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Review

Substrate binding and activation via pendant hydrogen-bonding groups as an approach to biomimetic homogeneous catalysis

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Abstract

In a biomimetic approach to organometallic catalysis, pendant hydrogen-bonding groups are shown to influence the chemistry of ligand binding and activation in an iridium complex. Such groups can bind a substrate by hydrogen bonding and so offer the possibility of a biomimetic approach to catalysis where binding is controlled via molecular recognition. Because catalyst design in this area may be challenging, combinatorial and rapid screening methods may be needed to assay potential catalysts and initial progress on developing these methods for hydrosilation of alkenes and imines is described. Catalysis of aldehyde imination and the origin of pK_a changes of bound H_2 are discussed.

Keywords: Hydrogen bonding; Combinatorial chemistry; Homogeneous catalysis; Hydrosilation; Biomimetic; Iridium

1. Introduction

Homogeneous catalysts generally employ coordinate bonds alone to bind the substrate in the catalytic reaction [1], yet metalloenzymes [2] use molecular recognition [3] and also bind the substrate via hydrogen bonding [4]. We have therefore embarked on a program of appending groups capable of hydrogen bonding and molecular recognition to the spectator ligands in typical metal complexes for application as homogeneous catalysts. The aim is not the modeling of enzyme sites but using hydrogen bonding in biomimetic homogeneous catalysis. In principle, this approach could lead to exceptional catalyst selectivity as a result of the high binding selectivity achievable in molecular recognition. While the ultimate goal has not yet been achieved, we have promising initial data which suggest that two-point substrate complexation, both by coordinate bonding to the metal and by hydrogen-bonding with a pendant group, can indeed be achieved readily.

In general, binding efficiency is unlikely to mirror catalytic efficiency because to achieve rate acceleration, the binding has to stabilize the transition state for the catalytic reaction, not simply bind the substrate itself. Indeed strong substrate binding on its own *inhibits* catalysis because it makes the transition state harder to achieve. The final outcome in terms of catalyst selectivity and rate relies on competition between a number of effects that have received little or no study and are therefore hard to predict. This means that designing an effective catalyst by computer modeling or other non-empirical methods is not possible at present. Certainly, the bioorganic molecular recognition literature includes relatively few examples of efficient catalysts [5].

Faced with this problem, we have begun a program which we are using combinatorial ligand synthesis followed by rapid screening of the resulting catalysts to identify useful catalytic materials. While combinatorial methods have proved very useful in the pharmaceutical industry, such methods are still under development for catalysis and there is still no generally accepted protocol.

The difficulties are more than simply practical, however. Some commentators have objected that combi-

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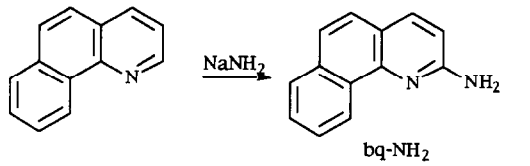
torial methods lack intellectual input and should be shunned by right-thinking individuals. This view fails to take account of several points. First, the library is not constructed at random but is chosen to test some hypothesis — in this case that hydrogen-bonding pendant groups will be useful in homogeneous catalysis. Once a successful catalyst has been discovered, one will want to know why that catalyst is successful. This will require classical mechanistic studies, presumably by conventional means. Finally, if the method does provide a much faster route to identifying interesting organometallic compounds for study, it will certainly be used widely by workers in the field. Just like good conventional experiments, combinatorial experiments will also have to be very carefully conceived, executed and interpreted, however. Control experiments will be necessary at all stages because nothing can be taken for granted in this area.

2. Ligands with hydrogen-bonding pendant groups

2.1. Choice of system

In looking for a suitable system, we sought a rigid chelate where the pendant group would be held firmly in such a way as to prohibit direct binding to the metal. Cyclometallated benzoquinolines seemed to offer a good test-bed for the idea because synthetic pathways to 2-substituted derivatives are available via the reaction of benzoquinoline with any of a variety of nucleophiles. For example, $NaNH_2$ brings about the conversion shown in Eq. (1). This ligand (denoted bq-NH_2) readily cyclometallates to give complexes such as **1** in which the ligand binding site *trans* to the high *trans* effect M-aryl bond is also adjacent to the pendant amino group. This group cannot itself bind to the metal however, but can hydrogen bond to an atom bound to the metal [6].



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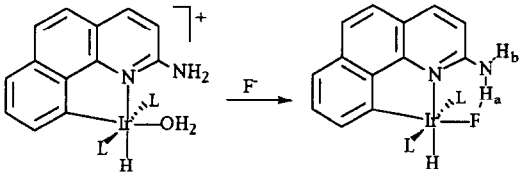

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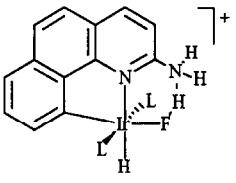
2.2. Fluoride and HF complexes

As an example of two-point binding via coordinate and hydrogen-bonding, **1** reacts with a fluoride ion to give the fluoro complex **2** (Eq. (2)). The resulting N–H···F hydrogen-bonding is most clearly evident from the prominent J(H···F) coupling of 52 Hz, but is also confirmed from the IR and other NMR spectroscopic data [6].

The strength of the hydrogen-bonding can be estimated from the barrier for the exchange of H_a and H_b in the variable temperature ^{1}H-NMR spectrum (12.4 kcal mol^{-1}). In the transition state for the rotation, the hydrogen bond and the delocalization energy of the nitrogen lone pair interacting with the arene ring are both lost, so the barriers in different compounds provide a relative ordering of the hydrogen bond energies. Our best estimate of the delocalization energy is 5.7 kcal mol^{-1}, based on a variety of criteria including quantum modeling in collaboration with Odile Eisenstein. With this assumption we have an estimate of the absolute hydrogen-bond energy: 6.7($\pm$1) kcal mol^{-1}. This value seems reasonable considering that F^- is one of the best hydrogen-bond acceptors. In earlier work, we still needed to assume that the conformation of the molecule is appropriate for hydrogen-bonding; a recent X-ray structure of **2** by Liable-Sands and co-workers [7] reassured us on this point, although the amino hydrogens were not located.

Protonation of **2** with $HBF_4{\cdot}Et_2O$ gives complex **3**, stable below -20°C only. The J(H···F) coupling is now 440 Hz, increased greatly from the 52 Hz value characteristic of a N–H···F interaction. This together with other coupling and NOE information therefore led us to assign the structure **3**, with an N···H–F group. This is best considered as a HF ligand hydrogen bonded to the pendant NH_2. Control experiments with bq and 2-methylbenzoquinoline (bq-CH_3) showed that the NH_2 group is essential. The purpose of the bq-CH_3 control was to model the steric effect of the pendant NH_2 with a non-hydrogen-bonding group. Although M–F···H–F (bifluoride) complexes are known, no other complex like **3** seems to have been reported.



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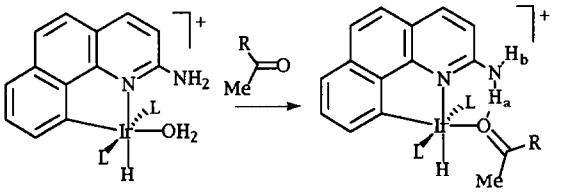
2.3. Ketone binding

A series of ketone complexes (**4**, acetone, a; hexanone) can be formed by the reaction of **1** with aliphatic ketones [8]. Binding is so effective that the 2-hexanone complex (**4b**) was obtained simply by recrystallizing **1** from CH_2Cl_2–*n*-hexane. This was ascribed to the presence of trace 2- and 3-hexanone

formed as a result of *n*-hexane autoxidation. Hydrogen-bonding is evident in **4** from spectroscopic and structural studies. For example the N···O distance of 2.897(7) Å is entirely appropriate for a hydrogen bonded species. Eq. (3) shows the hydrogen-binding in **4**. Binding is selective for 2-hexanone perhaps because of steric repulsion between the *endo* ethyl group of Et(CO)(*n*-Pr) and the Ir–H hydride.



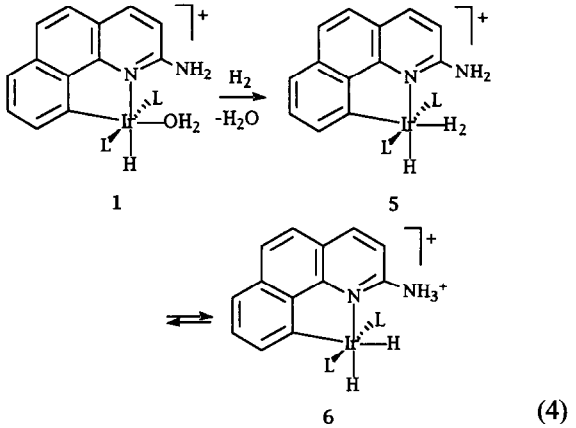
1 4

(R = Me, a; Bu^n, b) (3)

The two-point binding of the ketone prevents easy rotation about the Ir–$OCMe_2$ bond, a process that exchanges the two methyl groups. Where no hydrogen-bonding pendant group is present, the acetone complex shows a single methyl resonance at all accessible temperatures. In **4a**, in contrast, there is a decoalescence at −90°C and the two methyl groups resonate separately. Quantitative treatment of the data suggests the N–H···O hydrogen bond is worth about 3 kcal mol^{-1}. Work is currently in hand to examine more sophisticated examples of molecular recognition by appending more elaborate groups to the bq core.

2.4. Hydrogen activation

In order to investigate dihydrogen activation, a potential first step in a catalytic hydrogenation, we looked at the interaction of **1** (L = PPh_3) with H_2 to give **6**, a species in which the dihydrogen has been split heterolytically, hydride remaining on the metal and a proton being abstracted by the pendant amino group (Eq. (4)) [9]. In the absence of a pendant NH_2 group, a molecular hydrogen complex is formed in this system, so a plausible intermediate is **5** (Eq. (4)).



1 5 6 (4)

Quantum chemical studies by Odile Eisenstein suggested that the dihydrogen complex, **5**, should be slightly more stable than **6** (L = PH_3). This apparent disagreement suggested that tautomer **5** might be directly observable with a sufficiently electron-donor L. We wondered if the use of a stronger electron-donor phosphine than PPh_3 might be useful. We therefore moved to PBu^n_3, with the result that the dihydrogen complex (**5**, L = PBu^n_3) is now the stable form. This implies that the basicity of the Ir–H bond is affected strongly by the nature of the phosphine, a result that was verified computationally using the series PH_3, PFH_2, PHF_2, and PF_3. The acidity of ligands like H_2O that are bound via a lone pair are slightly affected by small differences in the ligand set. In contrast, the acidity of σ-complexes like $M(H_2)$ are very sensitive to the ligand environment. Hydride binds to the iridium much more strongly than H_2 does, leading to a strong acidification of H_2 on binding. The variability of the pK_a of bound H_2 seems to be related to the differential back donation from the metal that changes the binding energy for H_2 much more than for H.

2.5. Catalysis of imine formation

So far, we have only one result involving true catalysis [8]. We find that there is a small but significant increase in the rate of catalytic imine formation for the reaction of PhCHO and the bulky amine $MesNH_2$ (Mes = mesityl) to give PhCH=NMes when **1** is used as a catalyst, compared to the situation where the reaction is catalyzed by the analogous iridium complex (**7**) lacking a pendant NH_2 group. Under the conditions used (20°C, CD_2Cl_2, monitoring by NMR), the rate for **7** was 14 turnovers per h, while the rate for **1** was 18 turnovers per h.

One possible reason for the relatively disappointing rate increase may be that for effective catalysis, hydrogen-bonding must selectively stabilize the transition state for the catalytic reaction. If hydrogen-bonding stabilizes the ground state (catalyst with substrate bound) as much as it does the transition state, no catalytic acceleration is possible. Therefore, there must be a subtle mismatch between the hydrogen-bonding pendant group in the ground state but a match in the transition state. This may be difficult to achieve by rational design and so we are considering combinatorial methods to see if these can provide more effective catalysts.

3. Combinatorial and rapid screening methods

Combinatorial chemistry [10] involves: (i) the rapid parallel synthesis of a library of many compounds of related structure; (ii) an assay of these compounds for a

desired property; and (iii) the identification of the compounds called 'hits' that show the properties required. A large variety of structures can, in principle, be probed by the combinatorial method in a short time. Once an initial hit has been identified, a new library can be made that probes modifications of the initial hit to optimize the system.

The library is often made on polymer beads, following Merrifield's [11] concept of solid-phase synthesis on polystyrene, dating from 1963. Each bead or type of beads can contain a slightly different compound of the same general class and, usually after cleavage from the bead, each compound can be assayed separately. Bunin and Ellman [12] recognized that a chemically diverse library could be created by solid-phase organic synthesis (SPOS) [13] for nonpeptide organic compounds, where the substituents of a central core structure are permuted. For catalytic applications, we only have to design the SPOS to produce ligands, then attach the metal and the beads should now be active catalytically. If a suitable assay can be developed, it should then be possible to assay catalytic activity on the beads and identify hits. Several examples of this general plan have been published but there is still no general agreement on the exact methods to adopt, and we can expect that many different variants will be tried in the next few years. Others as well as ourselves have reviewed the area of combinatorial catalysis in detail very recently and so we will only discuss our own work here [14].

While combinatorial methods are well established for polypeptide and organic chemistry. There are still very few reports of their use in organometallic catalysis. Before attacking the hydrogen-bonding problem, we therefore felt that we needed to look at combinatorial methods and see how they could be applied to organometallic catalysis in general. It is not yet clear, for example, if it is possible to assay catalysts on-bead or if this is best done in reaction wells after cleavage.

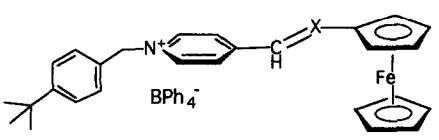
One of the challenges of the area is that several factors must be optimized before the overall program can work. First, a suitable catalytic reaction has to be chosen. Then a suitable rapid assay needs to be perfected. Ideally, we need a hierarchy of assays with an initial screen for activity. Unless high-selectivity, low-activity catalysts are acceptable, only those catalysts passing the activity test could be carried on to the selectivity assay, which ideally would already be a part of the activity assay. Finally, we need a suitable library. If this is to be on polymer beads to take advantage of combinatorial synthesis by SPOS, we need to be certain that the loading of the catalyst is low so that the rate is not limited by mass transfer into and out of the bead. This creates problems for the necessary cleavage steps to check that the correct ligand has been made; if the amount of ligand on the bead is small it will be much more difficult to carry out this control.

3.1. The catalytic reaction

We decided to use hydrosilation as our catalytic reaction. The substrates, silane and either alkene, ketone, or imine, are all easily handled liquids or solids, and the conditions are relatively mild. A wide range of metal complexes catalyzes the reactions, at least to some extent, and a wide variety of selectivity issues are of interest. For example, in alkene hydrosilation these are the ratio of linear to branched product, the ratio of silation to dehydrogenative silation and to hydrogenation. In alkyne hydrosilation, there is also an issue of *syn* versus *anti* silane addition [15]. In imine and ketone hydrosilation, asymmetric reactions are also of interest.

3.2. The assay

We wanted a simple assay with a visual indication that would allow us to follow simultaneously a whole set of parallel catalytic reactions. The obvious possibilities are a reactive dye or a reactive fluorophore [16]. In the initial work, we synthesized the organometallic dye, **8**, that bleaches undergoing a catalytic reaction, such as hydrosilation [17]. The dye must not have any interfering reactive groups, so we use a ferrocenyl group as an electron donor and a pyridinium group as the acceptor function; the bulky benzylic tail is needed to make the dye conveniently soluble. When the reactive C=C or C=N bond that joins the electron donor to the acceptor is saturated, the electronic connection between them is broken and the dye bleaches. The starting dye must absorb intensely ($\varepsilon\{\text{EtOAc}\} = 12\,600$, **8a**; 5200, **8b**) so as to mask any catalyst color and to be a sensitive indicator of the reaction. We can not only observe an initial bleaching time, t_i, which corresponds to the first observable color change relative to a control well, but also a final time, t_f, which corresponds to complete bleaching. We find that t_i corresponds to ca. 40% dye conversion and t_f to ca. 95%. A long t_i means a long induction time and a short value of $t_f - t_i$ means a high catalyst activity. Recording the data proved was possible using a digital camera. A Teflon block drilled with 70 reaction wells is used for the assay, which is carried out in a glove bag or glove box. With continuously monitoring a large set of catalysts, a hit is indicated by the dye bleaching in one of the reaction wells.



8 a, X = CH
b, X = N

We first applied the dye method to assaying a library of conventional catalysts for hydrosilation with Ph_2SiH_2; some catalysts in the library were known

previously to be active and some not. The best-known one, $RhCl(PPh_3)_3$, was very readily identified as a hit by the very rapid bleaching of dye **8** in the presence of silane. Among the most active catalysts of all, however, was a palladacycle never previously tried in hydrosilation. Controls demonstrated that catalyst, silane and substrate are all required for reaction to occur [17].

A limitation of this method is that the dye-substrate is a very nonstandard alkene with reactivity very much higher than conventional substrates and also a strong tendency to give competitive hydrogenation instead of hydrosilation, so we are now moving to more conventional substrates as indicators of reaction, for example, the use of a fluorescent alkene. Even so, the relative order of activity of different catalysts seems to be preserved between the dye-substrates and conventional ones.

3.3. The library

The most difficult part of the program has been grafting a set of ligands onto the Merrifield-type polystyrene beads — we generally use 1% divinylbenzene cross-linked polystyrene. We decided to attempt the synthesis of a phosphine library but the BuLi steps required to introduce $-PR_2$ groups in conventional solution synthesis tend to attack the resin and cause grafting of phosphorus throughout the system in a poorly controlled fashion. This means we still have poor control over phosphorus and of subsequent metal loading. However, various strategies are being followed to solve the remaining problems. Therefore, for the moment, our results are not of satisfactory quality. Even so, a significant hit was identified with resin-bound $NpPPh_2$ (Np = 1-naphthyl) and $[(cod)IrCl]_2$ as metal precursor [18]. The very strong propensity of the Np group to undergo cyclometallation may be related to the high activity observed.

4. Conclusions

Since enzymes use hydrogen-bonding together with metal-ion-mediated catalysis for achieving high selectivity and rate, we are pursuing a biomimetic approach in which hydrogen-bonding groups are incorporated into organometallic catalysts. Combinatorial methods have been considered for selecting ligand systems. This area is still at an early stage and there is no general agreement about how the principles of combinatorial chemistry can best be applied to the problem of organometallic catalysis. The method holds promising for future developments into a broadly useful method.

Acknowledgements

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