Ligand rotamers and redox isomerism: metallo-pseudo-prolines

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A ligand rotation which orientates the oxygen atom of an amide group towards or away from a neighbouring metal centre provides rotamers A and B with *E*° potentials which differ by 150 mV; oxidation of the metal centre of B switches the system from a state in which there is a small difference in the relative populations of the rotamers to one in which the *cis*-amide conformation greatly predominates; this new metallocycle system can be viewed as a pseudo-proline with redox sensitive rotameric properties.

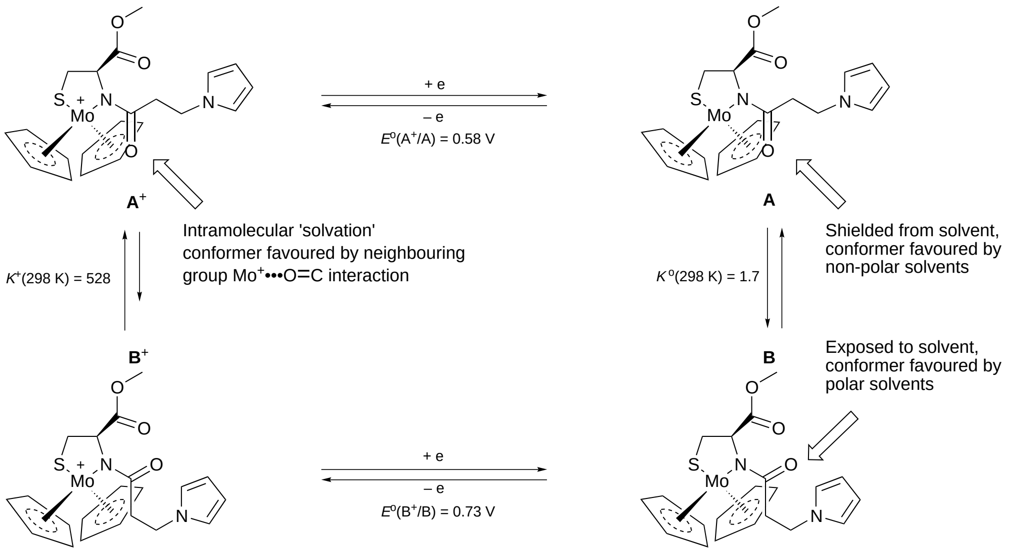
Redox-linked isomerism involving, for example, *cis–trans* rearrangement of ligands about a transition metal centre is a well established and much studied phenomenon, particularly for 17-/18-electron systems: well resolved redox processes for each isomer pair can sometimes be observed and the energetics and dynamics of interconversion of the geometric forms established.[1,2] Processes involving an essentially fixed geometric disposition of coordinating atoms about a transition metal centre and the isomerisation of a ligand rarely lead to discretely observable isomer redox processes[3] either because activation energy barriers are small and hence dynamics of isomer interconversion are fast, or because through-bond/through-space perturbations of the metal redox energetics in the two isomeric forms are weak or closely similar.

Herein we describe an exceptional system in which both the activation energy barrier for the interconversion of ligand states is sufficiently large, and electronic effects on the energetics of the redox chemistry sufficiently distinguished, to allow electrochemica observation of discrete redox isomers and their interconversion at and below ambient temperature, as set out in Scheme 1.

N-(3-Pyrrole-1-yl)propanoyl-L-cysteine methyl ester[4] (H_2L) reacts with [Mo(η-$C_5H_5)_2Cl_2$] in EtOH–NEt_3 to give [Mo(η-$C_5H_5)_2$L] which was isolated as an orange–brown crystalline material in 75% yield. ^{1}H NMR [CD_3CN, CD_2Cl_2 or $(CD_3)_2NCDO$] spectroscopy of the product shows two distinct sets of resonances in each solvent, indicative of the presence of two isomeric forms of the complex. ^{1}H NMR (CD_2Cl_2) exchange spectroscopy (EXSY) shows that the isomers interconvert. Cyclic voltammetry {MeCN, DMF or CH_2Cl_2–0.2 M [NBu_4][BF_4]; vitreous carbon} confirms the presence of two isomeric forms of [Mo(η-$C_5H_5)_2$L] (**A** and **B**) each of which undergoes reversible one-electron oxidation at *E*° potentials separated by *ca.* 150 mV, Fig. 1. On the cyclic voltammetric timescale the isomer pairs **A**/**B** and **A**$^+$/**B**$^+$ are interrelated by dynamic square-scheme equilibria[2] (Scheme 1).

Cyclic voltammograms were recorded in the DMF electrolyte over a range of temperatures and scan rates and thermodynamic and kinetic parameters obtained by digital simulation of the current–potential data (Digisim 2.0).† The equilibrium constant, $K°(298\ K) = 1.7 \pm 0.1$ for the conversion of **A** to **B** estimated from the electrochemical analysis in the DMF electrolyte is concordant with that independently determined by integration of the cyclopentadienyl and methyl ^{1}H NMR [$(CD_3)_2NCDO$] resonances.

X-Ray structural analysis of a crystalline sample of [Mo(η-$C_5H_5)_2$L], from intensity measurements of poor quality, shows two independent molecules which are distinct conformers of the same rotamer.[5] In both molecules the Mo is chelated by cysteinyl S and amide N atoms which form part of a five-membered metallocycle ring, the amide carbonyl group is essentially co-planar with the metallocycle and its oxygen atom is deployed *trans* to the metal atom. The principal difference between the two molecules is the arrangement of the pendant $CH_2CH_2(NC_4H_4)$ group. In solution, ^{1}H NMR [CD_3CN, CD_2Cl_2 or $(CD_3)_2NCDO$] data are consistent with free rotation



Scheme 1

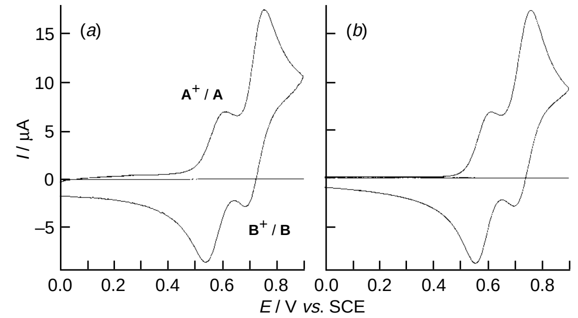


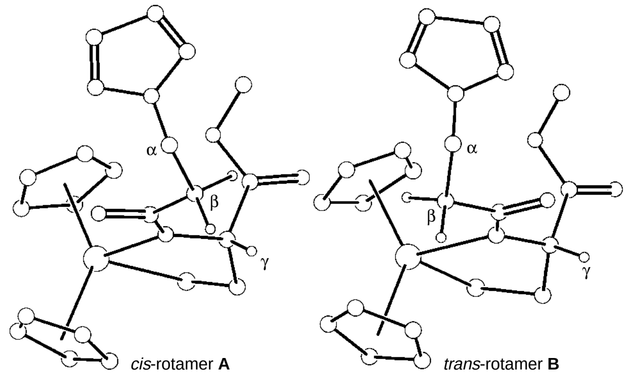
Fig. 1 Experimental (*a*) and simulated (*b*) cyclic voltammograms for [Mo(η-$C_5H_5)_2$L]. Experimental data recorded in DMF–0.2 M [NBu_4][BF_4] at a vitreous carbon working electrode of area 0.0707 cm^2; scan rate 100 mV s^{-1}, T 273 K; total concentration of [Mo(η-$C_5H_5)_2$L] 2.3 mM.

about the C–C and C–N bonds in the $CH_2CH_2(NC_4H_4)$ group; evidently the difference in the solid state structures does not bear on the solution isomerism.

Molecular mechanics calculations[6] (ChemX, MM2) based on the two crystallographic structures also preclude the geometric arrangement of the pendant $CH_2CH_2(NC_4H_4)$ group as the origin of the solution isomerism. The activation energy calculated for the interconversion of the two crystallographic forms is $\Delta H^{\ddagger}_{\text{calc.}} < 5$ kcal mol^{-1} (1 cal = 4.184 J) whereas the enthalpy of activation determined experimentally for the conversion of **A** to **B** in the DMF electrolyte is $\Delta H^{\ddagger}_{\text{exp.}} = 20.1$ kcal mol^{-1}. An activation energy barrier of this latter magnitude is more typically associated with processes involving restricted rotation about C–N amide bonds, *e.g.* DMF, 19.6 kcal mol^{-1}. MM2 calculations for the conversion of **A** to **B** through *cis–trans* amide bond isomerisation, as shown in Scheme 1, gives $\Delta H^{\ddagger}_{\text{calc}} = 24.7$ kcal mol^{-1} which is in good agreement with the experimental data.

Further support for the *cis–trans* amide bond isomerisation process was obtained by nuclear Overhauser effect (NOE) difference spectroscopy. Irradiation of the β methylene protons of rotamer **A** in CD_2Cl_2 showed NOE enhancement of the γ-H resonance of the chiral centre but no enhancement of the cyclopentadienyl ring proton resonances, Fig. 2. Conversely, irradiation of the β methylene protons of rotamer **B** in CD_3CN showed NOE enhancement of the cyclopentadienyl ring proton resonances but absence of NOE enhancement of the γ-H resonance, Fig. 2. This is consistent with the assignment of **A** and **B** as the *cis* and *trans*-amide isomers, respectively; the mean β-H–γ-H distances in the calculated structures are 2.3 and 4.5 Å for **A** and **B**, respectively.

The *cis–trans* amide bond isomerisation provides a rationale for other properties of the system. In the *cis* conformation the oxygen atom of the carbonyl is deployed towards the molybdenum atom (**A** calc. Mo···O distance, 3.23 Å) and through space interaction could contribute towards the stabilisation of the positive charge on the oxidised metal centre. The observation that $E°$ (*cis*-rotamer $\mathbf{A}^+/\mathbf{A}$) is negative of $E°$ (*trans*-rotamer $\mathbf{B}^+/\mathbf{B}$) is consistent with this (**B** calc. Mo···O distance, 4.3 Å). Stabilisation of $\mathbf{A}^+$ by what might be considered as intramolecular solvation by the amide oxygen explains why $\mathbf{A}^+$ is the thermodynamically favoured cation. The equilibrium constant for the conversion of $\mathbf{B}^+$ to $\mathbf{A}^+$ estimated from the electrochemical data is K^+ (298 K) (CH_2Cl_2) = 528, Scheme 1.



irradiated β methylene protons
show NOE with γ–CH of chiral centre

irradiated β methylene protons
show NOE with cyclopentadienyl protons

Fig. 2

The equilibrium between **A** and **B** is markedly solvent dependent: in polar solvents such as MeCN or DMF the *trans*-amide rotameter **B** is the more stable species, in the less polar solvent CH_2Cl_2 (or $CHCl_3$) the converse is true, for example, $K°$ (298 K) (CH_2Cl_2) = 0.5 for the conversion of **A** to **B**. In the *trans* configuration, the amide oxgyen of **B** is exposed on the surface of the molecule whereas in the *cis* configuration of **A** it is shielded by the cyclopentadienyl rings. Thus polar interactions of the amide carbonyl group presumably stabilise **B** with respect to **A**. Consistent with this, IR spectroscopy in MeCN shows two distinct amide C=O bands with that for the major isomer **B** at a significantly lower energy (1562 cm^{-1}) than that for **A** (1582 cm^{-1}).

In conclusion, a ligand rotational isomerism which places the oxygen atom of an amide group close to or distant from a neighbouring metal centre can lead to redox isomers with substantially different $E°$ potentials. In addition, it is evident that oxidation of the metal centre switches the system from a state in which there is a small difference in the relative thermodynamic stabilities of the isomers to one in which the *cis*-amide rotamer greatly predominates.

In a wider context, we note that the kinetics and energetics associated with *cis–trans* amide bond isomerism in prolines and in pseudo-prolines with ring heteroatoms is receiving considerable attention because of the importance of the rotamers in protein folding and recognition processes.[7] The metallocycle system described herein can be viewed as a pseudo-proline with redox-sensitive rotameric properties. Cyclopentadienyl ring substitution, N- or C-terminus modification, and/or changing the metal offer the prospect of refining the energetics and dynamics of the system. Notably, simply replacing the pyrrole group by a phenyl ring gives an analogous redox isomer system but with $K°$ (298 K) (DMF) now close to unity.

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Footnotes and References

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† *Simulation parameters.* Digism 2.0 CV: heterogenous electron-transfer rate constants $k_s = 10^4$ cm s^{-1} for all electron-transfer steps; electron-transfer coefficients $\alpha = 0.5$ for both rotamer couples; diffusion coefficients $D_{273\,K} = 2.0 \times 10^{-6}$ cm^2 s^{-1} for all rotamers; uncompensated resistance $R_u = 500\ \Omega$; double layer capacitance $c_{dl} = 1$ µF; scan rate $\nu = 100$ mV s^{-1} (simulation and experimental); electrode area = 0.0707 cm^2 (simulation and experimental); homogeneous rate-constants for decay of 17-electron cations, $k_{273\,K}$ ($\mathbf{A}^+$) = 3×10^{-2} s^{-1}, $k_{273\,K}$ ($\mathbf{B}^+$) = 5×10^{-2} s^{-1}; pre-equilibria enabled for all reactions; other values for D and k used for simulations at other temperatures.

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