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Elucidating the roles of enthalpy, entropy, and donor atom in the chelate effect for binding different bidentate ligands on the same metal center

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ABSTRACT

We present a thermodynamic study of the chelate effect for a series of P–P, N–N, and P–N bidentate ligands binding to $PdCl_2(MeCN)_2$ in acetonitrile (MeCN), using isothermal titration calorimetry (ITC) to measure the solution-phase binding thermodynamics. The chelate effect is considered to be an entropic effect, that is, the enthalpic contributions attributed to binding for comparable monodentate and bidentate ligands are nearly identical, meaning that changes in ΔG are due to favorable changes in ΔS upon displacement of bound solvent molecules. However, our results demonstrate that enhanced enthalpic contributions (i.e. large and exothermic) control the stability of the chelated complexes and generally are accompanied by large entropic penalties. We discuss the contribution of solvent reorganization and its role in enthalpy–entropy compensation for the binding equilibria studied.

1. Introduction

The design of sophisticated homogeneous catalysts relies on knowledge of different classes of ligands, such that the chosen ligands impart the desired activity and selectivity for a given chemistry. Altering the electronic and steric characteristics of the metal centers in organometallic complexes dictates the most likely reaction paths during catalytic processes. Polydentate ligands are frequently employed to provide thermodynamic stability via chelation to organometallic complexes, known as the chelate effect, that is unattainable with monodentate ligands [1]. As such, a great variety of polydentate ligands, primarily bidentate ligands, have been synthesized and studied in order to understand their effects on catalytic activity and selectivity. Bidentate ligands also impart steric effects unobtainable with monodentate ligands, which affect the activity and selectivity in ways that monodentate ligands cannot [2]. There is a great interest in quantifying the effects of bidentate ligands on the activities and selectivities of catalytic centers in solution in order to determine whether there are trends that can be applied across different classes of ligands. Additionally, these trends enable chemists to design new ligands that exploit these observed enhancements in catalytic activities and selectivities. From a steric standpoint, the catalytic activity and selectivity are controlled primarily by two factors: the bite angle, the angle the ligand forms with the metal center, and the conformational flexibility of the ligand, the ability of a ligand to assume a variety of bite angles with the metal center so long as the energy of the complex does not vary significantly from the most stable form of the complex [3]. Recently, there has been considerable effort in performing DFT calculations to study the electronics and energetics of bidentate ligands commonly used in homogeneous catalysis [4,5]. Primarily, these studies aim to quantify the energies of the HOMO and LUMO of each ligand, while considering each donor atom of the ligand as a separate entity and calculating the bond dissociation energies from model complexes such as $ZnCl_2$ and $PdCl_2$ for a series of P–P and P–N ligands [4,5].

Bidentate ligands, particularly those containing phosphorus and nitrogen donor atoms, are used in a wide variety of chemical transformations, owing to their unique abilities to enhance catalytic activity while controlling selectivity. Mixed bidentate ligands, such as P–N ligands, represent an intriguing avenue for combining two different types of donor atoms on the same ligand, which allows for moieties that have hard and soft basic properties simultaneously [6]. Blaser et al. discussed the roles of P–P and P–N bidentate ligands for the hydrogenation of a great number of substrates such as alkenes, ketones, aromatics, and nitriles, all while highlighting the variety of metal centers available for these hydrogenations and their chemo-, enantio-, and stereoselectivities [7].

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Chelating *N*-heterocyclic carbenes (NHCs) are a class of strong electron donor ligands via N atoms and are used in C–C bond formation reactions such as Heck reactions, Suzuki couplings, Sonogashira couplings, and other reactions such as transfer hydrogenations and hydrosilylation of terminal alkynes [8,9]. McCarthy and Guiry reviewed a variety of chiral P–P, N–N, and P–N bidentate ligands, among others, for use in designing asymmetric organometallic complexes for the asymmetric synthesis of enantiomerically pure compounds [10].

The main difficulty with ligand design is that amassing an exhaustive library of ligands for a certain class of catalytic reactions is both time-consuming and largely ineffective in terms of the number of ligands that must be studied in order to draw reasonable conclusions regarding catalytic performance from a class of ligands. Combinatorial chemistry and high-throughput screening are the main techniques for determining the ability of a synthesized ligand to alter catalytic activity and selectivity. In short, each ligand is determined to have a series of physical and chemical properties and is then tested for its catalytic performance, which is then measured against other ligands [11,12]. The ligands that best enhance the catalytic activity and selectivity are compared to one another in order to determine which ligand properties contribute most to the observed catalytic enhancements. This methodology is by no means uninformative, but difficulties in synthesizing bidentate ligands frequently require a great deal of effort and, to a large degree in its own right, serendipity in order to compose the optimal ligand(s) for a specific catalytic reaction [2].

In an effort to broaden the understanding of the effects of bidentate ligands on stabilizing metal centers in solution, we use calorimetry to *quantify* the thermodynamics of the chelate effect by examining the binding equilibria between a model compound, $PdCl_2(MeCN)_2$, in acetonitrile (MeCN) and various bidentate ligands (P–P, N–N, and P–N) and comparing the results to similar monodentate ligands, triphenylphosphine (PPh_3) and pyridine (py). We use isothermal titration calorimetry (ITC) to measure the equilibrium binding constants (K_i), binding enthalpies (ΔH_i), and reaction stoichiometry (n_i), all in a single experiment. Calorimetry is a natural complement to the DFT data available in the literature regarding the energetics of ligand binding to metal centers [4,5]. ITC is an appropriate technique because modern calorimeters are capable of measuring binding constants on the order of $10^9\ M^{-1}$ due to their nW level of sensitivity [13]. In particular, our analysis can be extended to understand these systems *in situ*, whereas DFT calculations cannot fully account for solvent effects and often treats reactive species in a vacuum. ITC is a viable alternative to van't Hoff analysis as a method for determining the thermodynamics of binding events. Horn et al. investigated the differences between ITC and van't Hoff analyses for experimental and simulated results using two different binding systems: complexation of Ba^{2+} ions with 18-crown-6 ether and complexation of 2'-CMP and RNase A [14]. They showed the enthalpies obtained from both analytical techniques were equal over the range of temperatures studied and within experimental error and concluded that each technique is valid for thermodynamic analysis of binding systems. ITC experiments can be conducted at different temperatures, which would allow for observation of the changes in the thermodynamic parameters as functions of temperature (e.g. $K_i(T)$, $\Delta H_i(T)$). We supplement our thermodynamic analysis with NMR and UV–Vis characterization and analysis of the reaction products and rationalize the obtained thermodynamic parameters, specifically ΔH and ΔS, with respect to the chelate effect, inherent properties of the tested ligands, as well as the subtle roles that solvation and solvent–solute (i.e., $PdCl_2(MeCN)_2$ and ligand are treated as solutes) interactions play in contributing to the stability of chelated complexes. We also discuss the presence of enthalpy–entropy compensation and how solvent reorganization manifests itself as a favorable contribution to enthalpy for all three types of ligands.

2. Experimental

2.1. Materials and solution preparations

$PdCl_2$ was obtained from Alfa Aesar, 1,2-bis(diphenylphosphino)ethane (diphos) was obtained from Strem, and MeCN was obtained from EMD. Pyridine (py), 1,5-bis(diphenylphosphino)pentane (dpppe), 2,2′-bipyridine (bpy), 4-(dimethylamino)phenyldiphenylphosphine (dmap), *o*-phenylenediamine (opd), and PPh_3 were obtained from Sigma while (*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine ((*R*)-(*S*)-PPFA)) and (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine ((*S*)-(*R*)-PPFA)) were obtained from Alfa Aesar. All chemicals were used without further purification.

All 0.75–2 mM solutions of $PdCl_2(MeCN)_2$ were prepared by dissolving 6.6–17.7 mg of anhydrous $PdCl_2$ in 50 mL of degassed MeCN and stirred vigorously overnight with gentle heating. The structure of $PdCl_2(MeCN)_2$ is *trans* as reported in the literature [15]. All ligand solutions were prepared immediately before each titration by dissolving the appropriate amount of ligand in degassed MeCN followed by vigorous stirring.

2.2. ITC experimental procedure for binding bidentate ligands to $PdCl_2(MeCN)_2$

ITC experiments were performed using a NanoITC calorimeter (TA Instruments, New Castle, DE) equipped with hastelloy cells ($V = 1.056$ mL). All titrations were carried out at 25 °C using a 250 μL syringe at a stirring rate of 250 rpm. The sample cell contained $PdCl_2(MeCN)_2$ and the reference cell contained pure MeCN. The "heat flow" baseline was allowed to equilibrate once the reference and sample solutions were loaded into the cells. Titrations began after equilibration of the power rating (note: the power rating is the thermal compensation of the calorimeter that is applied to the sample cell to keep it at the same temperature as the reference cell). Titrations were run as an incremental series of injections of the appropriate ligand into the $PdCl_2(MeCN)_2$ solution. Blank experiments were conducted under identical conditions with only solvent in the sample cell to experimentally determine the heat of mixing of the ligands with pure MeCN. These blanks were subtracted from the experiments with $PdCl_2(MeCN)_2$ in the cell and integrated to isolate the heat evolved from metal–ligand interactions. Data analysis was performed using NanoAnalyze v2.1 from TA Instruments using the Independent Sites algorithm (see the Supporting information for derivations of the models discussed within the present work) [16,17]. In NanoAnalyze, we chose the appropriate binding model and input initial guesses for each fitting parameter (K_i, ΔH_i, and n_i) and used the built-in optimizer to fit the integrated heat data from a specific ITC experiment. For all of our experiments, we did not fix the values of any of the thermodynamic fitting parameters (K_i, ΔH_i, and n_i) because we did not want to bias any of the variables (i.e. force a variable to assume a value during the fit because a fixed parameter was not able to compensate accordingly). Per standard ITC experimental practice, we held the injection volume, initial ligand concentration (i.e. the syringe concentration), and initial metal concentration (i.e. the sample cell concentration) constant throughout each experiment. The nonlinear fit converges when the sum of the squares of the differences between the measured heat (the integrated ITC heats from each peak of the thermogram) and the calculated heat (as a function of the initial guesses of the fitting parameters) reaches a minimum. We then refit the ITC data using the values (K_i, ΔH_i, and n_i)