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Amide bond cleavage initiated by coordination with transition metal ions and tuned by an auxiliary ligand

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Reaction of ligand **L**, N,N-bis(pyridin-2-ylmethyl)acetamide, with five transition metal salts, $FeCl_3·6H_2O$, $CuCl_2·2H_2O$, $Cu(ClO_4)_2·6H_2O$, $ZnCl_2$ and K_2PtCl_4/KI, produced five metal complexes, [(μ-O)(FeClL')($FeCl_3$)] (**1**), [$CuLCl_2$] (**2**), [CuBPA(ClO_4)(CHCN)] ClO_4 (**3**), [$ZnLCl_2$] (**4**) and [$PtLI_2$] (**5**), where **L'** = 1-(2,4,5-tri(pyridin-2-yl)-3-(pyridin-2-ylmethyl)imidazolidin-1-yl)ethanone which formed *in situ*, BPA = bis(pyridin-2-ylmethyl)amine. The ligand and complexes were characterized by a variety of spectroscopic techniques including X-ray single crystal diffraction where applicable. Depending on the metal ion and auxiliary ligand of the complex, the acetyl group of the ligand L could be either intact or cleaved. When ferric chloride hexahydrate was used, the deacetylation went even further and a novel heterocyclic compound (**L'**) formed *in situ*. A possible mechanism was proposed for the formation of the heterocyclic compound found in complex 1. Our results indicated that it is essential for a metal centre to bind to the amide bond and the metal centre is of appropriate Lewis acidity to cleave effectively the amide bond.

1. Introduction

Transition metal ions exhibit two distinct features, various oxidation states and Lewis acidity. Due to these properties, they play important roles in a number of areas, such as catalysis,[1, 2] metabolism in biology,[3, 4] medicine.[5] In catalysis, the two features are exploited by involving electron transfer and Lewis acid-base interactions, respectively. In biology, proteolysis catalysed by metalloproteins, usually zinc proteins,[6, 7] is a typical example of employing the acidity of a metal ion in a particular coordinating environment to cleave an amide bond. In this process, the amide is transformed into either a carboxylic acid or an ester. Amide bond or peptide bond is the key linkage of a protein and all proteins in a variety of living organisms possess particular functions. Apparently, scissoring an amide bond of a functional protein will certainly disable the functionality of the protein and therefore, is of potential applications in developing novel drugs. In synthetic chemistry, transforming an amide group into either carboxylic acid or ester is also of great usefulness in both protecting a carboxylic acid in synthesis and synthesising a novel ester.[8-11] When applying an amide as protection for a carboxylic acid, cleaving the amide bond becomes necessary for deprotection afterwards.[9, 12, 13] Because of the importance of those transformations, how effectively to cleave an amide bond has been long studied and exploring transition metal complexes as catalysts for cleaving an amide bond remains one of the most active research topics. Recent work published by Garg and his co-authorshas highlighted the importance of such a transformation.[8, 14] In this work, the transformation of an amide bond into an ester catalysed by Ni(II)-carbene complex under mild conditions was described. Its high reactivity is attributed to the highly unsaturated Ni(II) centre(two-coordinated) which was achieved by using a carbene ligand bearing two bulky substituents.

As one of our research themes, we have been keen on exploring the applications of transition metal complexes, particularly those base metals complexes, in catalyses such as sp^2 C—H bond activation.[15-17] Most recent progresses in the activation of sp^2 C-H activation can be seen in the recent review.[18] In nature, about one third of enzymes are metalloenzymes which play catalytic roles in metabolisms. Proteases are a family of metalloenzymes in which zinc ion is the active centre. Looking into those metalloenzymes can tell that the metals employed by the enzymes are readily available in the crust and cheap, such as iron, copper, zinc. Nature employs those metals to achieve particular functionalities by manipulating electronic effect, unusual coordinating geometry and the secondary coordinating atmosphere provided by protein domains. These distinct features possessed by natural systems are extremely inspiring in designing and synthesizing catalysts in synthetic chemistry. Although it is not possible to fully "clone" these features in synthesized transition metal complexes, it is likely to electronically and in some cases sterically tune the properties of a metal complex *via* ligand design and controlling the coordination of a metal ion under the natural inspiration. In the past few years, our focus has been on exploring the correlation between the catalytic activity of transition metal complexes and their property, for example, redox potentials.

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†Electronic supplementary information (ESI) available: CCDC 1469298, 1469425 and 1469299 contain the supplementary crystallographicdata for compounds **1**, **3** and **5**. These data can be obtained free of charge from TheCambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.For ESI and crystallographic data in CIF or other electronicformat seeDOI: 10.1039/x0xx00000x

Indeed, we previously found that both iron(III) and copper(II) complexes showed good correlation between their reduction potentials and catalytic activity on the direct hydroxylation of benzene into phenol.[16, 17, 19] As a part of our continual efforts devoted in this coordination chemistry, herein, we report our recent studies on the cleavage of an amide bond catalysed by transition metal ions.

As discussed above, a lot of efforts have been devoted into the chemistry of the cleavage and transformation of an amide bond and significant achievements have been made. However, some observations are not well explained and how the nature of a transition ion, its coordination mode and auxiliary ligands affect the cleaving and transforming chemistry of an amide bond is not explored. For example, Cu^{2+} turns out effecting the transformation of an amide bond. In general, $Cu(OTf)_2$ (OTf = trifluoacetic acetate) is more efficient than $CuCl_2$.[9, 10, 12, 13] However, for some substrates, reverse order was also observed.[10, 12, 13] Furthermore, CuCl as a weaker Lewis acid will be expected less efficient than $CuCl_2$. But it was reported that for some substrates, CuCl could be much more efficient than $CuCl_2$.[10] Apparently, chemistry behind these seemingly abnormal observations needs to be further explored. In this piece of work,we used N,N-bis(pyridin-2-ylmethyl)acetamide (**L**) and employed Fe^{3+}, Cu^{2+}, $Zn^{2+}$and Pt^{2+} to examine their capability of cleaving the amide bond in an attempt to clarify those seemingly contradict observations. It turned out that the charge of the metal ions, coordination numbers, auxiliary ligands of the complexes have roles to play in cleaving the amide bond. To cleave the amide bond, the bonding of the metal centre to the amide N atom is essential and further any enhancement on the Lewis acidity of the metal centre will promote the cleavage.

2. Experimental

2.1 General procedures

All the chemicals were obtained from commercial suppliers and used without further purification. Elemental analyses were performed on a Flash EA1112 instrument. NMR spectra were measured on Varian 400MR with tetramethylsilane as internal standard. Chemical shifts (δ) are expressed in ppm downfield to TMS at δ = 0 ppm and coupling constants (J). Infrared spectra were recorded using Scimitar 2000 (Varian). UV–Vis spectra were recorded on Cary 50 spectrophotometer (Varian). Electrochemistry was performed in a gas-tightened three-electrode system in which a vitreous carbon disk (φ = 1 mm) was used as a working electrode, a carbon strip as counter electrode, and Ag/AgCl (inner reference solution: 0.45 mol L^{-1} $[N^nBu_4]BF_4$ + 0.05 molL^{-1} $[N^nBu_4]Cl$ in dichloromethane) against which the potential of ferrocenium/ferrocene couple is 0.55 V in 0.5 mol L^{-1} $[N^nBu_4]BF_4$ in dichloromethane. All potentials reported in this work were quoted against ferrocenium/ferrocene couple.

2.2 Synthesis

2.2.1 N,N-bis(pyridin-2-ylmethyl)acetamide(**L**)

Bis(pyridin-2-ylmethyl) amine (0.9 g, 5 mmol) was dissolved in dry CH_2Cl_2 (30 mL) under N_2 atmosphere, which was cooled to 0 ^oC , after 5 min, 1 mL of triethylamine was added. To this solution was slowly added 0.6 mL of acetyl chloride. The solution was further stirred for 3 h at 0 ^oC and then allowed to warm slowly to room temperature. The reaction mixture was poured into water and extracted with dichloromethane. All organic extracts are collected and dried over Na_2SO_4 at reduced pressure. The residue was purified by chromatography eluting with eluent (EA:EtOH:Et_3N = 5 : 1 : 0.1) to give brown liquid (843 mg, 71%).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 4.6 Hz, 1H), 8.47 (d, J = 4.7 Hz, 1H), 7.64 (d,J = 9.3 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 9.3 Hz, 2H), 7.13 (d, J = 6.6 Hz, 1H), 4.75 (s, 2H), 4.68 (s, 2H), 2.21 (s, 3H); IR (KBr pellets): v_{CO} = 1649 cm^{-1}.

2.2.2 Complexes **1**—**5**

Complex **1**: A solution of $FeCl_3·6H_2O$ (0.54 g, 2.0 mmol) in methanol (2 mL) was mixed with a methanolic solution (3 mL) of an equivalent of ligand **L** (0.482 g, 2.0 mmol). The reaction turned yellow and then yellow solid formed gradually. After being stirred at 40°C for 10 h, the precipitate (0.89 g, 63%) was collected by filtration, washed successively with methanol, dichloromethane, diethyl ether, and then dried in *vacuo*. Crystals suitable for X-ray single crystal diffraction analysis were obtained from its solution in a solution of CH_3CN layered by diethyl ether at room temperature. Elemental analysis for complex **1** ($C_{26}H_{24}Cl_4Fe_2N_6O_2·CH_2Cl_2·CH_3OH$, FW = 821.91), calc. (%): C, 40.86; H, 3.67; N, 10.21; Found (%): C, 40.69; H, 3.88; N, 10.14; IR (KBr pellets): v_{CO}= 1655 cm^{-1}.

Complex **2**: A solution of $CuCl_2·2H_2O$ (0.34 g, 2.0 mmol) in methanol (2 mL) was mixed with a methanolic solution (3 mL) of one equivalent of ligand **L** (0.482 g, 2.0 mmol). After being stirred at 40°C for 10 h, a light blue and water-insoluble precipitate (0.61 g, 81%) was collected by filtration, washed successively with methanol, diethyl ether, and then dried in*vacuo*. Elemental analysis for complex **2** ($C_{14}H_{15}Cl_2CuN_3O$, FW = 373.98), calc. (%): C, 44.75; H, 4.02; N, 11.18. Found (%): C, 44.89; H, 4.00; N, 10.84; IR (KBr pellets): v_{CO}= 1691cm^{-1}.

Complex **3**: A solution of $Cu(ClO_4)_2·6H_2O$ (0.75 g, 1.5 mmol) in methanol (2 mL) was mixed with a methanolic (2 mL) solution of ligand**L** (0.362 g, 1.5 mmol). The solution was stirred at 40°C for 10 h to obtain a deep blue and water-soluble precipitate (0.63 g, 84%), which was collected by filtration, washed successively with methanol, diethyl ether, and dried in *vacuo*. Elemental analysis for complex **3**($C_{14}H_{16}Cl_2CuN_4O_8·0.5H_2O$, FW = 509.96), calc. (%): C, 32.86; H, 3.35; N, 10.95. Found (%): C, 32.92; H, 3.38; N, 10.79.

Complex **4**: A solution of $ZnCl_2$ (0.273 g, 2.0 mmol) in methanol (2 mL) with ligand **L** (0.482 g, 2.0 mmol) in methanol (3 mL). After being stirred at 40°C for 24 h, the precipitate (0.57 g, 76%) was collected by filtration, washed successively with small amounts of distilled water, methanol, diethyl ether, and then dried in *vacuo*. ^{1}H NMR (400 MHz, DMSO): δ 8.55 (d, J = 4.1 Hz, 1H), 8.47 (d, J = 4.0 Hz, 1H), 7.82-7.68 (m, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.24 (t, J = 8.1 Hz, 2H), 4.69 (s, 2H), 4.58 (s, 2H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 171.20, 157.88, 157.19, 149.90, 149.36, 137.49, 137.23, 123.08, 122.63, 122.08, 121.86, 53.79, 51.00, 22.02. Elemental analysis for complex **4**: ($C_{14}H_{15}Cl_2N_3OZn·1.6H_2O$, FW = 406.39), calc. (%): C, 41.38; H, 4.51; N, 10.34. Found (%): C, 40.89; H, 4.09; N, 10.21; IR (KBr pellet): v_{CO}= 1682 cm^{-1}.

Complex **5**: To a solution of K_2PtCl_4 (228 mg, 0.55 mmol) in distilled water (5 mL) was added KI (0.8 g), followed by the addition of a mixture of ligand **L** (133 mg, 0.55 mmol) in EtOH (3 mL). The reaction was stirred for overnight to produce a pale-yellow precipitate (290 mg, 76%), which was collected by filtration, washed successively with distilled water, EtOH and Ether, and dried in *vacuo*. ^{1}H NMR (400 MHz, DMSO): δ 9.32 (s, 1H), 9.22 (d, J = 5.4 Hz, 1H), 7.95 (t, J = 7.7 Hz, 1H), 7.88 (t, J = 7.7 Hz, 1H), 7.73 (s, 2H), 7.52-7.45 (m, 2H), 6.05 (s, 2H), 5.48 (d, J = 38.6 Hz, 2H), 2.20 (s, 3H). Elemental analysis forcomplex **5** ($C_{14}H_{15}I_2N_3OPt$, FW = 689.89), calc. (%): C 24.36; H 2.19; N 6.09. Found (%): C 24.18, H 2.54, N 5.86;IR (KBr pellets):ν_{CO}= 1656cm^{-1}.

2.3 Analysis of the products from the acidification of complex 1

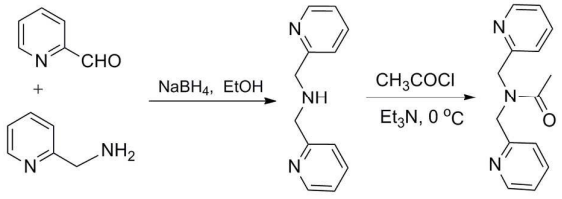
To a solution of complex **1** (300 mg, 0.43 mmol) in CH_3CN (5 mL) pre-cooled in ice-bath was added dilute hydrochloric acid (6 mol L^{-1}, 8 mL) and the reaction was stirred for 3 h before the pH of the reaction was adjusted to 8 with aqueous sodium hydroxide. The solution was further stirred for 2 h at ice temperature and then allowed to warm slowly to room temperature. The reaction was filtered to remove ferric hydroxide and the filtrate was extracted with dichloromethane (10 mL × 3). All the organic extracts were combined and dried over Na_2SO_4. After the removal of the solvents, the residual was redissolved in minimum CH_2Cl_2 which was separated using thin layer plate in eluent of EA:EtOH:Et_3N = 5 : 1 : 0.1 to produce a white solid which was ligand **L** (126 mg, 61%) as confirmed by NMR spectroscopy. Part of the extracts were also analysed by GC-MS to identify other related molecular fragments.

2.4 Abstraction of chloride ions from complex 2

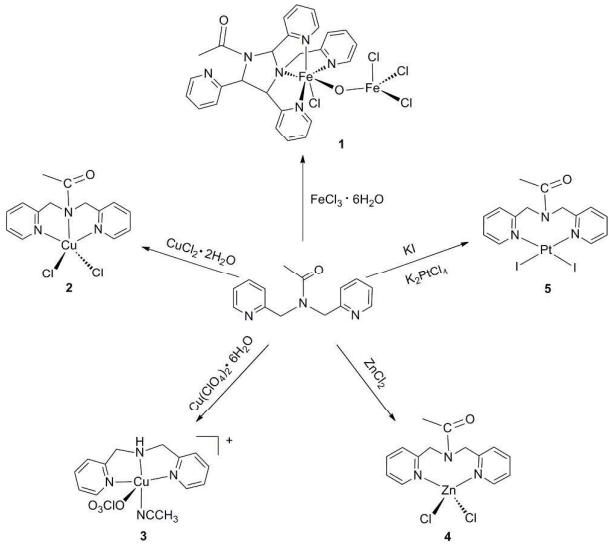
Complex **2** (112 mg, 0.3 mmol) was dissolved in acetonitrile (10 mL) followed by adding $AgBF_4$ (126 mg, 0.65 mmol). While white precipitate formed, the reaction turned from light blue to deep blue. The reaction was further stirred overnight before the precipitate was filtered off. By adding diethyl ether into the filtrate was crushed out a deep blue solid. The solid is soluble in polar solvents such as water, acetonitrile and ethanol and possesses an absorption band at 1696 cm^{-1}. The same reaction was carried out analogously in methanol to form a deep blue solid which did not show any absorption related to the amide carbonyl bond.

3. Results and discussion

3.1. Synthesis of ligand Land their transition metal complexes 1—5



Scheme 1 Synthesis of ligand **L**.



Scheme 2 Synthesis of complexes **1**—**5**.

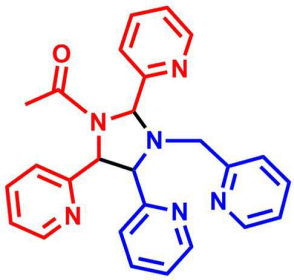


Fig. 1 Organic compound **L'**, 1-(2,4,5-tri(pyridin-2-yl)-3-(pyridin-2-ylmethyl)imidazolidin-1-yl)ethanone, in complex **1** formed *in-situ* during the coordination reaction.

The synthesis of the ligand is shown in Scheme 1. The bis(pyridin-2-ylmethyl) amine (BPA) was prepared by following the literature procedure.[16] The reaction of BPA with acetyl chloride led to the formation of ligand **L**.The synthetic routes of the five complexes are shown in Scheme 2. All the preparation was carried out in methanol. Treatment of $FeCl_3{\cdot}6H_2O$ with ligand **L** led to an unexpecteddinuclear complex **1** in which the ligand motif is not the ligand**L**, instead an *in-situ*formedmultidentate ligand was found, 1-(2,4,5-tri(pyridin-2-yl)-3-(pyridin-2-ylmethyl)imidazolidin-1-yl)ethanone(**L'**), Fig. 1. Apparently, this novel ligand derived from two equivalent of the precursor **L** *via* deacetylation and then cyclisation. The deacetylation was probably initiated by the coordination of the amide N to the metal centre. As for the diiron core, it could form beforehand since in the same reaction, yellow crystals co-existed and were identified crystallographically as dication $[Fe_2(\mu\text{–}O)Cl_3]^{2-}$ with protonated ligand (H_2L^{2+}) as its counter ion (Fig. S1). It was well established that the structure of iron(III) chloride hexahydrate is an octahedral complex with a

formula of *trans*-$[Fe(H_2O)_4Cl_2]Cl{\cdot}2H_2O$.[20] In other word, the oxide-bridged diiron core was formed when the trichloride salt was dispersed in methanol. Such a diiron salt with an organic cation as a counter ion is not unprecedented.[21-23] Probably, the ligand as a base protonated one of the coordinated water molecule to form the bridging oxide. The diiron centre, $[Fe_2(\mu{-}O)Cl_3]^{2-}$, then reacted with the ligand to form complex **1** whose analogue was found in the literatures.[24, 25]

When ligand **L** reacted with a number of other transition metals, Cu^{2+}, Zn^{2+} and Pt^{2+}, complexes **2** and **3**, **4** and **5** were isolated. The identities of these complexes were established by crystallographic analysis and/or elemental analysis. The acetyl group where applicable was confirmed by its characteristic absorption band between 1650 and 1700 cm^{-1} (**1**: 1655 cm^{-1}; **2**: 1691 cm^{-1}; **4**: 1682 cm^{-1}; **5**: 1656 cm^{-1}). The reaction was performed in methanol and $CuCl_2$, $Cu(ClO_4)_2$, $ZnCl_2$ and K_2PtCl_4 were used to prepare complexes **2**, **3**, **4** and **5**, respectively. Depending on the metal and auxiliary ligand, the reaction underwent from deacetylation and further cyclisation (**1**), deacetylation only (**3**) to ligand **L** intact during its coordination with the metal ions (**2**, **4** and **5**). These results suggest strongly that both the metal centre and the auxiliary ligand play important roles in the deacetylation of the ligand and further cyclisation. How possibly the roles are played will be discussed later.

Amongst the five complexes, both crystal structural analysis and/or microanalysis showed that complexes **1**, **2**, **4** and **5** are uncharged. This argument was further confirmed by conductivity measurements. In acetonitrile, the conductivities of these complexes (**1**, **2**, **4**, **5**) are 63.8, 3.1, 73.6 and 3.7 μs cm^{-1}, respectively. The conductivity is well below the value (92-199 μs cm^{-1}) for a monoionic species.[26] However, the conductivity of complex **3** is 264.0 μs cm^{-1}, which falls into the region of conductivities (220-300 μs cm^{-1}) for complexes with two charges.[26] This suggests that both the chlorate and acetonitrile bind weakly to the metal centre in complex **3** and dissociate in solution. This is not unprecedented for complexes of this type. We even reported that a Cu(II) complex with acetonitrile as its sixth ligand exhibited capability of colourimetric sensitivity in response to a variety of anions *via* replacing the bound solvent.[27]

3.2. X-ray single-crystal diffraction analysis

Amongst the five complexes, the structures of complexes **1**, **3** and **5** were established by crystallographic analysis. The crystals of these complexes suitable for X-ray single crystal diffraction analysis were grown from diffusing diethyl ether vapour into their solutions in CH_3CN at room temperature. Their structures are shown in Figs. 2-4 and their crystallographic data are tabulated in Table 1. In Tables 2-**4** are summarised the selected bonding parameters for complexes **1**, **3** and **5**, respectively.

Complex**1**is a neutral dinuclear complex whose analogous structure was revealed before.[28, 29] In this dinuclear complex,an oxide ion (O^{2-}) bridges the two Fe (III) centres together. One iron (III) adopted an octahedral geometry and the other tetrahedral conformation. Both complexes **3** and **5** crystallized in monoclinic crystal system. Complex **3** possesses overall a square pyramidal conformation with one chlorate O bound at apical position. In complex **5**, Pt(II) adopts its most common geometry, square planar structure.

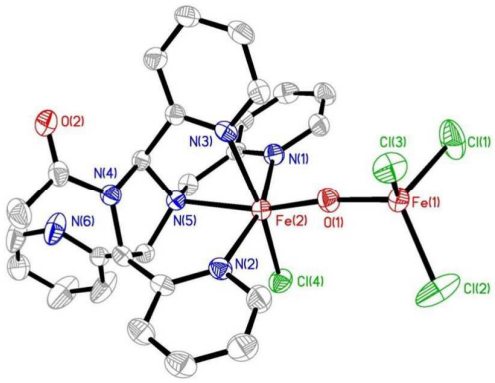


Fig. 2 ORTEP view of complex **1** with 30% probability level ellipsoids. The hydrogen atoms are omitted for clarity.

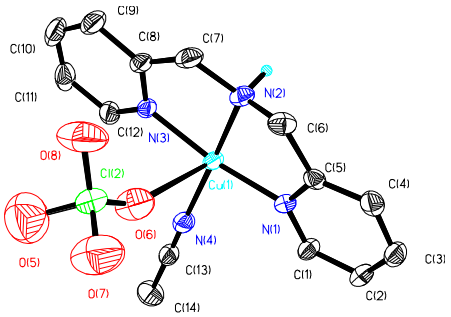


Fig. 3 ORTEP view of complex **3** with 30% probability level ellipsoids. The hydrogen atoms are omitted for clarity.

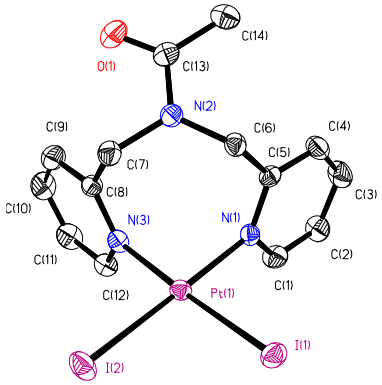


Fig. 4 ORTEP view of complex **5** with 30% probability level ellipsoids. The hydrogen atoms are omitted for clarity.

Table 1 Crystallographic data for complexes **1**, **3** and **5**.

	1	3	5
formula	$C_{26}H_{24}Cl_4Fe_2N_6O_2$	$C_{14}H_{16}Cl_2CuN_4O_8$	$C_{14}H_{15}I_2N_3OPt$
Fw	706.01	502.75	690.18
crystal system	Monoclinic	Monoclinic	Monoclinic
space group	*P2(1)/c*	*P21/c*	*P21/c*
a, Å	15.282(2)	8.3006(9)	6.8996(3)
b, Å	12.8506(11)	31.460(2)	18.4289(6)
c, Å	15.2433(17)	8.4990(9)	13.6830(4)
α, deg.	90	90	90
β, deg.	91.425(13)	118.640(14)	94.233(3)
γ, deg.	90	90	90
V, Å^3	2992.6(6)	1947.9(3)	1735.08(11)
Z	4	4	4
D_{calcd}, Mg/m^3	1.567	1.714	2.642
Reflections collected	11483	5085	6128
Reflections independent (R_{int})	5259 (0.0333)	3111 (0.0237)	3065 (0.0267)
Goodness-of-fit on F^2	1.072	1.136	1.053
R (*I*> 2σ*I*)	0.0557, 0.1325	0.0754, 0.1785	0.0283, 0.0572

Table 2 Selected bond lengths (Å) and angles (°) for complex **1**.

Fe(1)-O(1)	1.7559(29)	Fe(1)-Cl(2)	2.2003(14)
Fe(1)-Cl(1)	2.2113(14)	Fe(1)-Cl(3)	2.2314(15)
Fe(2)-O(1)	1.7907(3)	Fe(2)-N(1)	2.1454(32)
Fe(2)-N(2)	2.1753(32)	Fe(2)-N(3)	2.2068(32)
Fe(2)-N(5)	2.3107(33)	Fe(2)-Cl(4)	2.3122(12)
O(1)-Fe(1)-Cl(2)	110.48(10)	O(1)-Fe(1)-Cl(1)	107.51(10)
Cl(2)-Fe(1)-Cl(1)	110.87(8)	O(1)-Fe(1)-Cl(3)	108.34(11)
Cl(2)-Fe(1)-Cl(3)	109.09(6)	Cl(1)-Fe(1)-Cl(3)	110.51(7)
O(1)-Fe(2)-N(1)	98.25(13)	O(1)-Fe(2)-N(2)	97.56(13)
N(1)-Fe(2)-N(2)	163.12(14)	O(1)-Fe(2)-N(3)	90.76(13)
N(1)-Fe(2)-N(3)	79.68(12)	N(2)-Fe(2)-N(3)	94.25(12)
O(1)-Fe(2)-N(5)	166.15(12)	N(1)-Fe(2)-N(5)	76.34(12)
N(2)-Fe(2)-N(5)	86.93(12)	N(3)-Fe(2)-N(5)	75.79(12)
O(1)-Fe(2)-Cl(4)	102.35(10)	N(1)-Fe(2)-Cl(4)	90.76(9)
N(2)-Fe(2)-Cl(4)	91.61(9)	N(3)-Fe(2)-Cl(4)	164.81(10)
N(5)-Fe(2)-Cl(4)	90.57(8)	Fe(1)-O(1)-Fe(2)	172.48(16)

Table 3 Selected bond lengths (Å) and angles (°) for complex **3**.

Cu(1)-N(3)	1.973(6)	Cu(1)-N(4)	1.979(7)
Cu(1)-N(1)	1.983(6)	Cu(1)-N(2)	1.992(6)
N(3)-Cu(1)-N(4)	96.5(3)	N(3)-Cu(1)-N(1)	166.1(3)
N(4)-Cu(1)-N(1)	96.3(3)	N(3)-Cu(1)-N(2)	83.4(3)
N(4)-Cu(1)-N(2)	175.4(3)	N(1)-Cu(1)-N(2)	83.4(3)

Table 4 Selected bond lengths (Å) and angles (°) for complex **5**.

Pt(1)-N(3)	2.041(5)	Pt(1)-N(1)	2.053(4)
Pt(1)-I(1)	2.5865(5)	Pt(1)-I(2)	2.5869(5)
N(3)-Pt(1)-N(1)	88.05(19)	N(3)-Pt(1)-I(1)	177.27(12)
N(1)-Pt(1)-I(1)	89.24(14)	N(3)-Pt(1)-I(2)	89.72(12)
N(1)-Pt(1)-I(2)	177.19(13)	I(1)-Pt(1)-I(2)	93.000(16)

3.3 Possible mechanism of the amide bond cleavage

Reaction of the ligand, N,N-bis(pyridin-2-ylmethyl)acetamide, with transition metal ions (Fe^{3+}, Cu^{2+}, Zn^{2+} and Pt^{2+}) led to formation of drastically various products depending on both the metal ions and their anions. It turned out that ferric chloride exerted the most significant influence on the reaction. In the reaction, not only did deacetylation occur, but also a heterocycle was formed, Figs. 1 and 2.

Although it is difficult to figure out the exact mechanism of forming the hetrocycle, apparently, the cyclic ring formed with two molecules of the ligand, one of which was deacetylated during the reaction. By considering the structure of the heterocycle, it can be

speculated that one ligand undergoes deacetylation which concertedly accompanies attacking one of the two ethylene carbon atoms of the other ligand by the amide N atom (probably imide N). Once the two processes complete, the second ethylene carbon atom will be nucleophilic enough to attack one of the ethylene carbon atom to close the heterocyclic ring. This mechanistic argument is based on the assumptions that one ligand coordinates fully to the iron centre while the other one also coordinates to the same metal ion with probably only one of the two pyridinyl N atom which ensures that the whole molecule is brought to such proximity with necessary flexibility that the heterocycle formation can proceed.

To explore whether this chemistry may have universal applications in forming heterocycles initiated by the coordination of a transition metal ion, we first tried to isolate the organic compound by acidifying the iron complex. To our surprise, only the ligand (**L**) was isolated in about 61% yield (Fig. S2) and failed to obtain the heterocycle compound. Both crystalstructural and elemental analyses establish conclusively the composition of complex **1**. Furthermore, analyzing the extract with CH_2Cl_2 from the neutralized acidified solution by GC-MS did detect fragments associated with the cyclic compound (**L'**, FW = 436.5) apart from peaks related to ligand **L**. As shown in Fig. S3, the peak at 393.3 corresponds to the fragment from deacetylation of **L'** (acetyl group, FW = 43.0) whereas the peak at 344.2 can be assigned to the fragment losing a pyridinylmehtyl group (FW = 92.1) from the parent molecule **L'**. If the two groups were both cleaved, the peak at 302.1 belongs certainly to such a fragment. All the experimental evidences point to that the heterocycle collapsed during the acidification to give the main product **L**. It seems that the cyclic compound cannot tolerate the acidification and undergoes decomposition. To confirm whether it is vulnerable to acidic condition due to its crowded substituents on the ring, DFT calculations were performed. But to our big surprise again, the results suggest that the protonation do not destabilize the organic moiety (Fig. S4). Therefore, it is still unknown what occurred during this process.

The acetyl group of ligand **L** is extremely sensitive to both the metal centre and the auxiliary ligand. By varying the metal centre from Fe^{3+} to Cu^{2+}, the acetyl group can be either cleaved or intact depending on the nature of the auxiliary ligand. However, no heterocycle **L'** was detected. In the reaction with $CuCl_2$, the entire ligand is not affected in the resultant complex **2** while in complex **3** derived from perchlorate salt, the acetyl group is cleaved and methyl acetate was detected (Figs. S5 and 6). In complex **2**, the auxiliary ligand is two chlorides whereas in complex **3**, the ligand is replaced by one perchlorate and a solvent molecule. By further varying the metal ions to both Zn^{2+} and Pt^{2+}, the acetyl group remains intact in the complexes (**4** and **5**) (Scheme 2). By examining the structural features of these complexes, it is feasible to conclude that to cleave the acetyl group, it is essential for the amide N to bind to the metal centre. In complex **2**, despite the binding of amide N to the copper centre, the acetyl group was not cleaved due to the strong electron-donating capability of the two Cl^- ions as the auxiliary ligand which weakens the bond of the amide N with the copper (II) centre. When the two Cl^- ions were replaced by relatively poorer electron-donating ligands (perchlorate and CH_3CN) in complex **3**, the acetyl group was *in-situ* cleaved upon coordination to the metal centre. This argument is further supported by their reduction potentials which reflect directly the electron density of the copper centre. The reduction potential of complex **2** is more negative by 110 mV than that of complex **3** (Figs. S7—9). The potential shift suggests that the copper centre in complex 2 is richer in electron than that in complex **3**. The relatively high electron density on the copper centre in complex **2** weakens the polarizing capability of the metal centre on the amide bond through the binding of the metal to the amide N atom. For both Zn^{2+} and Pt^{2+}, they are typically four-coordinated and the amide N atom does not involve any coordination with the metal centers at all as indicated by their structures in solid state. Consequently, the acetyl group remains intact in the last two complexes. Therefore, the Lewis acidity of the metal ions is the controlling factor in the deacetylation of the ligand.

To further explore the chemistry behind the amide bond cleavage catalysed a transition metal ion upon coordination, we abstracted the chloride ions in complex **2** using $AgBF_4$ to form a complex analogous to complex **3** in acetonitrile. A water-soluble and deep blue solid analogous to complex **3** was obtained. However, the absorption band at 1696 cm^{-1} of the isolated product (Fig. S10) indicates clearly the acetyl group remains intact after the chloride abstraction. MS signals (Figs. S11 and S12) of both the isolated product and the reaction solution suggested also no any fragments related to the de-acetylated product. To find out whether the cleavage of the amide needs to be facilitated by concerted attack from a nucleophile, we performed the reaction analogously in methanol and the amide bond is successfully cleaved. Thisresult suggests that the cleavage of the amide bond was completed *via* the abstraction of chlorides (ligand exchange) and the nucleophilic attack by methanol in a concerted manner since no any absorption band around 1700 cm^{-1} was observed (Fig. S13).

Apparently, that $CuCl_2$ exhibits better efficiency than $Cu(OTf)_2$ [9, 10, 12, 13] seems to be against the correlation between the Lewis acidity of a metal ion and reaction efficiency. But it is noteworthy that in these cases, the coordinating ligands are analogous to ligand **L** but one of the three coordinating atoms is a tertiary amine N atom. Otherwise, all those reported results comply with what we observed. Possibly, this alternation in coordinating atoms changed the coordination sphere around the metal centre and then the acidity. Without crystal structural evidence, it is hard to figure out the exact cause. As for the report that CuCl could effect the transformation of an amide,[10] one possible explanation is that the metal centre might be oxidized into Cu^{2+} since it was not stated whether the reaction was strictly performed under inert atmosphere. If this is true, then it is not surprising that CuCl could have comparable efficiency to $Cu(OTf)_2$. Certainly, for CuCl, there is a possibility that as a low valent metal, it may involve binding to carbonyl carbon atom to facilitate the cleavage. Apart from the above mentioned cases, the results reported in the literatures [9, 10, 12, 13] are generally in an agreement with our observations. The role of the Lewis acidity in this amide transformation / cleavage chemistry is further supported by that high valent metal (Zr^{4+} and Hf^{4+}) complexes enable the reaction rapidly at room temperature.[11]

Conclusions

In summary, we have described the reaction of the ligand **L**, N,N-bis(pyridin-2-ylmethyl)acetamide,with five metal salts involving Fe^{3+}, Cu^{2+}, Zn^{2+} and Pt^{2+}. Five complexes **1**–**5** were isolated and characterized. In the reaction with $FeCl_3$, not only the acetyl group of the ligand was cleaved, but also the deacetylated ligand further reacted with another molecule of ligand **L** to form *in situ* a heterocyclic ligand **L'** upon coordination, 1-(2,4,5-tri(pyridin-2-yl)-3-(pyridin-2-ylmethyl)imidazolidin-1-yl)ethanone. Its reaction with Cu^{2+} revealed how the auxiliary ligand affects the cleavage of the amide bond mediated by the metal centre. When the auxiliary ligand is a stronger electron donor such as Cl^-, the amide remains intact in complex **2**. Without direct coordination with the amide N atom by the metal centres in complexes **4** and **5** due to the four coordination number favoured by the two metal ions can be feasibly met by the two pyridinyl N atoms and two halides (Cl^-or I^-), deacetylation did not occur during the coordination reaction. The reaction of ligand **L** with those transition metal salts demonstrate well how the cleavage of the amide bond can be tuned delicately by the metal centre, its Lewis acidity and its auxiliary ligand(s).

The cleavage of an amide bond is the key step in proteins hydrolysis and also can find applications in synthetic chemistry. Cleaving the amide bonds of a functional protein will certainly disrupt its functionality, which, therefore, may be one of the strategies to be employed in the design of inorganic drugs. Thus, exploring the chemistry of amide bond cleavage promoted by transition metal complexes as shown in this work is of significance in syntheticchemistry and possibly in designing and developing novel inorganic drugs as well.

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Notes and references

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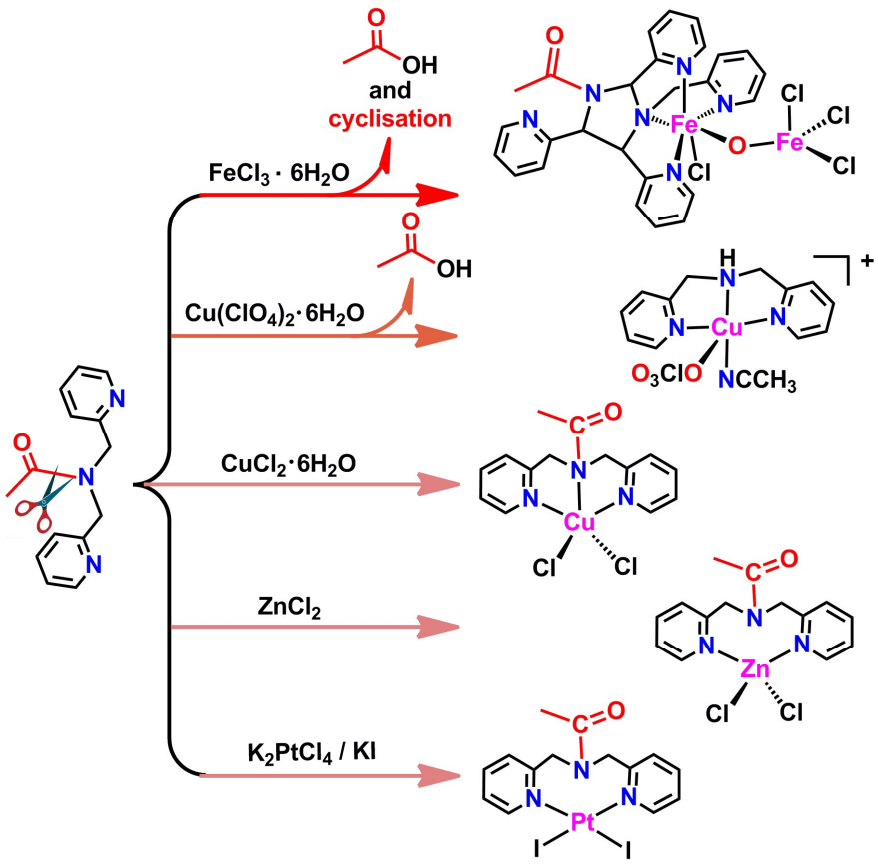
Graphical Abstract



It is essential for a metal centre binds to the amide bond and the metal centre is of sufficient Lewis acidity which can be tuned by auxiliary ligands to scissor effectively the amide bond.