

NMR studies of the configurational isomerism of metal cyclam and bicyclam complexes in aqueous solution

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Cyclams are of interest in fields as diverse as catalysis, selective metal recovery and recycling, sensors, and therapy and diagnosis. There is current medical interest in the drug AMD3100, a bicyclam containing two cyclam units connected by a aromatic linker (AMD3100, Xyl-bicyclam.8HCl). It is a highly potent and selective HIV inhibitor that interacts with the co-receptor CXCR4 and has recently been on Phase II clinical trials. For transition metal complexes of AMD3100, the anti-HIV activity depends on the bound metal. The configurations of metal-coordinated cyclam ring are likely to be critical for the recognition processes. Each of the 4 metal-coordinated N atoms is chiral, and the N-H bonds lie above or below the mean ligand plane, giving five possible configurational isomers (R,R,R,R; R,R,R,S; etc).

Our solution NMR studies of metal complexes of cyclams and bicyclams indicate that for some metal complexes several configurational isomers coexist in aqueous solution and hence give rise to very complicated NMR spectra, being highly dependent on the solution conditions, including the presence of other ligands, and on time. We have studied this configurational isomerism by various NMR techniques including ^1H , ^{15}N and ^{13}C -HSQC, ^{15}N and ^{13}C -HMBC, TOCSY, COSY, NOESY, and ROESY. The ^1H and ^{13}C signals of each isomer are overlapped in a small chemical shift range so it is important to optimise the NMR methods (parameters, pulse programs, etc) to obtain the maximum structural information.

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