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Stereoselective Recognition of an Aziridine with a Co(III) Complex: A Potential Transition-State Analogue for Catalytic Epoxidation

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Over the years highly stereoselective receptors and catalysts have been reported for a variety of substrates. Currently there is considerable interest in undertanding the origin of enantioselectivity in many of these systems.[1] We recently showed that such understanding can be useful for developing Co(III) complexes that chelate amino acids with high and predictable stereoselectivities.[2] In general, it is more challenging to understand stereoselective coordination of monodentate ligands such as amines than that of bidentate ligands such as amino acids. Here we report stereoselective coordination of a monodentate ligand, (2*R*,3*S*)-2-phenyl-3-methylaziridine, to a Co(III) complex. Although understanding aziridine recognition is interesting in its own right, it may also provide valuable insight into the origin of stereoselectivity in catalytic formation and hydrolysis of epoxides. In a series of elegant studies it has been shown that **L**-Mn(III) is an excellent catalyst for epoxidizing alkenes[3] and that **L**-Co(III) is an excellent catalyst for hydrolyzing epoxides[4] (where **L** is the salen ligand formed from trans-1,2-diaminocyclohexane and 3,5-di-tert-butyl-2-hydroxybenzaldehyde).

We determined the crystal structures of (2*R*,3*S*)-2-phenyl-3-methylaziridine[5] coordinated to (*R*,*R*)**L**-Co(III) and (*S*,*S*)**L**-Co(III).[6] Figure 1 shows the crystal structure of two molecules of (2*R*,3*S*)-2-phenyl-3-methylaziridine coordinated to (*R*,*R*)**L**-Co(III).[7] The positioning of the two aziridines relative to the metal complex is approximately the same. Interestingly, the aziridine molecule coordinates in such a way that it is positioned over two quadrants of the cobalt complex (O−Co−O and N−Co−O quadrants). As expected, the two aziridine ring hydrogens (attached to C) point toward the metal complex while the two bulky substituents (methyl and phenyl groups) point away from the metal (Figure 1). One of the two aziridine ring hydrogens is positioned between the two oxygen atoms of the metal complex, while the other hydrogen is positioned between the oxygen and the imine nitrogen. Apparently, this arrangement minimizes the steric interactions between the two aziridine ring hydrogens and the metal complex. The relatively open O−Co−O quadrant appears favorable for accepting one of the two aziridine ring hydrogens. This structure contrasts with the proposed structure for epoxide coordinated to **L**-Mn(III).[8] In the proposed structure, the entire three-membered ring of the coordinated epoxide is positioned over the N−Co−O quadrant.

It is clear from Figure 1 that the Co(III) complex is tilted with one of the phenoxides pointing up and the other pointing down. The structure of the complex determined by molecular mechanics computation also shows the same tilt.[9] The coordinated aziridine is positioned on the side where the phenoxide group is tilting away from the coordinated aziridine. This should minimize steric interactions between the coordinated aziridine and the receptor. Molecular mechanics computation shows that the position of the aziridine in the crystal structure is the lowest-energy position.

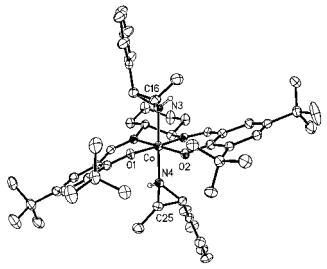

Figure 1. Crystal structure (ORTEP representation) of two aziridines coordinated to (*R*,*R*)**L**-Co(III). Dihedral angles for C16−N3−Co−O1 and C25−N4−Co−O2 are 45.80° and 38.55° respectively.

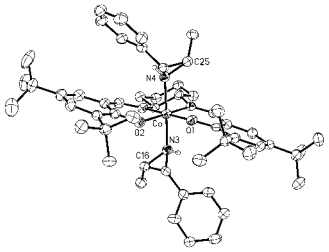

Figure 2. Crystal structure (ORTEP representation) of two aziridines coordinated to (*S*,*S*)**L**-Co(III). Dihedral angles for C24−N4−Co−O1 and C15−N3−Co−O2 are 40.71° and 44.22° respectively.

Figure 2 shows the crystal structure of two molecules of (2*R*,3*S*)-2-phenyl-3-methylaziridine coordinated to (*S*,*S*)**L**-Co(III).[10] This structure is analogous to that of the other isomer (Figure 1) in that the aziridine is positioned over the same two quadrants of the cobalt complex (O−Co−O and N−Co−O). Furthermore, the coordinated aziridine in Figure 2 is also positioned on the side that the phenoxide group is tilting away from the coordinated aziridine. Thus, relative orientations of the aziridine rings in Figures 1 and 2 are the same. Only the relative positions of the methyl and phenyl substituents have been interchanged in the two structures. Molecular mechanics computation of the two complexes starting with their respective crystal structures reveals that the aziridine complex with (*S*,*S*)**L**-Co(III) is more stable than that with (*R*,*R*)**L**-Co(III) by about 4 kcal/mol. This energy difference reduces to about 2 kcal/mol when only one aziridine is coordinated to the metal complexes with the other position occupied by ammonia.

Interestingly, (2*R*,3*S*)-2-phenyl-3-methylaziridine binds to both (*S*,*S*)**L**-Co(III) and (*R*,*R*)**L**-Co(III) rapidly and reversibly but the process is slow on the NMR time scale. Thus, different ^{1}H NMR signals can be observed for free and coordinated aziridines. The slow ligand exchange often makes Co(III) complexes ideal for detailed binding and mechanistic studies.[11] When (2*R*,3*S*)-2-phenyl-3-methylaziridine (1.5 mM) is added to excess (*R*,*R*)**L**-Co(III) (15 mM) in deuterated chloroform, two doublets appear for the aziridine methyl group (Figure 3A). The major doublet at 0.326 ppm is due

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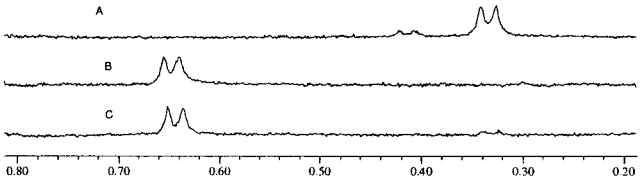

Figure 3. ^{1}H NMR signal of the aziridine methyl group when added to (A) (*R*,*R*)**L**-Co(III), (B) (*S*,*S*)**L**-Co(III), and (C) equal mixtures of (*R*,*R*)-**L**-Co(III) and (*S*,*S*)**L**-Co(III).

to the singly coordinated aziridine and the minor doublet at 0.408 ppm is due to the free aziridine.[12] In contrast, when (2*R*,3*S*)-2-phenyl-3-methylaziridine (1.5 mM) is added to excess (*S*,*S*)**L**-Co(III) (15 mM) the chemical shift due to the methyl group of the singly coordinated aziridine appear at 0.637 ppm with no trace of free aziridine (Figure 3B). When (2*R*,3*S*)-2-phenyl-3-methylaziridine (1.5 mM) is added to equal mixtures of (*R*,*R*)**L**-Co(III) and (*S*,*S*)**L**-Co(III) (15 mM each), the doublet corresponding to the methyl group of aziridine coordinated to (*S*,*S*)**L**-Co(III) can be observed as the major product (Figure 3C). Another doublet due to a small amount of the aziridine coordinated to (*R*,*R*)**L**-Co(III) can also be detected. The integration ratio for the two doublets is about 3:1. These results clearly indicate that (2*R*,3*S*)-2-phenyl-3-methylaziridine binds considerably more tightly to (*S*,*S*)**L**-Co(III) than to (*R*,*R*)**L**-Co(III), consistent with molecular mechanics computation.

It is quite remarkable that the ^{1}H NMR chemical shifts of the aziridine methyl group are dramatically different when the aziridine is coordinated to (*R*,*R*)**L**-Co(III) and (*S*,*S*)**L**-Co(III). Surprisingly, the ^{1}H NMR signal of the aziridine methyl group is upfield-shifted when the aziridine is coordinated to (*R*,*R*)**L**-Co(III). Close examination of the X-ray structure (Figure 1) and the computed structure reveals that the methyl group is positioned directly over the center of one of the phenoxy aromatic rings. This should have a shielding effect on the methyl hydrogens resulting in the upfield shift. When the aziridine is coordinated to (*S*,*S*)**L**-Co(III), the signal of the methyl group is downfield-shifted as expected. The interestingly large difference (0.311 ppm) in the chemical shifts of the aziridine methyl group in the two complexes is a clear indication of the different environments around the methyl group.

The origin of the above stereoselective recognition may be considered by examining the two crystal structures. Taking the mirror image of Figure 2 and superimposing onto Figure 1, we find that the two structures are essentially the same except for the positioning of the methyl and phenyl substituents on the aziridine ring. The aziridine phenyl rings in Figure 2 appear to make van der Waals contact with the di-*tert*-butylphenoxy groups.[13] In contrast, the aziridine phenyl rings in Figure 1 do not appear to interact at all with the di-*tert*-butylphenoxy groups. Thus, favorable interaction between the aziridine phenyl group and the di-*tert*-butylphenoxy moiety of the Co(III) complex may be at the core of the stereoselective recognition.

It is interesting to compare the stereoselective recognition of aziridine to catalytic epoxidation with **L**-Mn(III). While (*S*,*S*)**L**-Co(III) binds stereoselectively to (2*R*,3*S*)-2-phenyl-3-methylaziridine, (*S*,*S*)**L**-Mn(III) catalyzes the formation of (2*S*,3*R*)-2-phenyl-3-methylepoxide with high enantiomeric excess. This opposing sense of stereospecificity may mean that the two processes cannot be related. Alternatively, the two may be related if the following three assumptions are valid. The first assumption is that the transition state for **L**-Mn(III)-catalyzed epoxidation of *cis*-β-methylstyrene resembles the corresponding epoxide coordinated manganese complex. The second assumption is that changing the metal from Mn(III) to Co(III) does not alter the sense of stereoselective recognition of epoxides, and the final assumption is that aziridines coordinate to the Co(III) complex with the same sense of stereoselectivity as the corresponding epoxides. With these three assumptions, *cis*-2-phenyl-3-methylaziridine coordinated to **L**-Co(III) could be considered a transition-state analogue for the catalytic epoxidation reaction. According to the extended Hammond postulate, the more stable epoxide−catalyst complex is expected to form more rapidly than the less stable one. Thus, (2*R*,3*S*)-2-phenyl-3-methylepoxide coordinated to (*S*,*S*)**L**-Mn(III) is expected to form more rapidly on the basis of the observation that (2*R*,3*S*)-2-phenyl-3-methylaziridine binds more tightly to (*S*,*S*)**L**-Co(III). If expulsion of the epoxide from the catalyst is the rate-determining step, the tighter binding epoxide should dissociate more slowly from (*S*,*S*)**L**-Mn(III) or revert to the starting alkene, and the major product could be (2*S*,3*R*)-2-phenyl-3-methylepoxide in agreement with the experimental result. It would be interesting to further investigate the validity of the three assumptions and the extended Hammond postulate for this system.

The same computation that shows the correct positioning of the aziridine to the cobalt complex also shows that the positioning of the epoxide is essentially the same as that for the aziridine whether the metal is Mn(III) or Co(III). While it is difficult to prove that the structures in Figures 1 and 2 or any other structures are suitable transition-state analogues for the epoxidation reaction, understanding stereoselective recognition of monodentate aziridines is a challenging and interesting problem in its own right. The two structures and the NMR (Figure 3) together with computation provide valuable insight into the origin of stereoselective recognition of aziridines.

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Supporting Information Available: X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Three equivalents of the aziridine was added to the cobalt complexes dissolved in methylene chloride. Slow diffusion of hexane into the methylene chloride solution gave brown needlelike crystals of the complexes.
(7) Crystal structure data for figure **1**: orthorhombic, space group $P2_12_12_1$, a = 12.5835(3) Å, b = 16.5181(5) Å, c = 29.7871(8) Å, Z = 4; $R[I > 2\sigma(I)]$ = 0.0591, wR(all data) = 0.1469, GOF 1.057.
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(9) Molecular mechanics computation was performed using Quantum Cache version 3.2 from Oxford Molecular Ltd. For tilted salen complexes, see also: (a) Jacobsen, H.; Cavallo, L. *Chemistry−A Eur. J.* **2001**, *7*, 800−807. (b) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515−530.
(10) Crystal structure data for figure **2**: monoclinic, space group $P2_1$, a = 14.3448(4) Å, b = 27.2950(7) Å, c = 16.2612(5) Å, β = 91.495(9)°, Z = 4; $R[I > 2\sigma(I)]$ = 0.0769, wR (all data) = 0.2088, GOF = 1.218.
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(12) At high concentrations of aziridine, complex with two aziridines coordinated to the metal can also be detected by NMR.
(13) The top phenyl aziridine group is close to being parallel but staggered with the phenoxy group, while the bottom phenyl aziridine is close to being perpendicular to the phenoxy group. Both types of interactions are known to be favorable. Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584−1584. Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23−28.

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