Nonrigid diastereomers: epimerization at chiral metal centers or chiral ligand conformations?

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Opinion

Variable temperature NMR studies of chiral metal complexes can reveal two diastereomers at lower temperatures. A *caveat* is presented regarding the possibility that chiral ligand conformations may be involved rather than epimeric chiral metal centers.

Chiral transition metal organometallics were first resolved more than a quarter of a century ago.[1–6] A large class of these complexes are piano-stool type structures containing an η^6-arene or η^5-cyclopentadienyl ligand, such as **1**, **2**,[5,6] **3**,[7,8] **4**,[9,10] **5**,[11,12] and **6**.[13]

1   **2**   **3**   **4**   **5**   **6**
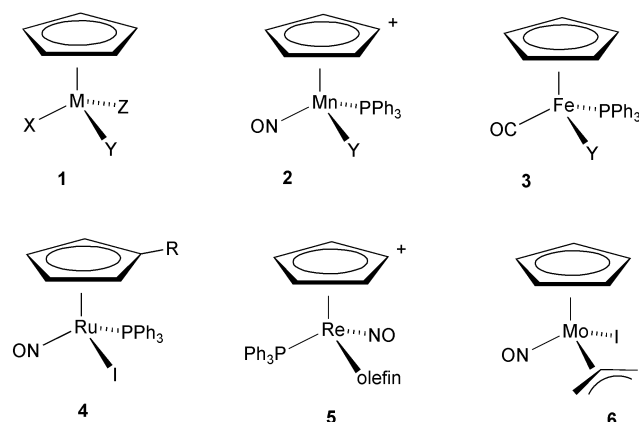
The metal-centered chirality often has a long term stability to racemization ($\gg$1 day) and there have been frequent applications of these chiral-at-metal compounds in asymmetric synthesis. If there are chiral ligands present diastereomers are formed and the relative stability of these diastereomers can often provide a metal complex that is highly enriched in one diastereomer owing to unfavorable steric interactions in the other epimer. This epimerization at the metal center can occur after the initial formation of the complex and this ultimately results in a distribution of product diastereomers that reflects the thermodynamic equilibrium. This is most often observed in compounds with enantiopure chiral chelating ligands.
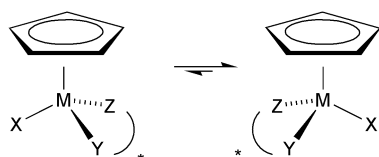
The relative stability of diastereomers is of critical importance in asymmetric catalysis, and especially in strategies involving chiral poisoning and asymmetric activation of asymmetric catalysis.[14,15] Hence, when adding a chiral chelating ligand to a cyclopentadienyl or arene complex, the issue of the kinetic and thermodynamic stability of the diastereomers is crucial. If a mixture of diastereomers is obtained on crystallization, a single crystal of either one might be selected for analysis, possibly giving a false indication of the predominant isomer formed. Crystallization can also yield a single isomer, *even the minor isomer*, owing to solubility differences. In either case, X-ray crystallography may not provide a definitive answer for distinguishing the major diastereomer present in solution. Generally, however, obtaining an NMR spectrum of a dissolved portion of a crystal used for an X-ray determination provides a clear indication of the NMR chemical shifts of the diastereomer that was analyzed.

In this context it is important to recognize the time scale on which diastereomers might interconvert. Frequently, one is dealing with second and third row low-spin d^6 transition metals, such as Rh(III), Ir(III) and Ru(II), that would be expected to have relatively slow rates of reaction for any process involving ligand-metal bond breaking. Thus, one must take care when evaluating a diastereomeric ratio to ensure that a thermodynamic equilibrium has been reached if one is trying to establish that a given ligand forces a particular configuration at the metal. As pointed out by Brunner,[16] there have been a number of cases in which 100% diastereoselectivity has been claimed for a given ligand, but subsequent evidence has suggested that two diastereomers had been formed in significant concentrations.[17–19]

It has been suggested[16] that evaluation of the temperature dependant NMR should be used to determine if, in fact, the diastereomers are interconverting rapidly and averaged NMR spectra give the impression that there is only one isomer present. In some cases this may truly be the situation; however, we have noted that sometimes conformational equilibria in the ligands can also give rise to epimers being observed in the NMR.[20,21] These epimers are the result of the interconversion of chiral conformations of the ligands and not of epimerization at the metal.

With the advent of high field NMR instruments, the chemical shifts of resonances arising from different conformations of ligands (such as different phenyl orientations having slow rotation about the P–C and/or P–M bond) start to become observable because the extent of averaging depends upon the square of the chemical shift differences in each epimeric conformation. Thus, on lowering the temperature in NMR experiments, broadening may occur owing to hindered rotation about a C_{phenyl}–P bond. It is entirely possible that complicated ligands might have sufficient hindrance that the barrier might increase to levels of $\sim$15 kcal mol^{-1} and therefore produce effects that would be observable at room temperature.

If one measures a diastereomeric ratio (dr) in one solvent, it may appear that only one diastereomer is present (dr $\sim$ 100%). It is generally prudent to try to observe this equilibrium in a

different solvent where changes in polarity might favor the observation of a less stable diastereomer. This further brings into question the rate at which diastereomers interconvert. If crystallization had allowed the separation of diastereomers and the interconversion were slow then only one isomer would be observed, suggesting a dr = 100%. If the interconversion were faster ($\sim$minutes), switching from $CDCl_3$ to CD_2Cl_2 might well provide an observation of a different dr by NMR.

If the diastereomers interconvert rapidly, the interconversion can be detected by variable temperature/dynamic NMR studies. Thus, what may appear as one isomer at ambient temperature may appear as two isomers at low temperature. As mentioned above, Brunner has warned that care must be taken here and recommended variable temperature NMR be routinely used if only one diastereomer is observed at ambient temperatures. For example, Chakravarty[17,18] and Nelson[19] have revised their original opinions regarding diastereomeric ratios in their products on the basis of observation of two species in the NMR. Herein, however, lies the signficant problem. One can observe two isomers, but are they epimers differing at configuration of the metal or diastereomers resulting from different conformations of the ligand such as phenyl group orientations? Two distinct species can be observed on the NMR time scale, but it is extraordinarily difficult to distinguish the origin of the isomerism. One obviously has two isomers, but the type of isomerism is unknown. For ^{1}H NMR spectra to be averaged to sharp resonances at room temperature requires interconversion rates greater than 100 s^{-1}. This is a high rate of interconversion and high interconversion rates are typically associated with conformational changes. Even in most cases of the relatively fast epimerization of (η^6-arene) ruthenium salen complexes, half-lives on the order of one-half hour are observed. Generally one might expect that dissociation of one donor would be required for epimerization. For a coordinatively saturated low-spin d^6 complex of a second or third row transition metal, such dissociation often involves a $\Delta G^* > 25 \text{ kcal mol}^{-1}$.[22] Hence, many chiral metal centers from this class of metal compounds are stable for extended periods. Thus, when when one observes dynamic NMR in these systems the question poses itself—"Why is this low-spin d^6 transition metal complex isomerizing at a rate 100 times a second or higher?" Although diastereomers may be involved in many cases, it is prudent to consider conformational interconversions within the ligands as an alternative explanation of the DNMR behavior.

Conformational changes often occur with low barriers. On lowering the temperature, decoalescence of resonances ascribable to two conformers at $-100\,^\circ$C corresponds to a barrier of $\sim$10 kcal mol^{-1}. Since the rate at which resonances will coalesce depends on the reciprocal square of the chemical shift difference, the increasing use of higher field NMR spectrometers yields a greater number of instances where conformational effects are a source of broadening that can be observed. Nevertheless, conformational interconversions do occur at rates that can be studied by NMR, and although barriers are low, there have been extensive studies of hindered rotation at P–M bonds.[23–31] Different conformations of phenyl groups generally interconvert with low barriers, but the effects can be observed at lower temperatures.[21,30–36] Phenyl conformations on phosphines represent a potential element of chirality and diastereomeric conformations of phenyl groups could give two observable ^{31}P NMR or a corresponding doubling of all observed resonances in the ^{1}H NMR. An analog of the propeller chirality in PPh_3 can arise from PPh_2 groups that are present in many frequently used ligands. If there are additional elements of steric interaction present, the phenyl rotation might well have its hindrance increased by several kcal mol^{-1} and be readily observable by NMR. Thus, one would see two sets of resonances due to diastereomers, but they would be diastereomeric conformers, not diastereomers differing in

configuration at the metal. Notably, hindered phenyl rotation has been observed in BINAP complexes.[37–39]
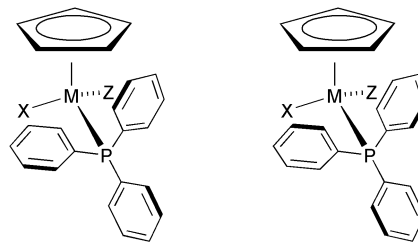
A specific blocking of rotation might bring this barrier higher. We believe this may occur in some Josiphos, 1-[(R)-2-(diphenylphosphino)ferrocenyl]ethyldi-t-butylphosphine, derivatives that we have made where a phenyl rotation may be blocked by the nearby ferrocenyl moiety. Further, even more diastereomers are possible owing to the complication of slowing ring conformation interconversions as observed in palladium complexes of Josiphos.[40,41]
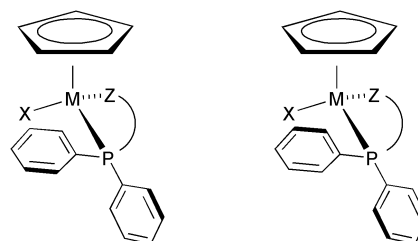
Another potential source of diastereomeric conformations is the hindered rotation of the polyhapto ring. This type of rotation has been reviewed by McGlinchey[42,43] and, for example, a barrier for rotation in compounds of the type (η^6-1,4-$C_6H_4R_2$) $Fe(CO)(SiCl_3)_2$ was found to be $\sim$11 kcal mol^{-1}.[44] Some of these effects are electronic in origin, but the presence of substituents on the other ligands could raise this barrier.[45] For example, in cymene complexes a blocking group from a ligand could prevent complete rotation of the cymene ring. This appears to be the origin of the observation of additional isomers in some (η^6-cymene)Ru(QUINAP) complexes[20] (see Fig. 1).

In the case of cymene complexes, if the isomerism is not observed after replacement of the cymene with benzene, then there is a good chance that hindered arene rotation is involved. For situations where a particularly labile or hemilabile ligand is present, there are real possibilities that metal-centered epimerization could be observed by DNMR. In these cases, one can potentially distinguish epimers arising from differing chirality at the metal or conformations of ligands by NMR NOE studies or CD studies; however, either may be subject to ambiguities. We suggest that the distinct possibility exists that conformational epimerization may account for diastereomers detected by NMR in some cases and we hope that the foregoing comments may serve as a *caveat* for future interpretations of metal-centered epimerization.
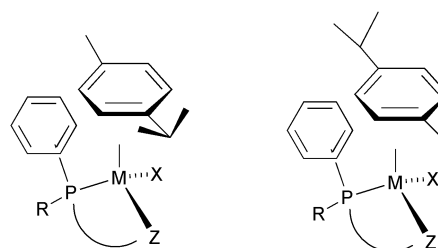

Fig. 1 An example where a phenyl group on a phosphine blocks the rotation of the cymene ring. Although the cymene is not locked into position the arene substituents cannot pass by the phenyl. This is a generalized example, but any group on the chelating ligand that is forced toward the η^6-ring could potentially act as a blocking group.

Acknowledgements

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