is evident is that the conformation of the hydroxy ligand changed in comparison with its conformation in the allyl complex. The structure was stabilized by an interaction between the protons in the two hydroxy groups and Pd (H–Pd 2.300 Å/2.663 Å). The O–H bonds were slightly elongated compared with the free ligand, the one closest to palladium (H–Pd 2.300 Å) by ~0.01 Å. The
hydroxy protons were situated above and below the coordination plane and were found to point toward palladium, which is in contrast to the situation in the allyl complex 3a, where the hydroxy proton close to palladium points away from the metal.

The energies of the olefin complexes with the methoxy-containing ligand (4b and 5b) were calculated and complex 4b, which gives the (R)-enantiomer of the product, was found to be lower in energy by 1.1 kcal/mol, in agreement with the experiments using malonate (89% ee of the (S)-product). The O—C—C—N dihedral angles were 176.3° and 175.2°. The methoxy-containing ligand was thus found to change its conformation on nucleophilic attack to one having two anti-periplanar methoxy groups.

To elucidate whether the conformational change observed for the hydroxy-substituted ligand really had an influence on the stereoselectivity of the catalytic process, the transition state structures of simplified systems 6a and 6b (Scheme 5) were computed. NH3 was chosen as a model of the nucleophile to simplify the calculations.

The conformations of the ligands in the transition state were similar to those found in the olefin complexes, indeed justifying our assumption that the relative energies of the olefin complexes can explain the stereochemical outcome of the catalytic reaction. The transition state for the complex with the hydroxy-containing ligand (Fig. 2) seems to be stabilized by the interaction between palladium and the protons in the hydroxy groups (Pd—H ~ 2.6 Å). This finding may also explain the increased activity of this catalyst; reactions were completed within 6.5 h when ligand 2a was used and within 24 h when ligand 2b was used. The O—H bonds were not elongated in the transition state, however. The O—C—C—N dihedral angles in the transition state structure of the hydroxy-containing complex were 62.0° and 61.8° and in that of the methoxy-containing complex they were 180.0° and −175.0°. In the reaction with the hydroxy-containing ligand, the transition state leading to the observed product was found to be lower in energy than that leading to the product with opposite absolute configuration by 1.94 kcal/mol.

Balavoine and coworkers (21) recently investigated an analogous case, 7a and 7b (Scheme 6), and found that the hydroxy- and methoxy-substituted ligands serve as pseudo-enantiomers, yielding different product enantiomers (92% and 85% ee, respectively). Our results suggest that the reversed stereoselectivity observed by Balavoine and coworkers on O-methylation of 7a may originate in the same kind of conformational change as found in 1a and 2a. To study this possibility, the structures of the relevant π-allyl and π-olefin complexes, resulting from nucleophilic attack at the pro-R and pro-S allyl positions, were calculated. The O—C—C—N dihedral angles were 69.3° and −178.6° in the allyl complex with the hydroxy-containing ligand (8a) and 68.0° and −175.0° in the allyl complex with the methoxy-containing ligand (8b; Scheme 7). Similarly to what was found in 3a, the hydroxy proton close to palladium pointed away from the metal in the allyl complex 8a. Calculations of the two olefin complexes with the hydroxy-functionalized ligand (9a and 10a; Scheme 8) showed that in the lowest energy conformations for 9a and 10a all O—C—C—N dihedral angles were between 62° and 65°. The calculated energy difference between the complexes was 1.6 kcal/mol, and the favored olefin complex (9a) was the one that experimentally was shown to lead to product (92% ee of (S)-enantiomer was formed). However, the energy difference found was very small, and many local minima existed for both 9a and 10a. What is evident is that the conformation of the hydroxy ligand changed compared with its conformation in the allyl complex in the same way as for ligand 2a. The structure was stabilized by an interaction between the protons in the two hydroxy groups and Pd (H—Pd 2.357/2.464 Å). The two O—H bonds were slightly elongated, by ~0.01 Å compared with the free ligand, also in this case. The bis(oxazoline) backbone was much more bent in complex 9a than in complex 10a. The ligand in complex 10a adopted a close to C2-symmetric conformation, whereas both hydroxy groups in the ligand in complex 9a resided above the coordination plane. In the complexes with the methoxy-containing ligand, 9b and 10b, both O—C—C—N dihedral angles were close to 180°, the olefin complex leading to product with (S) absolute configuration [corresponding to (R) absolute configuration with dimethyl malonate as nucleophile] was 1.5 kcal/mol lower in energy than that leading to the (R)-product. This finding is in accordance with experimental results (85% ee of the (R)-product). Balavoine and coworkers also observed that the hydroxy ligand exhibited considerably
higher reactivity, yielding full conversion within 2 h, as compared with 96 h for the methoxy ligand. This dramatic difference can be explained by a Pd–HO interaction stabilizing the transition state involving the hydroxy-containing complex.

In contrast to the situation with 2a,b and 7a,b, the rates of the catalytic reactions using 1a and 1b (R' = R = H) were found to be similar. This difference might be because different steps are rate-determining. To check this possibility, reactions in the presence of 1a and 1b were conducted with different nucleophiles. The rate-determining step may either be the oxidative addition or the nucleophilic attack. Indeed, changing to the less reactive methyl acetoacetate did not affect the rate of reaction, indicating that nucleophilic addition is not rate-determining. Changing to the even less reactive 2,4-pentanedione resulted in considerably decreased reaction rates, indicating that the rate-determining step was now the nucleophilic attack. The reactions were, however, too slow to allow a reliable comparison between 1a and 1b.

**Nature of the Pd–HO Interaction.** Interactions between protons bound to oxygen or nitrogen and late transition metals in low oxidation states have lately been observed in several cases (22–26). The interaction exhibits features similar to those of the classical hydrogen bond (27), with elongated O–H bonds, short M–H distances, and large O–H–M bond angles. The electron-rich metal center serves as the hydrogen bond acceptor. This type of hydrogen bond is commonly found in the solid state, but it has also been observed in solution (28). To our knowledge, no report of hydrogen bonds involving Pd(0) has appeared, although Ni(0) has been shown theoretically to act as hydrogen bond acceptor (29). Another example involving a d10 metal is provided by the adsorption of water on Pt(111), as hydrogen bond acceptor (29). Another example involving a Pd(0) olefin complex is different from an agostic interaction. Whereas the agostic interaction involves an electron-deficient metal center and represents a three-center two-electron bond, this type of weak hydrogen bonding involves a basic metal center and represents a three-center four-electron bond.

Taken together, the data obtained show that the geometries of the Pd(0) olefin complexes with hydroxy-substituted ligands fulfill the requirements of a Pd–HO hydrogen bond. The N–C–O dihedral angles, Pd–H, Pd–O, and O–H distances and O–H–Pd bond angles in the olefin complexes 4a and 5a are summarized in Table 1. The palladium–hydrogen distances were in the range of 2.300–3.052 Å, whereas the palladium–oxygen distances were considerably longer, and the O–H bonds in the complexes were slightly elongated compared with the free ligands. In contrast to the situation in the Pd(II) allyl complexes, the hydroxy protons were found to point toward palladium in the olefin complexes. The palladium–hydrogen–oxygen angles involving the hydrogen groups situated closest to palladium were found to be 149.4° and 157.3°. These results, together with the observed stabilization of the transition state in reactions with the hydroxy-containing ligands, are consistent with the interpretation of the interaction as a hydrogen bond (22) and exclude metal-coordinated ligand interacting by means of the oxygen lone pair.

**Conclusions**

A Pd–HO hydrogen bond in Pd(0) olefin complexes of hydroxyl-containing ligands has been identified by density functional theory computations. The presence of the hydrogen bond affects the stereochemistry and the rate of palladium-catalyzed allylic alkylations and thus explains the different behavior of hydroxy- and methoxy-containing ligands in the catalytic process. Exploiting the use of other ligands containing 4-hydroxymethyl-substituted oxazolines is needed to study whether the enhancement of stereoselectivity and reactivity found here is a more general phenomenon.

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