Solvent-tunable inversion of chirality transfer from carbon to copper†

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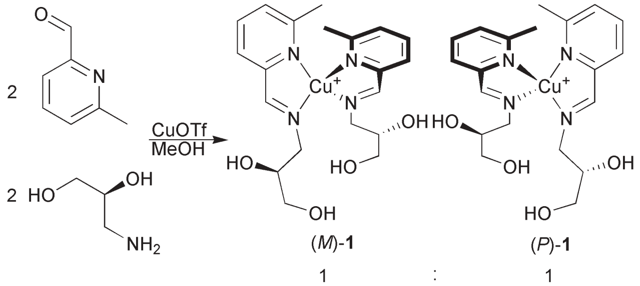
A change of solvent causes an inversion of the stereochemistry at copper of the chiral Cu^I complex described herein.

The stereochemistry of a configurationally labile metal centre may be influenced by chiral ligands,[1] a process of central importance in the context of asymmetric catalysis[2] as chiral information is transferred from the ligand through the metal to the substrate. The economic importance of this process, operating in concert with intellectual curiosity, has prompted a great deal of recent interest into the fundamentals of chiral information transfer in the last few years.[3–8]

We present here a simple system in which the transfer of chiral information from ligands to a metal may be modulated to the point of inversion by solvent effects. The replacement of dichloromethane by hydrogen bond accepting solvents reversed the diastereomeric induction, thus giving the opposite metal-centred chirality even though the ligands' chirality did not change.

The reaction of $Cu(NCMe)_4O_3SCF_3$ (1 equiv.) with *S*-3-amino-1,2-propanediol (2 equiv.) and 6-methyl-pyridine-2-carbaldehyde (2 equiv.) in anaerobic methanol provides a one-pot template synthesis[9] of complex **1**, incorporating a new chiral ligand, in quantitative yield (Scheme 1). The ^{1}H and ^{13}C NMR spectra of this complex showed two distinct sets of signals at room temperature in a 1 : 1 ratio, corresponding to the *P* (Δ) and *M* (Λ) diastereomers shown in Scheme 1. These signals coalesced at 313 K, which corresponds to an energetic barrier of 70 kJ mol^{-1} to interconversion,[10] similar to what has been seen in related complexes.[11,12]

Silver(I) and zinc(II) complexes of the same ligand showed broad NMR spectra, possibly related to the interaction of the metal centres with the hydroxyl groups of the ligands: these metals are capable of expanding their coordination spheres beyond four ligands, unlike copper(I).



Scheme 1 The synthesis of the two diastereomers of **1** from copper(I) trifluoromethanesulfonate and ligand subcomponents.[13]

Although solutions of **1** absorbed too strongly to allow the measurement of its optical rotation, **1** gave a weak circular dichroism (CD) spectrum in methanol ($\Delta\varepsilon_{max} = -0.9$ M^{-1} cm^{-1} at 277 nm, 293 K), similar in intensity to what was observed for the free ligand ($\Delta\varepsilon_{max} = 1.1$ M^{-1} cm^{-1} at 212 nm, $\Delta\varepsilon = -0.77$ M^{-1} cm^{-1} at 241 nm, 293 K). This suggested that the ligands' chromophores were only feebly influenced by the carbon stereocentres, both in the absence and presence of the metal ion. The CD spectrum was featureless at the complex's metal-to-ligand charge-transfer (MLCT) band, which was observed in the UV spectrum as a broad absorption at 475 nm. This indicated that there was no net diastereomeric excess at the copper stereocentre,[14] corroborating the NMR evidence for the presence of a 1 : 1 mixture of diastereomers. The methylene group between the chiral carbon and the imine nitrogen appeared to insulate the copper(I) stereocentre from the transfer of chiral information in methanol. The ligands' hydroxyl groups may interact with the solvent in many nearly isoenergetic ways, serving as both acceptors and donors of hydrogen bonds.

In contrast to what was observed in methanol, **1** gave only one set of NMR signals in dichloromethane-d_2, even when cooled to 183 K. If the complex were undergoing rapid diastereomer interconversion at this temperature, the barrier would have to be less than 35 kJ mol^{-1}. This would be substantially lower than what has been observed in similar complexes in nonpolar solvents,[11,12] which suggests that we were instead observing the presence of a single diastereomer. The significant ($\Delta\varepsilon_{max} = -9.8$ M^{-1} cm^{-1} at 296 nm, 293 K) CD spectrum of the complex in this solvent (Fig. 1) is likewise consistent with the presence of a single diastereomer.

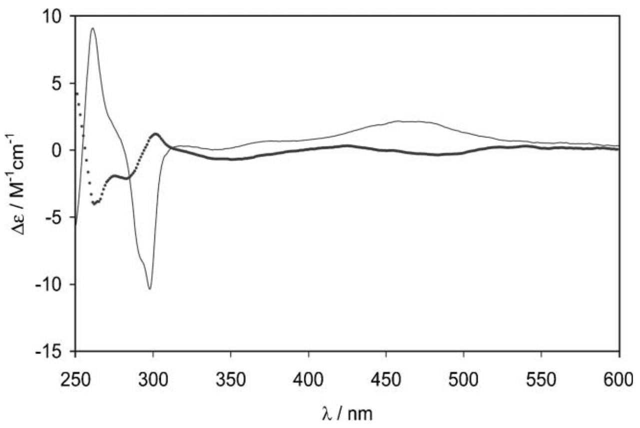


Fig. 1 CD spectra of **1** at 293 K in CH_2Cl_2 (solid line) and DMSO (dotted line).

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Thummel *et al.*,[15] van Koten *et al.*,[12] as well as Yagi *et al.*[16] have successfully identified the preferred diastereomer of more rigid systems by comparing the steric properties of both diastereomers. Given the conformational flexibility of our ligand, we reasoned that this technique might not be applicable. Fabbrizzi *et al.*,[4] Siegel *et al.*[17] and Lehn *et al.*[18] have correlated a positive Cotton effect at the metal-to-ligand charge-transfer (MLCT) band of copper(I) diimine complexes with metal centres of *P* helicity, and Ziegler and von Zelewsky have grounded these observations in theory.[14] Based thus upon von Zelewsky's MLCT helicity rule,[14] we interpreted the positive Cotton effect of the MLCT band ($\Delta\varepsilon = +2.2\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$ at 467 nm) of complex **1** in dichloromethane as indicative of a *P* (Δ) configuration at the $\mathrm{Cu^I}$ centre.

In DMSO solution, two sets of ^{1}H and ^{13}C resonances were observed at room temperature, indicative of the presence of both diastereomers. Integration of the imine resonances indicated that one diastereomer is present in 20% excess, however. The presence of this diastereomeric excess is confirmed by the CD spectrum, which shows features having approximately 20% of the intensity of those observed in dichloromethane (Fig. 1). Remarkably, the Cotton effects of the observed transitions were inverted in DMSO, which indicated that the majority diastereomer had the opposite (*M*) configuration at copper from the (*P*) configuration observed in dichloromethane.

Solvent effects on chirality are a topic of considerable interest. Recent examples include a helicene-containing foldamer in which the choice of solvent drastically changes the transfer of chiral information,[5] polymers whose helicity reverses upon a change of solvent,[6] an acetylating agent whose stereoselectivity may be reversed in different solvents,[7] and a bis-porphyrin system in which solvent changes switch the supramolecular chirality.[8] We are not aware, however, of another complex in which the chirality transfer from ligand to metal may be inverted by a change of solvent.

In the case of dichloromethane, the hydroxyl groups of **1** would be expected to interact only weakly with the solvent environment, allowing for the formation of intramolecular hydrogen bonds (Fig. 2, right). These would tend to rigidify the structure. Greater rigidity would be expected to lead to more efficient transfer of chiral information from carbon to copper, as is observed in many helicates.[12,16–19]

In contrast, dimethylsulfoxide would be expected to interact strongly with the hydroxyl groups of **1**, acting as a hydrogen bond acceptor (Fig. 2, left). The effect upon **1** should be to pull the hydroxyl groups apart into the solvent medium. One of the two diastereomers should allow for more energetically favourable interactions between the hydroxyl groups and the solvent, leading to the observed diastereoselectivity.

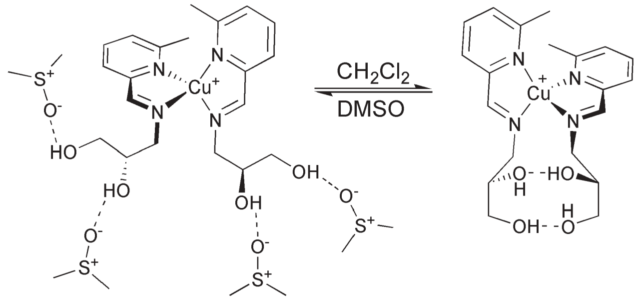

Fig. 2 Postulated structures of **1** in DMSO (left, *M* predominating) and CH_2Cl_2 (right, *P* exclusively).

The behaviors of the hydroxyl peaks in the NMR spectra of **1** in dichloromethane and DMSO were consistent with these postulated differences in solution structure. In dichloromethane, two hydroxyl peaks were observed at room temperature. These peaks were much broader than the other peaks in the spectrum, although they sharpened somewhat upon cooling, which suggested an intermediate rate of exchange between the corresponding protons. This would be expected for the structure shown in Fig. 2 on the right, in which proximity should allow the protons to exchange between adjacent oxygen atoms. In DMSO, well-resolved hydroxyl peaks were observed. These protons were coupled (J = 5 Hz) to the protons on their nearest carbon neighbors; this coupling constant established the maximum possible exchange rate of these protons. The relative slowness of this exchange was consistent with a structure such as that shown on the left in Fig. 2: the formation of strong hydrogen bonds would "freeze" the protons within the complex, inhibiting their exchange between different hydroxyl groups.

The addition of DMSO to a dichloromethane solution of **1** brought about a rapid drop in the observed diastereomeric excess, as measured by ^{1}H NMR integration (Fig. 3). This observation was likewise consistent with a strong association between DMSO and **1**. The solvent's negatively-charged oxygen atoms thus act as better hydrogen bond acceptors than the complex's own hydroxyl groups, breaking up the rigidifying intramolecular hydrogen bonds and leading to the observed inversion of diastereoselectivity.

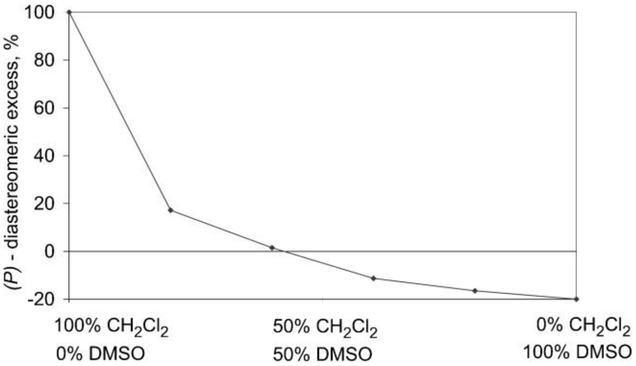

Fig. 3 Observed diastereomeric excess obtained through ^{1}H integration of imine peaks as a function of solvent composition.

The solvatochromic β parameter is a measure of the hydrogen bond acceptor ability of a given solvent.[20] Following the model of Fig. 2, we reasoned that a linear free energy relationship might exist between β and the logarithm of the equilibrium constant between the two diastereomers. Diastereomeric excesses were thus measured for the deuterated solvents noted in Fig. 4; these were chosen to have varying degrees of acceptor ability and no H-bond donor ability (α = 0).[20] In each case the identity of the major diastereomer was determined by CD and the ratio of the two diastereomers was determined by ^{1}H NMR integration. The equilibrium constants were plotted against 10^{β}, instead of plotting log(K) *vs.* β, in order to allow the inclusion of tetrachloroethane, for which K_{MP}‡ and $\beta = 0$. A free energy relationship was shown to exist; these data clearly indicated that better hydrogen bond

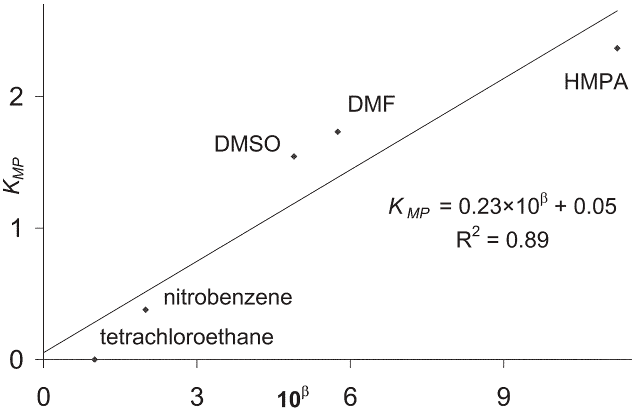

Fig. 4 The equilibrium constants between *M* and *P* diastereomers of **1** (K_{MP})‡ plotted against the antilog of the H-bond acceptor ability of the solvent (β);[20] the linear least-squares fit is shown.

acceptors more strongly stabilised the *M* form of complex **1**. The imperfect linear correlation indicates, however, that other factors played important roles as well. HMPA gave the highest diastereomeric excess noted for (*M*)-**1**, 41%.

This means of controlling the chirality at configurationally labile metal centres might be developed into a means of readily controlling the stereoselectivity of a metal-catalyzed reaction: it would be extremely useful to be able to derive both enantiomers of a product from a single chiral metal complex. Another interesting application might be to "capture" a chiral metal centre through imine exchange[13] with an achiral amine, removing the chiral carbons but keeping the optical activity. The chiral amines would thus serve as a "scaffold", imprinting their chirality upon a construction while remaining absent from the final product. Complex **1** appears to have too low a barrier to racemization for this to be practical, but other assemblies[21] may possess the necessary stability.

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‡ For complex **1**, we define the equilibrium constant K_{MP} = %*M*/%*P*.

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