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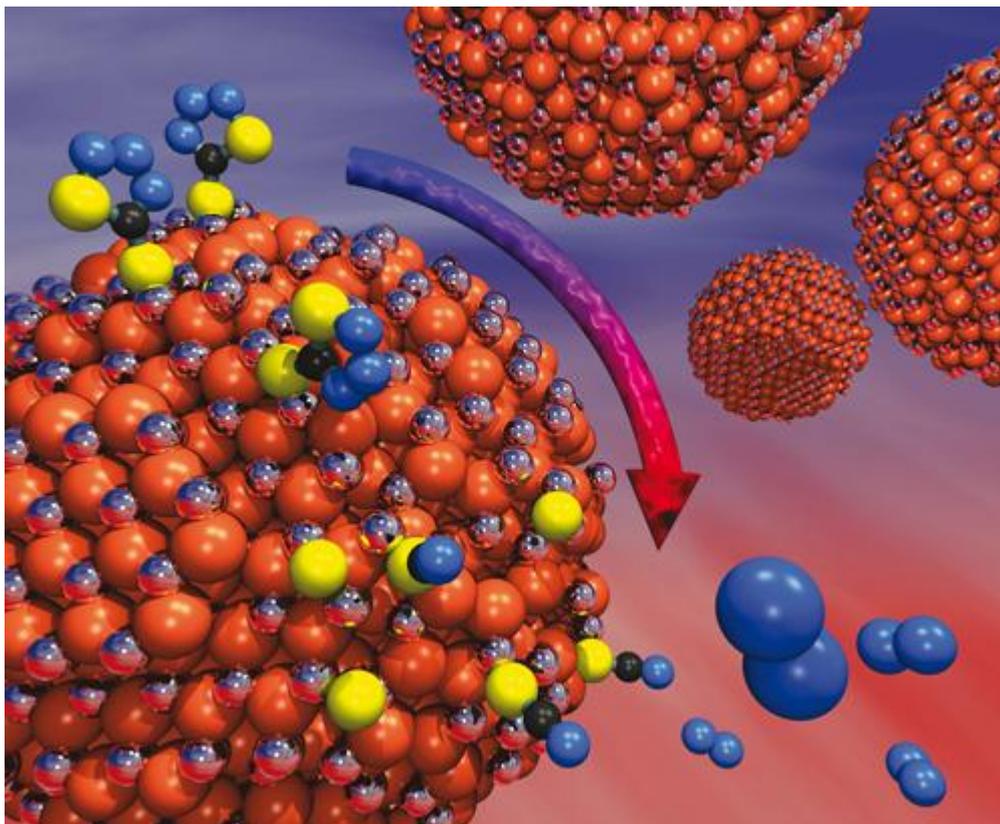


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Cycloaddition reactivity studies of first-row transition metal–azide complexes and alkynes: an inorganic click reaction for metalloenzyme inhibitor synthesis†

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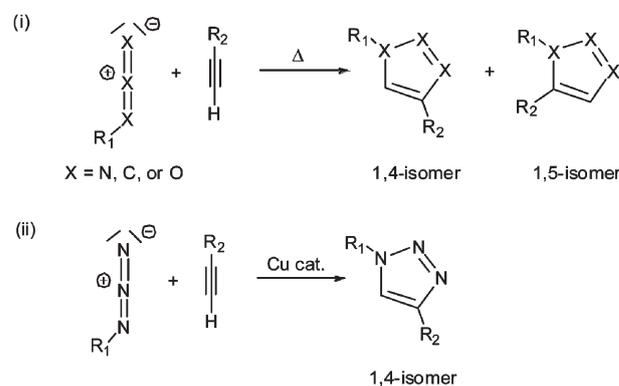
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The studies described herein focus on the 1,3-dipolar cycloaddition reaction between first-row transition metal–azide complexes and alkyne reagents, *i.e.* an inorganic variant of the extensively used “click reaction”. The reaction between the azide complexes of biologically-relevant metals (*e.g.*, Fe, Co and Ni) found in metalloenzyme active sites and alkyne reagents has been investigated as a proof-of-principle for a novel method of developing metalloenzyme triazole-based inhibitors. Six Fe, Co and Ni mono-azide complexes employing salen- and cyclam-type ligands have been synthesized and characterized. The scope of the targeted inorganic azide–alkyne click reaction was investigated using the electron-deficient alkyne dimethyl acetylenedicarboxylate. Of the six metal–azide complexes tested, the Co and Ni complexes of the 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (Me₄cyclam) ligand showed a successful cycloaddition reaction and formation of the corresponding metal–triazolate products, which were crystallographically characterized. Moreover, use of less electron deficient alkynes resulted in a loss of cycloaddition reactivity. Analysis of the structural parameters of the investigated metal–azide complexes suggests that a more symmetric structure and charge distribution within the azide moiety is needed for the formation of a metal–triazolate product. Overall, these results suggest that a successful cycloaddition reaction between a metal–azide complex and an alkyne substrate is dependent both on the ligand and metal oxidation state, that determine the electronic properties of the bound azide, as well as the electron deficient nature of the alkyne employed.

Introduction

The use of fast, irreversible reactions appropriately called “click reactions” is a simple and popular approach to the synthesis of functionalized molecules by joining two fragments together.¹ These click reactions proceed under mild conditions with quantitative yields and high regioselectivity. Examples of such reactions include nucleophilic ring opening (with epoxides and aziridines), non-aldol type carbonyl reactions (formation of hydrazones and heterocycles), or additions to carbon–carbon multiple bonds (*i.e.*, Michael additions or oxidative formation of epoxides).¹ From this last group, the Huisgen 1,3-dipolar cycloadditions are the most commonly used click reactions.² These cycloaddition reactions involve a 1,3-dipole (*i.e.*, an azide) and an unsaturated dipolarophile (*e.g.*, an alkyne, Scheme 1, i). Among various types of 1,3-dipoles, organic



Scheme 1 (i) Huisgen 1,3-dipolar cycloaddition; (ii) Cu-catalyzed azide–alkyne cycloaddition (CuAAC).

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azides are particularly important as they provide an entry into the synthesis of triazoles and tetrazoles.² These heterocycle derivatives have found use in important applications such as pharmaceuticals, chemical biology,³ or energetic materials.⁴

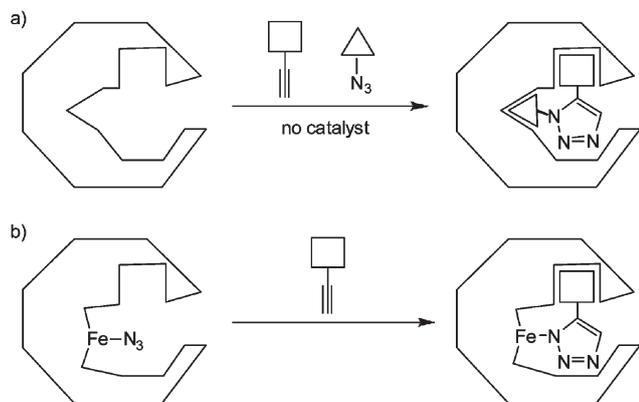
Since the first report of a regioselective 1,3-dipolar cycloaddition reaction in 2002,⁵ tremendous scientific efforts have been devoted to studying these click reactions. The Cu-catalyzed

azide–alkyne cycloaddition reaction (CuAAC) (Scheme 1, ii) occurs in various solvents at room temperature and the 1,4-substituted isomer is obtained regioselectively. All these characteristics make the CuAAC an excellent prototype for the click reaction.

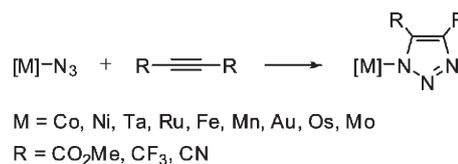
The catalyst-free AAC reaction has also led to the development of “*in situ* click reactions” in enzyme inhibitor design for drug discovery,⁶ in which the targeted enzymes are allowed to assemble new inhibitors by linking azides and alkynes that bind to adjacent sites on the protein.^{7,8} The increase in their local concentration likely accelerates the cycloaddition reaction, a high-affinity inhibitor being formed (Scheme 2a).⁷ Thus, the enzyme itself, serving as the reaction vessel, promotes the synthesis of its highest-affinity inhibitor. In contrast, although metal ions are used as catalysts for the cycloaddition reaction,⁵ the reaction between a metalloenzyme–azide adduct and an alkyne-derived substrate has not been explored for metalloenzymes (Scheme 2b).⁹

In this context, we are interested in studying the cycloaddition reaction between a metal–azide complex and an alkyne (*i.e.*, an “inorganic” click reaction) as a proof-of-concept for the enzyme-templated reaction.¹⁰ Performing this reaction at the active site of a metalloenzyme and using an alkyne substrate analogue should lead to a novel approach for the synthesis of high-affinity inhibitors. A successful cycloaddition reaction would lead to formation of the triazole product, which can be detected upon protein denaturation. The identified triazoles can then be independently synthesized through a non-enzymatic methodology and used for enzyme inhibition studies.

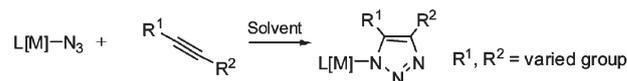
A survey of the literature reveals that reactions between metal–azide complexes and electron deficient alkynes have been observed for a few neutral Co¹¹ and Ni¹² coordination compounds, as well as several organometallic complexes of Ta,¹³ Ru,^{14–16} Fe,¹⁵ Mn,¹⁷ Au,¹⁸ Os,¹⁹ and Mo²⁰ (Scheme 3). In addition, a “fully” inorganic click reaction between a metal–azide and a metal–acetylide has been reported recently.²¹ By contrast, such cycloaddition reactions for biomimetic metal complexes with N- and O-donor ligand systems are much more rare.^{11a,12} In this context, several Fe–, Co– and Ni–azide



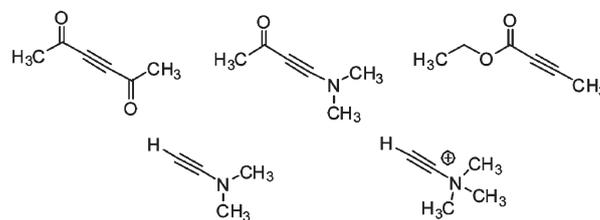
Scheme 2 (a) Use of the azide–alkyne cycloaddition (AAC) reaction to synthesize a high-affinity inhibitor from two inhibitors with different binding sites (ref. 7); (b) an inorganic azide–alkyne cycloaddition reaction proposed herein as a novel metalloenzyme inhibitor design strategy.



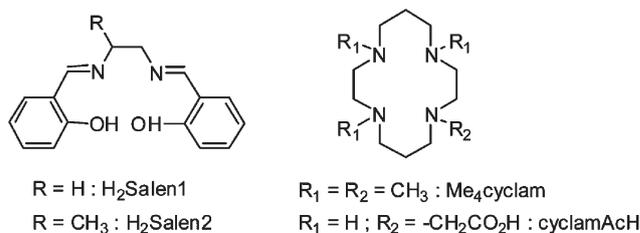
Scheme 3 Reported reactions between metal–azide complexes and electron-deficient alkynes.



Tested alkynes:



Scheme 4 Targeted synthesis of metal–triazolate complexes through the cycloaddition of metal–azide complexes and alkynes. The ligands employed are shown in Scheme 5.



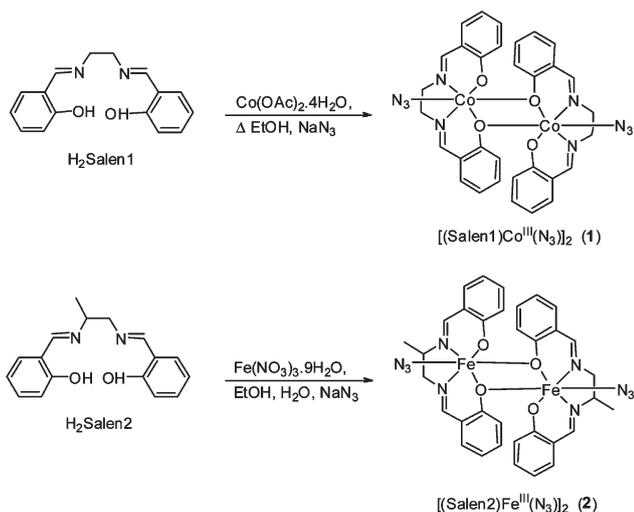
Scheme 5 Biomimetic ligands employed in this study.

complexes that are structural models of metalloenzyme active sites²² have been synthesized and their cycloaddition reactivity toward alkynes has been investigated (Schemes 4 and 5). The reaction of these azide complexes with different alkynes was studied to determine the scope of the cycloaddition chemistry with respect to the metal coordination geometry and oxidation state, as well as the electronic properties of the alkyne reagent.

Results and discussion

Synthesis of salen-type ligands

The metal–azide complexes employing salen-type ligands have been synthesized following literature procedures and employing two ligands, *N,N'*-bis(salicylidene)-1,2-ethylenediimine (H₂salen1) and *N,N'*-bis(salicylidene)-1,2-propylenediimine (H₂salen2, Scheme 5). H₂Salen1 and H₂Salen2 were synthesized by condensation of 2 equiv. salicylaldehyde and 1 equiv. ethylenediamine or 1,2-diaminopropane,²³ respectively, in ethanol over a period of 2 h.



Scheme 6 Synthetic method for the synthesis of metal-azide complexes with H₂Salen1 and H₂Salen2.

A solution of H₂Salen1 was mixed with equimolar solutions of cobalt acetate in ethanol and sodium azide in water (Scheme 6), and slow evaporation of the filtered solution led to crystallization of [(salen1)Co^{III}(N₃)₂], **1** (Table 1). When the same reaction is performed with H₂Salen2 and iron nitrate (Scheme 6), crystals of [(salen2)Fe^{III}(N₃)₂], **2** were obtained. Similarly, the [(salen1)Fe^{III}(N₃)₂] and [(salen2)Co^{III}(N₃)₂] complexes were synthesized and characterized by ESI-MS, however no pure crystalline products could be obtained. Interestingly, formation of a mononuclear [(salen2)Fe^{III}N₃] complex was reported previously under similar reaction conditions,^{23a} although the room-temperature X-ray structure for that complex reveals intermolecular Fe–O interactions analogous to those observed for **2**.

Structures of [(salen1)Co^{III}(N₃)₂] (**1**) and [(salen2)Fe^{III}(N₃)₂] (**2**)

The asymmetric unit of both **1** and **2** consists of one-half of the dinuclear structure, the other half being generated by projection through a crystallographic inversion centre. Fig. 1 shows the molecular structure and atom labelling of both complexes. The two M^{III} ions of the two dinuclear complexes are bridged by two phenolate μ-O atoms. The octahedral coordination of each M^{III} ion is completed by the tetradentate Schiff-base ligand and a terminal N₃[−] ion. The two N₃[−] ligands are *trans* relative to the M–M vector, as imposed by the crystallographic inversion centre.

The M1–O2¹ bond is longer than the M1–O2 bond (Table 2) is likely due to either the greater *trans* influence of the N₃[−] compared to the imine N atom^{23b} or a better orbital overlap of the O2 atom with the metal centre. The M1–N3 distances (1.932 Å for cobalt and 2.015 Å for iron complexes, respectively) are in the range of the other M^{III} complexes reported in the literature.^{23a,24} The M1–O2 bond is longer than the M1–O1 bond due to the interaction of O2 with M1¹. The average M–N(imine) bond length is 1.883 and 2.103 Å for cobalt and iron complexes, respectively. The three *trans* angles at the M^{III} atom are between 158.6 and 177.6°. The distorted octahedral geometry of the

Table 1 Crystallographic data for [(salen1)Co^{III}(N₃)₂] (**1**), [(salen2)Fe^{III}(N₃)₂] (**2**), [(Me₄cyclam)Ni^{II}(N₃)₂]PF₆ (**3**), [(Me₄cyclam)Co^{II}(N₃)₂]ClO₄ (**4**), [(cycclam)Co^{III}(N₃)₂]ClO₄ (**6**), {(Me₄cyclam)-Ni^{II}(N₃)₂(CO₂Me)₂}ClO₄ (**7**) and [(Me₄cyclam)Co^{II}(N₃)₂](CO₂Me)₂]ClO₄ (**8**)

	1	2	3	4	6	7	8
Formula	C ₃₄ H ₃₂ Cl ₄ Co ₂ N ₁₀ O ₄	C ₃₄ H ₃₂ Fe ₂ N ₁₀ O ₄	C ₁₄ H ₃₂ F ₆ N ₇ NiP	C ₁₄ H ₃₂ ClCoN ₇ O ₄	C ₁₂ H ₂₅ ClCoN ₇ O ₆	C ₂₀ H ₃₈ CIN ₇ NiO ₈	C ₂₀ H ₃₈ ClCoN ₇ O ₈
<i>M_r</i>	904.36	756.40	502.15	456.85	457.77	598.73	598.95
Color	Brown plates	Red plates	Green needles	Violet plates	Violet plates	Blue plates	Red plates
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> <i>n</i> <i>n</i> <i>a</i>	<i>P</i> <i>n</i> <i>a</i> 2 ₁	<i>P</i> <i>b</i> <i>c</i> <i>a</i>	<i>C</i> 2/ <i>c</i>	<i>C</i> 2/ <i>c</i>
<i>a</i> /Å	9.1697(7)	8.5467(9)	14.4194(15)	13.9561(9)	13.4690(11)	12.2771(7)	12.4963
<i>b</i> /Å	14.4120(10)	13.5994(16)	9.7386(10)	15.2417(10)	13.3584(12)	15.7842(9)	16.1164(15)
<i>c</i> /Å	13.6075(11)	14.4097(18)	14.4293(15)	9.2732(5)	20.0722(14)	14.1558(8)	14.2264(14)
<i>β</i> /°	91.467(3)	103.693(6)	90	90	90	104.624(3)	105.206(5)
<i>V</i> /Å ³	1797.7(2)	1627.2(3)	2026.2(4)	1972.5(2)	3611.5(5)	2654.3(3)	2764.8(5)
<i>Z</i>	2	2	4	4	8	4	4
<i>T</i> /K	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	293(2)
<i>λ</i> /Å	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
<i>D_c</i> /g cm ^{−3}	1.671	1.544	1.646	1.538	1.684	1.498	1.439
<i>μ</i> /mm ^{−1}	1.276	1.544	1.107	1.042	1.146	0.889	0.772
<i>R</i> , <i>R_w</i> ^a	0.0322, 0.0702	0.1011, 0.1458	0.0361, 0.0740	0.0244, 0.0506	0.0734, 0.0853	0.0512, 0.1094	0.0591, 0.1599

$$^a R = \frac{\sum |F_o| - |F_c|}{\sum |F_o|}; R_w = \frac{[\sum w(F_o - F_c)^2]^{1/2}}{[\sum w(F_o)^2]^{1/2}}$$

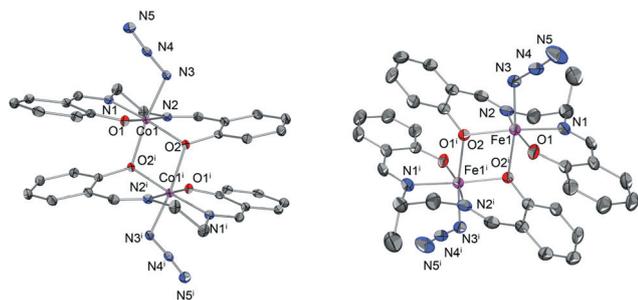


Fig. 1 View of the molecular structure and atom labelling of (left) [(salen1)Co^{III}(N₃)₂] (**1**) and (right) [(salen2)Fe^{III}(N₃)₂] (**2**). Hydrogen atoms have been omitted for clarity.

metal centre is also suggested by the *cis* angles that vary from 77.7 to 107.5° in the case of the Fe complex, and from 85.5° to 95.0° for the Co complex. As a result of the centre of symmetry, the M₂O₂ core of both complexes is perfectly planar.

Synthesis of cyclam-type ligands

The cyclam-type ligands were chosen based on their ability to stabilize mononuclear metal–azide complexes that are more structurally similar to the metalloenzyme active sites. As such, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (Me₄cyclam) and 1,4,8,11-tetraazacyclotetradecane-1-acetic acid (cyclamAcH) were chosen for the synthesis of metal–azide complexes (Scheme 5). The synthesis of Me₄cyclam (Scheme 7) has been successfully accomplished following a literature procedure²⁵ to obtain the ligand in high yield. The isolated product is highly hygroscopic and was dried under vacuum for 2 h at 50 °C before the metal complexation reaction. The synthesis of the cyclamAcH ligand was also accomplished by employing a modified version of a published procedure (Scheme 7),²⁶ a higher yield of the product being obtained by extending the reaction time to 4 h, washing with CHCl₃, and treating the final product with HCl (*vide infra*).

Synthesis and structures of metal–azide complexes derived from cyclam-type ligands

As described in the literature,²⁷ mononuclear metal–azide complexes derived from the Me₄cyclam ligand were obtained for Co and Ni: [(Me₄cyclam)Ni^{II}(N₃)₂]⁺ (**3**) and [(Me₄cyclam)Co^{II}(N₃)₂]⁺ (**4**), respectively. Mixing of 1 equiv. ligand with 1 equiv. Ni or Co perchlorate in ethanol, followed by addition of 5 equiv. aqueous NaN₃ and heating at 70 °C for 1 h led to formation of green or violet crystals upon standing at low temperature. A summary of the X-ray experimental data is provided in Table 1.

The crystal structure of these compounds (Fig. 2) and the bond lengths and angles (Table 2) are similar to those previously reported.²⁷ The cyclam adopts the *trans*-I configuration as described by Bosnich *et al.*,²⁸ which is the most favoured configuration for this kind of complexes. The four methyl substituents of the ring are positioned on the same side of the molecule as the azide ligand, which fits into the cavity formed by the methyl groups. The coordination geometry of the metal centre

varies from square pyramidal for the nickel complex (τ value of ~ 0) to a more distorted trigonal bipyramidal geometry for the cobalt complex (τ value of 0.45).²⁹

For first-row transition metals, the coordination chemistry of monofunctionalized cyclam derivatives has mainly focused on complexes of Ni^{II}, Cu^{II} and Co^{II}.³⁰ In 2000, Wiegardt *et al.*, described the synthesis and characterization of a monofunctionalized Fe^{III} complex of 1,4,8,11-tetraazacyclotetradecane-1-acetic acid, cyclamAcH, as a precursor for the synthesis of high-valent Fe complexes.²² As described therein, the cyclamAcH ligand provides upon deprotonation a monoanionic pentacoordinate framework for the synthesis of a series of complexes with a single, variable coordination site. Thus, the cyclamAcH ligand is particularly appealing for our studies. In addition, the presence of a carboxylate group makes the corresponding metal complexes more similar to the coordination environment found in non-heme iron enzymes, where a carboxylate group coordinates to the Fe centre.³¹ The synthesis of the cyclamAcH complexes was performed as described by Wiegardt *et al.* with a slight variation (Scheme 8). Ferric chloride was treated with cyclamAcH in a refluxing aqueous solution for 90 min. After cooling this solution at room temperature and addition of an excess of sodium azide, a clear red solution formed after 2 h. Addition of an excess of KPF₆ yields a microcrystalline solid of [(cyclamAc)Fe^{III}(N₃)]PF₆ (**5**) upon cooling at 4 °C overnight. This compound was fully characterized by ESI-MS, UV-vis and IR spectroscopy, and the results are in full agreement with the compound previously described.²²

When the same reaction is performed in the presence of Co(ClO₄)₆·6H₂O, a dark violet powder is obtained. Crystals of [(cyclamAc)Co^{III}(N₃)]ClO₄ (**6**) were obtained by slow diffusion of diethyl ether in an acetonitrile solution. A summary of the X-ray experimental data is provided in Table 1. A representation of the [(cyclamAc)Co^{III}(N₃)]⁺ cation is shown in Fig. 3, with selected bond distances and angles listed in Table 2.

The Co^{III} ion sits in a compressed octahedral environment with three of the four ligand N atoms (*i.e.*, N1, N4 and N3) occupying the equatorial positions along with the carboxylate O atom (Fig. 3); the fourth N atom (N2) occupies one of the axial sites with the azide ligand situated *trans* to the N2 atom. By contrast to the *trans*-III ligand configuration in **5**,²² the cyclamAc ligand adopts the *cis*-V²⁸ configuration in **6**, which implies a dramatic configuration change. The complex exhibits a longer Co–N2 distance (1.994 Å) compared to the Co–N1 (1.962 Å) and Co–N3 (1.982 Å) distances, as expected for the slightly stronger *trans* influence of the carboxylate group. The Co–N3 bond distance (1.982 Å) is slightly longer than the Co–N1 distance (1.962 Å), likely due to the presence of the acetate arm bonded to N3. The Co–N_{azide} and Co–O_{acetate} distances are 1.936 and 1.899 Å, similar to those reported for the iron complex.²¹ To the best of our knowledge, complex **6** represents the first example of a cyclamAc metal complex where the macrocyclic ligand adopts the less-common *cis*-V configuration.³²

IR characterization of the metal–azide complexes

For all metal–azide complexes synthesized, their characteristic azide stretches were measured by IR spectroscopy. Spectra were

Table 2 Selected bond distances (Å) and angles (°) for [(salen1)Co^{III}(N₃)₂] (1), [(salen2)Fe^{III}(N₃)₂] (2), [(Me₄cyclam)Ni^{II}(N₃)]PF₆ (3), [(Me₄cyclam)Co^{II}(N₃)]ClO₄ (4), [(cyclamAc)Co^{III}(N₃)]ClO₄ (6), {(Me₄cyclam)Ni^{II}[N₃C₂(CO₂Me)₂]}ClO₄ (7) and {(Me₄cyclam)Co^{II}[N₃C₂(CO₂Me)₂]}ClO₄ (8)

	1	2	3	4	6	7	8			
M1–N1	1.8738(13)	2.087(4)	M1–N1	2.1959(8)	2.1192(15)	Co–N1	1.962(2)	M1–N1	2.1131(12)	2.1990(19)
M1–N2	1.8916(14)	2.118(4)	M1–N1 ⁱ	2.1295(8)	2.1136(15)	Co–N2	1.994(2)	M1–N1 ⁱ	2.1131(12)	2.1990(19)
M1–N3	1.9319(14)	2.015(4)	M1–N2	2.1323(8)	2.2184(15)	Co–N3	1.982(2)	M1–N2	2.1472(13)	2.1292(18)
M1–O1	1.8798(11)	1.881(3)	M1–N2 ⁱ	2.1323(8)	2.2357(15)	Co–N4	1.972(2)	M1–N2 ⁱ	2.1472(13)	2.1292(18)
M1–O2	1.9333(11)	1.981(3)	M1–N3	1.9887(12)	1.9742(13)	Co–N5	1.936(2)	M1–N3	2.0017(17)	2.030(3)
O1–O2 ⁱ	2.0217(11)	2.169(3)	N3–N4	1.1805(18)	1.183(2)	Co–O1	1.8995(11)	N3–N4	1.3304(15)	1.326(2)
O2–M1 ⁱ	2.0216(11)	2.169(3)	N5–N5	1.153(2)	1.160(2)	C12–O1	1.283(3)	N3–N4 ⁱ	1.3304(15)	1.326(2)
N3–N4	1.209(2)	1.209(5)				C12–O2	1.224(3)			
N4–N5	1.150(2)	1.132(6)				N5–N6	1.208(3)			
						N6–N7	1.151(3)			
O2–M1–O1	88.01(5)	107.51(13)	N1–M1–N1 ⁱ	94.24(5)	93.34(6)	N4–Co–N1	85.79(9)	N1–M1–N1 ⁱ	147.39(8)	167.65(12)
O2–M1–N2	91.64(5)	84.40(14)	N2–M1–N2 ⁱ	91.68(5)	92.11(6)	N4–Co–N3	94.33(9)	N2–M1–N2 ⁱ	171.73(8)	140.94(12)
O1–M1–N2	177.65(5)	165.83(14)	N1–M1–N2	84.86(3)	83.27(6)	N3–Co–O1	87.29(8)	N1–M1–N2	85.13(5)	83.91(8)
O2–M1–N1	174.22(5)	158.61(15)	N1 ⁱ –M1–N2 ⁱ	84.85(3)	83.78(6)	N1–Co–O1	92.61(9)	N1 ⁱ –M1–N2 ⁱ	85.13(5)	83.91(8)
O1–M1–N1	95.04(5)	88.56(15)	N2 ⁱ –M1–N1	164.09(3)	141.50(6)	N1–Co–N3	179.42(9)	N2 ⁱ –M1–N1	92.54(5)	91.96(8)
N2–M1–N1	85.51(6)	78.08(16)	N2–M1–N1 ⁱ	164.09(3)	168.63(5)	N4–Co–O1	177.21(8)	N2–M1–N1 ⁱ	92.54(5)	91.96(8)
O2–M1–O2 ⁱ	81.46(5)	77.75(12)	N2–M1–N3	94.32(4)	94.18(6)	N2–Co–N5	175.68(10)	N2–M1–N3	94.14(4)	109.53(6)
O1–M1–O2 ⁱ	93.08(5)	91.48(13)	N2 ⁱ –M1–N3	94.32(4)	97.19(6)	Co–N5–N6	119.03(18)	N2 ⁱ –M1–N3	94.14(4)	109.53(6)
N2–M1–O2 ⁱ	89.17(5)	83.43(13)	N1–M1–N3	101.42(3)	109.03(7)	N5–N6–N7	175.4(3)	N1–M1–N3	106.31(4)	96.17(6)
N1–M1–O2 ⁱ	93.46(5)	88.05(13)	N1 ⁱ –M1–N3	101.42(3)	109.42(7)			N1 ⁱ –M1–N3	106.31(4)	96.17(6)
O2–M1–N3	92.32(5)	94.36(14)	M1–N3–N4	133.24(12)	134.22(12)					
O1–M1–N3	89.49(6)	95.53(15)	N3–N4–N5	177.4(2)	178.13(19)					
N2–M1–N3	88.20(6)	91.09(15)								
N1–M1–N3	92.62(6)	98.12(15)								
O1 ⁱ –M1–N3	173.15(5)	170.76(14)								
M1–N3–N4	117.20(11)	124.6(3)								
N3–N4–N5	175.73(17)	176.4(5)								

measured as thin films obtained from dichloromethane solutions on a NaCl plate. The azide stretching frequencies, $\nu(\text{N}_3)_{\text{asym}}$, for all these complexes were found between 2015 and 2070 cm^{-1} , typical for such azide adducts (Table 3).

Reaction of metal–azide complexes with dimethyl acetylenedicarboxylate

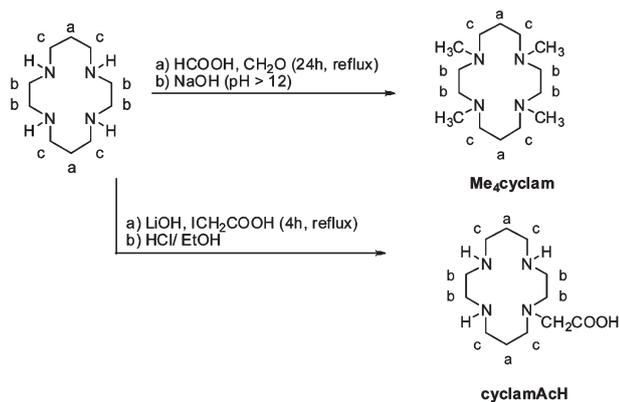
A summary of the cycloaddition reactions between the synthesized metal–azide complexes and dimethyl acetylenedicarboxylate is shown in Scheme 9. Typically, 1 equiv. of metal–azide complex was treated with an excess of dimethyl acetylenedicarboxylate (4–5 equiv.) in chloroform at room temperature or acetonitrile at 50 °C, and the reaction was followed by IR spectroscopy. The acetonitrile reaction at 50 °C was performed for the complexes where no reaction was observed in chloroform at RT. In the cases when the 1,3-dipolar cycloaddition occurs, the formation of the N(2)-bound 4,5-bis(methoxycarbonyl)-1,2,3-triazolate complex was confirmed by the disappearance of the $\nu(\text{N}_3)_{\text{asym}}$ stretch in the IR spectrum and the appearance of sharp peaks assigned to the stretching frequencies of the C=O, N=N and C–O bonds, and ring vibrations of the triazolate product, as reported previously.^{11a,19}

When the cycloaddition reaction was attempted for the (salen)Co– and (salen)Fe–azide complexes **1** and **2**, no decrease in the intensity of the azide stretching frequency was observed even after 6 days, either at RT or 50 °C in chloroform or acetonitrile, indicating that the cycloaddition reaction does not occur for these complexes. For both **1** and **2**, the potential dissociation of

the dinuclear complexes into mononuclear species in solution needs to be considered; however, the weak axial metal–O interactions (*vide supra*) are not expected to have an appreciable effect on the rate of the azide–alkyne cycloaddition reaction for the dinuclear vs. mononuclear species.

Interestingly, treatment of 1 equiv. of [(Me₄cyclam)Ni^{II}(N₃)]PF₆ (**3**) with 5 equiv. of dimethyl acetylenedicarboxylate under stirring in CHCl₃ at RT shows the complete disappearance of the azide peak (2070 cm^{-1}) after 6 h and the appearance of stretches at 1726 cm^{-1} ($\nu(\text{C}=\text{O})$), 1480 cm^{-1} ($\nu(\text{N}=\text{N})$),¹⁹ 1270 cm^{-1} ($\nu(\text{C}-\text{O})$), and triazolate ring vibrations at 826, 806 and 778 cm^{-1} , corresponding to the formation of a triazolate species (Fig. 4).¹¹ Crystals of the product {(Me₄cyclam)Ni^{II}[N₃C₂(CO₂Me)₂]}ClO₄ (**7**) were obtained by slow diffusion of hexane into a dichloromethane solution. Similar results were obtained for [(Me₄cyclam)Co^{II}(N₃)]ClO₄ (**4**), which was treated with 5 equiv. dimethyl acetylenedicarboxylate in chloroform to lead to the disappearance of the azide stretch at 2070 cm^{-1} and appearance of stretches at 1728, 1479, 1261 cm^{-1} , and triazolate ring vibrations at 822, 805 and 779 cm^{-1} , respectively.^{11a,19} Crystals of {(Me₄cyclam)Co^{II}[N₃C₂(CO₂Me)₂]}ClO₄ (**8**) were obtained by slow diffusion of hexane into a dichloromethane solution of the isolated product.

By contrast, when the (cyclamAc)Fe– and (cyclamAc)Co–azide complexes **5** and **6** were treated with an excess of dimethyl acetylenedicarboxylate, no disappearance of the azide stretch at 2052 cm^{-1} was observed even after 5 days, either in acetonitrile or chloroform at RT or 50 °C. Overall, the lack of a cycloaddition reaction suggests that subtle changes in the electronic properties and ligand environment of the metal centre



Scheme 7 Synthesis of cyclam-derived ligands.

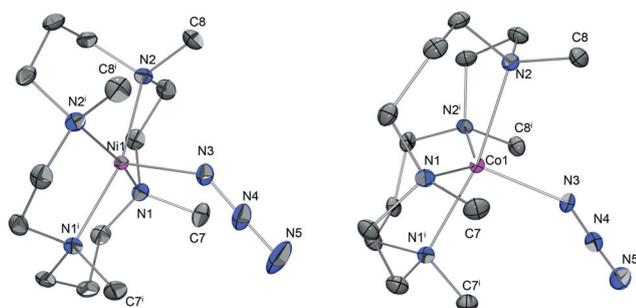
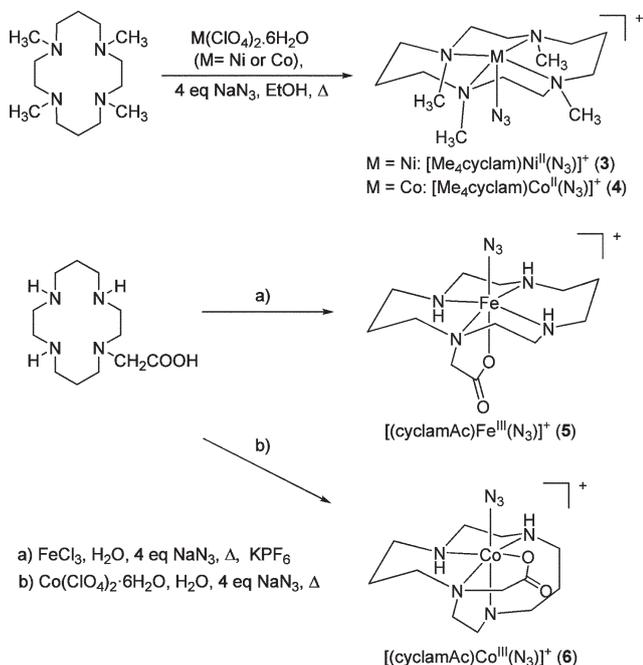


Fig. 2 View of the molecular structure and atom labelling of the monocations of (left) $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]\text{PF}_6$ (**3**) and (right) $[(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}(\text{N}_3)]\text{ClO}_4$ (**4**). The counteranions and hydrogen atoms have been omitted for clarity.



Scheme 8 Synthesis of metal-azide complexes using cyclam-derived ligands.

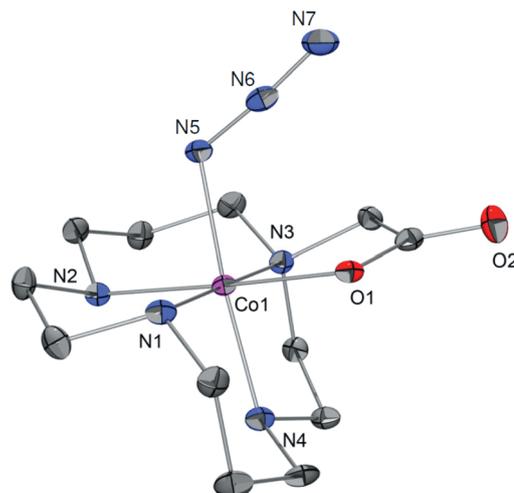


Fig. 3 View of the molecular structure and atom labelling of the monocation of $[(\text{cyclamAc})\text{Co}^{\text{III}}(\text{N}_3)]\text{ClO}_4$ (**6**). The counter-anion and hydrogen atoms have been omitted for clarity.

Table 3 Azide stretching frequencies, $\nu(\text{N}_3)_{\text{asym}}$, for the metal-azide complexes described herein. IR spectra were measured as thin films

Complex	$\nu(\text{N}_3)_{\text{asym}}/\text{cm}^{-1}$
$[(\text{salen}1)\text{Co}^{\text{III}}(\text{N}_3)]_2$	2015
$[(\text{salen}2)\text{Fe}^{\text{III}}(\text{N}_3)]_2$	2058
$[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]\text{PF}_6^a$	2070
$[(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}(\text{N}_3)]\text{ClO}_4$	2070
$[(\text{cyclamAc})\text{Fe}^{\text{III}}(\text{N}_3)]\text{PF}_6^b$	2046
$[(\text{cyclamAc})\text{Co}^{\text{III}}(\text{N}_3)]\text{ClO}_4$	2052

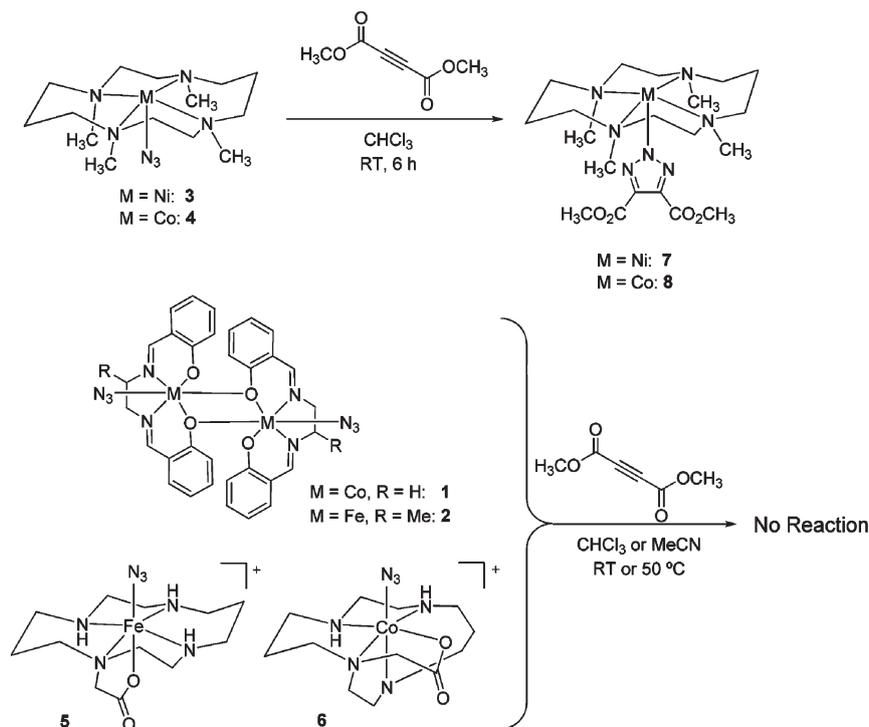
^a Lit. value 2066 cm^{-1} (ref. 27b). ^b Lit. value 2051 cm^{-1} (ref. 22).

are critical in the successful formation of the triazolate product (*vide infra*).

Structures of metal-triazolate complexes 7 and 8

Complexes $\{(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2]\}\text{ClO}_4$ (**7**) and $\{(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2]\}\text{ClO}_4$ (**8**) were characterized by X-ray single crystal analysis (Fig. 5). The experimental crystallographic data are summarized in Table 1 and selected bond lengths and angles are given in Table 2.

Both complexes **7** and **8** crystallize in the same space group (monoclinic $C2/c$). In both structures the metal ion exhibits a square-pyramidal coordination geometry where the N atoms of the Me₄cyclam ligand occupy the equatorial positions and the triazolate anion is bound axially (Fig. 5). The 4,5-bis(methoxycarbonyl)-1,2,3-triazolate ligand binds symmetrically to the metal centre, through its central N(3) atom, and the triazole plane adopts a staggered orientation relative to the methyl groups of Me₄cyclam in order to minimize steric repulsions. Given this C_2 symmetry of the cations of **7** and **8**, the two sets of equivalent $\text{M}-\text{N}_{\text{ligand}}$ distances are 2.113 and 2.147 Å for the Ni complex and 2.129 and 2.199 Å for the Co complex, while the $\text{M}-\text{N}_{\text{triazolate}}$ distances are 2.002 and 2.030 Å for **7** and **8**, respectively (Table 2). To the best of our knowledge, complexes **7** and **8**



Scheme 9 Survey of the cycloaddition reaction for various metal-azide complexes and the electron-deficient alkyne dimethyl acetylenedicarboxylate.

represent the first structurally characterized Ni^{II} - and Co^{II} -triazolate complexes formed upon a cycloaddition reaction; only one other structurally characterized Co^{III} -triazolate complex has been reported to date.³³ Moreover, **7** and **8** are the first metal-triazolate complexes with a five-coordinated geometry around the metal ion.³²

Factors determining the cycloaddition reaction for metal-azide complexes

In order to discern the factors that lead to a successful cycloaddition reaction between an alkyne and various metal-azide complexes, we compared relevant metrical parameters of the azide complexes obtained herein and two other structurally characterized Co^{III} -azide complexes^{33,34} that have been previously shown to undergo a cycloaddition reaction with dimethyl acetylenedicarboxylate.¹¹ Analysis of metrical parameters reveals that metal-azide complexes that lead to triazole formation exhibit longer metal-azide bonds (>1.955 Å, Table 4), which could be due to either the presence of axial donors with stronger *trans* influence (*e.g.*, PPh_3 or py),¹¹ or the presence of metal centers in lower oxidation states (*e.g.*, Ni^{II} and Co^{II}). However, while the Fe-azide bond length in $[(\text{salen}2)\text{Fe}^{\text{III}}(\text{N}_3)]_2$ is 2.015 Å, no cycloaddition reaction was observed for this complex. By contrast, shorter proximal N-N bonds ($\text{N}-\text{N}_{\text{prox}}$) of the bound azide ligand are observed for the complexes undergoing the cycloaddition reaction (Table 4). In addition, the difference between the long and short N-N bonds of the azide ligand (*i.e.*, $\text{N}-\text{N}_{\text{prox}}$ and $\text{N}-\text{N}_{\text{dist}}$, respectively) is smaller (<0.029 Å) for these complexes *vs.* those that do not form

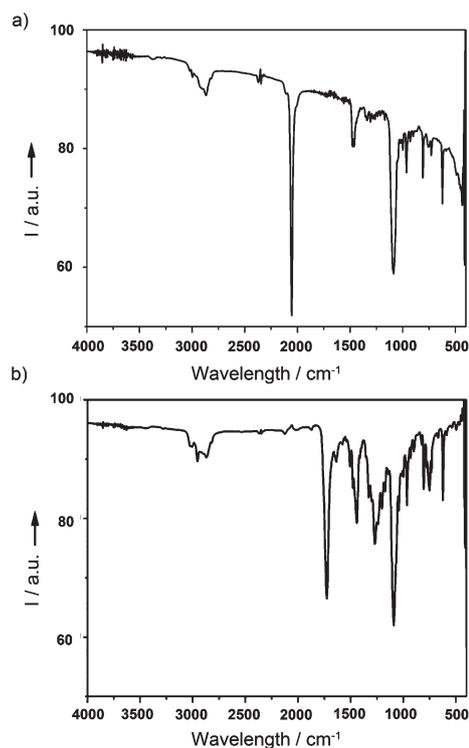


Fig. 4 The cycloaddition reaction between $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]\text{ClO}_4$ and dimethyl acetylenedicarboxylate in CHCl_3 monitored by IR: (a) before addition of alkyne and (b) after 6 h.

triazolate adducts (>0.053 Å). This bond length difference ($\text{N}-\text{N}_{\text{prox}} - \text{N}-\text{N}_{\text{dist}}$) provides a measure of the contribution of

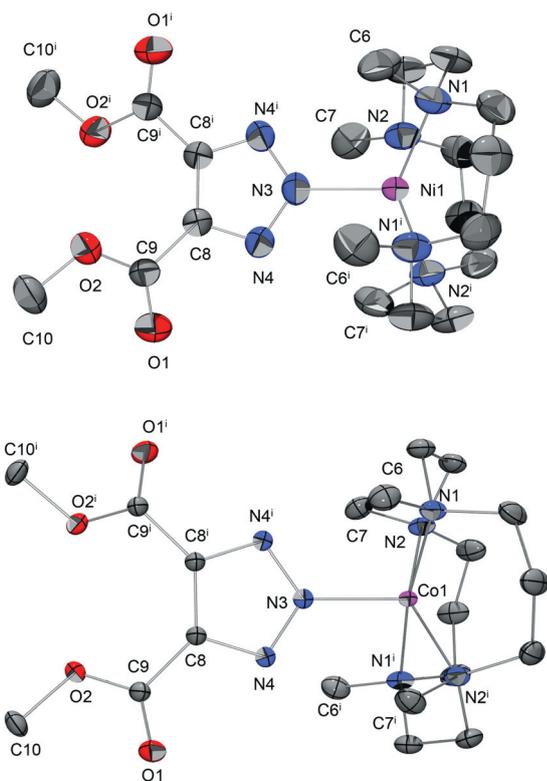
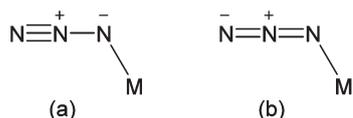


Fig. 5 View of the molecular structure and atom labelling of the monoaddition of (top) $\{(\text{Me}_4\text{cyclamNi}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2])\}\text{ClO}_4$ (**7**) and (bottom) $\{(\text{Me}_4\text{cyclamCo}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2])\}\text{ClO}_4$ (**8**). The counteranion and hydrogen atoms have been omitted for clarity.

the two possible resonance forms (a) or (b) to the electronic structure of the metal-azide complexes, and strongly suggests that the azide groups with a greater contribution from the resonance form (b) (*i.e.*, with a more symmetric charge density distribution) are expected to undergo the cycloaddition reaction more easily.



Reaction of metal-azide complexes with other alkynes

Our results suggest that the Ni- and Co-azide complexes **7** and **8** with the Me_4cyclam ligand can undergo a cycloaddition reaction with dimethyl acetylenedicarboxylate to yield the corresponding 1,4-triazolate products. Since the alkyne employed above is very electron deficient, we set out to investigate the click reaction of **7** and **8** with less electron deficient alkynes (Scheme 10). The selected alkynes were chosen as they resemble the methylated amine substrates of the histone demethylase enzymes, a new class of non-heme iron enzymes.³⁵ The cycloaddition studies were performed similarly to those with dimethyl acetylenedicarboxylate, by adding 5 equiv. alkyne to 1 equiv. metal-azide complex in either chloroform or acetonitrile at RT or 50 °C and followed by IR for the disappearance of the azide

Table 4 Comparison of relevant structural parameters for metal-azide complexes

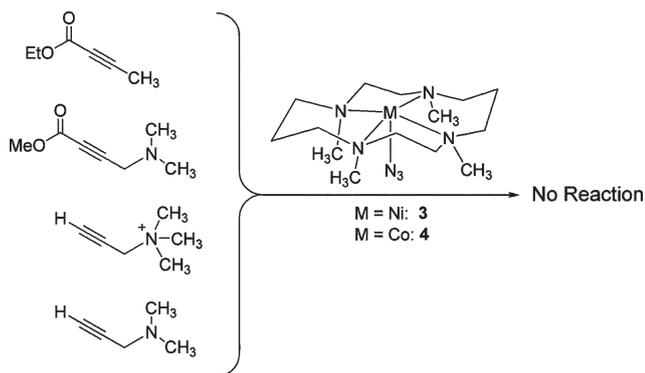
Complex	$d/\text{Å}$			
	M–N ₃	N–N _{prox}	N–N _{dist}	(N–N) _{prox} – (N–N) _{dist}
$[(\text{salen1})\text{Co}^{\text{III}}(\text{N}_3)]_2^a$	1.932	1.209	1.150	0.059
$[(\text{salen2})\text{Fe}^{\text{III}}(\text{N}_3)]_2^a$	2.015	1.209	1.132	0.077
$[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]\text{PF}_6^a$	1.989	1.180	1.153	0.027
$[(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}(\text{N}_3)]\text{ClO}_4^a$	1.974	1.183	1.160	0.023
$[(\text{cyclamAc})\text{Fe}^{\text{III}}(\text{N}_3)]\text{PF}_6^a$	1.931	1.209	1.156	0.053
$[(\text{cyclamAc})\text{Co}^{\text{III}}(\text{N}_3)]\text{ClO}_4^a$	1.936	1.208	1.151	0.057
$(\text{PPh}_3)\text{Co}^{\text{III}}(\text{DH})_2\text{N}_3^b$	2.014	1.180	1.161	0.019
$(\text{py})\text{Co}^{\text{III}}(\text{DH})_2\text{N}_3^c$	1.955	1.155	1.126	0.029

The azide adducts highlighted in bold yield triazole products.^a This work. ^b Ref. 33. ^c Ref. 34, DH = dimethylglyoximate.

stretch and the appearance of the triazolate product stretches. For all substrates investigated, no triazolate product was obtained when either **7** or **8** was used as the starting material, suggesting that a highly electron deficient alkyne is required for the cycloaddition reaction to occur. Overall, these studies imply that the targeted inorganic azide-alkyne cycloaddition reaction can only occur for a limited set of metal-azide complexes and only when very electron deficient alkynes are employed. Alternatively, use of metal complexes in other oxidation states or stabilized by ligands with various electronic properties may allow for the cycloaddition reaction to proceed for less electron-deficient alkynes. Such additional studies are currently underway.

Conclusion

In summary, we have synthesized and structurally characterized a series of Fe, Co and Ni mono-azide complexes that employ biomimetic salen- and cyclam-derived ligands. The obtained metal-azide complexes were investigated for their ability to undergo an azide-alkyne cycloaddition reaction – an “inorganic click reaction”, with several alkyne substrates. Our studies reveal that one Co-azide and one Ni-azide complex of the neutral ligand Me_4cyclam react with the electron deficient alkyne dimethyl acetylenedicarboxylate to generate the metal-triazolate products, which were structurally characterized. Use of less electron deficient alkynes did not generate the corresponding cycloaddition products. In addition, use of the anionic ligand cyclamAc seems to abolish the ability of the corresponding metal-azide complexes to react with any alkyne, suggesting that even subtle changes in the electronic properties of the metal centre leads to an azide ligand whose polarity renders it unreactive toward a cycloaddition reaction. Analysis of the structural parameters of the investigated metal-azide complexes suggests that a more symmetric charge density distribution within the azide moiety is needed for the formation of the metal-triazolate product. In this context, it will be interesting to study whether the azide adducts of non-heme iron enzymes, as opposed to small inorganic model complexes, are capable of undergoing a cycloaddition reaction with alkyne substrate analogues. It is expected that the active site of these enzymes will promote the “click reaction” to a greater extent than a model complex by



Scheme 10 Alkyne substrates employed in the cycloaddition reaction with the $[(\text{Me}_4\text{cyclam})\text{M}^{\text{II}}(\text{N}_3)]\text{ClO}_4$ complexes ($\text{M} = \text{Ni}, \text{Co}$).

increasing the local concentration of the two substrates and thus the rate of the cycloaddition reaction. Our current research efforts are aimed at employing such enzyme-templated cycloaddition reactions for the development of specific inhibitors for non-heme iron enzymes. Of particular interest are histone demethylases, a new class of non-heme iron enzymes that have recently been shown to be overexpressed in cancer cells.³⁶ Thus, high-affinity histone demethylase inhibitors that exhibit increased specificity can be used in the development of alternative cancer therapeutics.³⁵

Experimental section

Commercially available reagents were used as received. All reagents, organic and inorganic, were of high purity grade and obtained from E. Merck, Fluka, Chemie and Aldrich Co. The solvents were dried by passing over an alumina column.

Physical measurements

^1H (300.121 MHz) NMR spectra were recorded on a Varian Mercury-300 spectrometer. Chemical shifts are reported in ppm and referenced to residual solvent resonance peaks. Infrared spectra were measured as thin films on a KBr or NaCl plate using a Perkin Elmer Spectrum BX FT-IR spectrometer in the 4000–400 cm^{-1} range. UV-Vis spectra were recorded on a Varian Cary 50 Bio spectrophotometer. ESI-MS experiments were performed on a Bruker Maxis QTOF mass spectrometer with an electron spray ionization source at the Washington University Mass Spectrometry Resource, a NIH Research Resource supported by Grant No. P41RR0954.

X-Ray crystallography

X-Ray diffraction quality crystals of **1–4** were obtained by slow evaporation of the mother liqueur. The Co complex **6** was crystallized by slow diffusion of anhydrous diethyl ether into a solution of acetonitrile. The metal–triazolate complexes **7** and **8** were obtained by slow diffusion of hexane in a dichloromethane solution. Suitable crystals of appropriate dimensions were mounted on Mitgen loops in random orientations. Preliminary examination and data collection were performed using a Bruker

Kappa Apex-II Charge Coupled Device (CCD) Detector system single-crystal X-Ray diffractometer equipped with an Oxford Cryostream LT device. Data were collected using graphite-monochromated Mo- $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) from a fine-focus sealed-tube X-ray source. Preliminary unit cell constants were determined with a set of 36 narrow frame scans. Typical data sets consist of a combination of ω and ϕ scan frames with typical scan width of 0.5° and counting time of 15–30 s per frame at a crystal to detector distance of $\sim 4.0 \text{ cm}$. The collected frames were integrated using an orientation matrix determined from the narrow frame scans. Apex II and SAINT software packages³⁷ were used for data collection and data integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by global refinement of reflections from the complete data set. Data were corrected for systematic errors using SADABS³⁷ based on the Laue symmetry using equivalent reflections. Structure solutions and refinement were carried out using the SHELXTL-PLUS software package.³⁸ The structures were refined with full-matrix least-squares refinement by minimizing $\sum w(F_o^2 - F_c^2)^2$. All non-hydrogen atoms were refined anisotropically to convergence. All H atoms were added in the calculated position and were refined using appropriate riding models (AFIX m3). Selected crystals data and structure refinement parameters are listed in Tables 1 and 2. All data were collected at 100 K, except complex **7** for which data were collected at both 100 and 300 K. For the structural characterization of **7**, multiple data sets were collected on different crystals at room temperature and at 100 K. The perchlorate anion in the structure of **7** is disordered and sits on a 2-fold rotation axis. To be able to resolve the disorder, the symmetry equivalent atoms were generated and refined with half the expected occupancies and with PART-1/-2 instructions. The Ni(Me_4cyclam) fragment of the complex shows whole molecule disorder and the disorder was modeled as two overlapping motifs. The relative occupancies were refined using free variables. The disordered atoms were refined with geometrical restraints and displacement parameter restraints as listed in the .CIF file.

Synthesis of ligands

The N,N' -bis(salicylidene)-1,2-ethylenediimine ($\text{H}_2\text{salen1}$) and N,N' -bis(salicylidene)-1,2-propylenediimine ($\text{H}_2\text{salen2}$) ligands were synthesized by stirring 2 equiv. of 1,2-ethyldiamine or 1,2-diaminopropane, respectively, and 1 equiv. of salicylaldehyde in ethanol for 2 h.²³ The final solution was used for the synthesis of the corresponding metal complexes.

Synthesis of 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (Me_4cyclam). The Me_4cyclam ligand was synthesized following a literature procedure,²⁵ with some slight modifications. A solution containing 1.5 g of cyclam (7.5 mmol), 8.5 mL of 98% aqueous formic acid, 6.6 mL of formaldehyde (38% aqueous solution) and 5 mL of water was refluxed for 24 h. The reaction mixture was diluted with 15 mL of water, transferred to a 100 mL beaker, and cooled in an ice-bath. A concentrated solution of sodium hydroxide (15 g of NaOH dissolved in 50 mL of water) was slowly added with stirring until $\text{pH} > 12$. The temperature of the solution was kept below 25°C . The solution was then extracted with $5 \times 50 \text{ mL}$ portions of

CHCl_3 , the extracts were combined and dried over sodium sulphate, and then were concentrated to yield an oily residue. The residue crystallized at 4 °C overnight and the product was dried under vacuum for 2 h at 50 °C. Yield 80%. $^1\text{H NMR}$ (δ , CDCl_3 , 300 MHz): 1.643 (q, $^3J(\text{H-H}) = 7$ Hz, 4H, H_a), 2.198 (s, 12 H, 4Me), 2.427 (m, 16 H, $\text{H}_{b,c}$). ESI-MS: m/z 257.3, 257.3 expected for $[\text{Me}_4\text{cyclamH}]^+$.

Synthesis of 1,4,8,11-tetraazacyclotetradecane-1-acetic acid tetrahydrochloride (cyclamAc \cdot 4HCl). The cyclamAcH ligand was synthesized following a literature procedure,²⁶ with some slight modifications. To 1 g (5 mmol) of cyclam dissolved in 15 mL of EtOH and 3 mL of H_2O , 48 mg (2 mmol) of LiOH and 186 mg (1 mmol) of ICH_2COOH dissolved in 4 mL of H_2O were added at 5 °C. The mixture was refluxed for 4 h. The EtOH was then evaporated, and the alkaline aqueous solution was treated with CHCl_3 (4×10 mL) to remove non-reacted cyclam. The aqueous solution was dried at vacuum. Addition of 2 mL of HCl and 2 mL of EtOH lead to precipitation of the protonated tetrachloride product, which can be converted to the free-base form upon neutralization with NaOH. Yield: 41%. $^1\text{H NMR}$ (δ , CDCl_3 , 300 MHz): 1.94 (m, 4H, H_a), 2.8–3.5 (m, 16 H, $\text{H}_{b,c}$), 3.6 (s, 2H, CH_2COOH). ESI-MS: m/z : 259.19, 259.21 expected for $[\text{cyclamAcH}]^+$.

Synthesis of metal–azide complexes

(a) Derived from salen ligands

Synthesis of $[(\text{salen1})\text{Co}^{\text{III}}(\text{N}_3)]_2$. To a solution of $\text{H}_2\text{Salen1}$ (27 mg, 0.1 mmol) in EtOH heated at 60 °C, a solution of $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (20 mg, 0.1 mmol) in 5 mL of EtOH and an aqueous solution (2 mL) of NaN_3 (6.5 mg, 0.1 mmol) were added. The solution was stirred at 60 °C for 30 min to form a brown precipitate. The reaction was cooled to room temperature and the solid was collected by filtration. X-Ray quality crystals were obtained by slow evaporation of the resulting solution in air. Yield: 91%. FTIR (NaCl , cm^{-1}): 2015($\nu(\text{N}_3)$), 1645, 1557 ($\nu(\text{C}=\text{N})$), 1471, 1447, 1338 ($\nu(\text{C}-\text{N})$), 1287. UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 390 (8300), 314 (12 400), 257 (43 000). Anal. Calc. for $\text{C}_{32}\text{H}_{28}\text{Co}_2\text{N}_{10}\text{O}_4 \cdot 7\text{H}_2\text{O}$ (MW 860.60): C, 44.66; H, 4.92; N, 16.28. Found: C, 44.57; H, 4.70; N, 16.00%. ESI-MS: m/z 325.00, 325.04 expected for $[(\text{salen1})\text{Co}^{\text{III}}]^+$; 692.09, 692.10 expected for $[(\text{salen1})\text{Co}^{\text{III}}\text{N}_3\text{Co}^{\text{III}}(\text{salen1})]^+$.

Synthesis of $[(\text{salen2})\text{Fe}^{\text{III}}(\text{N}_3)]_2$. To a solution of $\text{H}_2\text{Salen2}$ (57 mg, 0.2 mmol), an ethanol solution (10 mL) of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (80.8 mg, 0.2 mmol) and an aqueous solution (4 mL) of NaN_3 (13 mg, 0.2 mmol) were added under stirring. After allowing the resulting purple solution to stand in air for 10 days, black crystals were formed upon slow evaporation of the solvent. Yield: 77%. FTIR (NaCl , cm^{-1}): 2926, 2355 ($\nu(\text{C}-\text{H})$), 2058($\nu(\text{N}_3)$), 1618, 1598, 1541 ($\nu(\text{C}=\text{N})$), 1468, 1444, 1391 ($\nu(\text{C}-\text{N})$), 1299. UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 454 (2575), 319 (6167), 294 (sh) 256 (13 500). Anal. Calc. for $\text{C}_{34}\text{H}_{32}\text{Fe}_2\text{N}_{10}\text{O}_4 \cdot 4\text{CH}_3\text{CH}_2\text{OH} \cdot 2\text{H}_2\text{O}$ (MW 976.68): C, 51.65; H, 6.19; N, 14.34. Found: C, 52.11; H, 5.85; N, 13.94%. ESI-MS: m/z 336.05, 336.08 expected for $[(\text{salen2})\text{Fe}^{\text{III}}]^+$.

(b) Derived from cyclam ligands

Synthesis of $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]$ ($X = \text{ClO}_4^-$ or PF_6^-): $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]\text{ClO}_4^{27a,b}$ To a stirred solution of Me_4cyclam (100 mg, 0.4 mmol) in 5 mL of ethanol was added an aqueous solution (5 mL) of NaN_3 (100 mg, 1.5 mmol). After 1 min, solid $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was added to the stirred solution (142.85 mg, 0.4 mmol). The solution was heated to 70 °C and stirred for 1 h. The resulting light green solution was cooled to room temperature, filtered to remove the excess NaN_3 , and then kept at 4 °C. After 48 h, green needle crystals formed. Yield: 60%. FTIR (NaCl , cm^{-1}): 3392, 2996, 2939, 2864 ($\nu(\text{C}-\text{H})$), 2070 ($\nu(\text{N}_3)$), 1471, 1433, 1324, 1307 ($\nu(\text{C}-\text{N})$), 1288, 1240, 1088 ($\nu(\text{ClO}_4^-)$). UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 683 (85), 375 (2450). Anal. Calc. for $\text{C}_{14}\text{H}_{32}\text{NiN}_7\text{ClO}_4$ (MW 456.59): C, 36.83; H, 7.06; N, 21.47. Found: C, 36.79; H, 7.62; N, 21.46%. ESI-MS: m/z 359.16, 359.20 expected for $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]^+$.

Using the same procedure but starting with $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and upon addition of an excess of KPF_6 , the complex $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]\text{PF}_6$ was formed as green needle crystals suitable for X-ray crystallography. ESI-MS (m/z): 359.16, 359.20 expected for $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]^+$.

Synthesis of $[(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}(\text{N}_3)]\text{ClO}_4^{27c}$ To a stirred solution of Me_4cyclam (100 mg, 0.4 mmol) in 5 mL of ethanol was added an aqueous solution (5 mL) of NaN_3 (100 mg, 1.5 mmol). After 1 min, solid $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was added to the stirred solution (143 mg, 0.4 mmol). The solution was heated at 70 °C and stirred for 1 h. The resulting dark-purple solution was cooled to room temperature, filtered to remove the excess NaN_3 , and then kept at 4 °C. After 48 h, dark-purple crystals formed. Yield: 67%. FTIR (NaCl , cm^{-1}): 3014, 2925, 2867 ($\nu(\text{C}-\text{H})$), 2070 ($\nu(\text{N}_3)$), 1476, 1089, 1275. UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 597 (118), 337 (2973). Anal. Calc. for $\text{C}_{14}\text{H}_{32}\text{CoN}_7\text{ClO}_4$ (MW 456.83): C, 36.81; H, 7.06; N, 21.46. Found: C, 36.35; H, 7.06; N, 21.45%. ESI-MS: $m/z = 358.16$, 358.21 expected for $[(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}(\text{N}_3)]^+$.

Synthesis of $[(\text{cyclamAc})\text{Fe}^{\text{III}}(\text{N}_3)]\text{PF}_6^{22}$ To 150 mg of cyclamAcH (0.58 mmol) dissolved in 5 mL degassed water was added 94.73 mg (0.58 mmol) of FeCl_3 in 5 mL degassed water. The resulting solution was brought to a gentle reflux and heated for 90 min as an orange color developed. The solution was cooled to room temperature and excess NaN_3 was added (124 mg, 1.9 mmol) to yield a dark-red solution. The resulting solution was stirred for 2 h at room temperature and subsequently filtered to yield a clear red filtrate. Addition of an aqueous solution (5 mL) of 350 mg KPF_6 (1.9 mmol) yielded red–orange microcrystals upon cooling at 4 °C overnight that were collected by filtration, washed with 2×10 mL diethyl ether, and dried under vacuum. Yield: 45%. FTIR (NaCl , cm^{-1}): 3260 ($\nu(\text{N}-\text{H})$), 2046 ($\nu(\text{N}_3)$), 1651 ($\nu(\text{C}=\text{O})$), 838, 558 ($\nu(\text{PF}_6^-)$). UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 460 (2500), 305 (4535), 276 (sh), 245 (11175). ESI-MS: $m/z = 355.18$, 355.14 expected for $[(\text{cyclamAc})\text{Fe}^{\text{III}}(\text{N}_3)]^+$.

Synthesis of $[(\text{cyclamAc})\text{Co}^{\text{III}}(\text{N}_3)]\text{ClO}_4$. To 150 mg of cyclamAcH (0.58 mmol), dissolved in 5 mL degassed water was added 214.41 mg (0.58 mmol) of $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in 5 mL degassed water. The resulting solution was brought to a gentle reflux and heated for 90 min as an orange color developed. The solution was cooled to room temperature and an excess of NaN_3

was added (124 mg, 1.9 mmol) to yield a dark-purple solution. The resulting solution was concentrated to 2 mL and excess NaN_3 was filtered. The solvent was then removed and the purple product was washed with 2×10 mL diethyl ether, collected by filtration, and dried under vacuum. X-ray quality crystals were obtained by slow diffusion of ether into a MeCN solution. Yield: 50%. FTIR (NaCl, cm^{-1}): 2923 ($\nu(\text{N-H})$), 2052 ($\nu(\text{N}_3)$), 1686 ($\nu(\text{C=O})$), 837, 560. UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 545 (200), 317 (4727). Anal. Calc. for $\text{C}_{12}\text{H}_{25}\text{ClCo-N}_7\text{O}_6 \cdot 7\text{H}_2\text{O}$ (MW 581.85): C, 24.77; H, 6.41; N, 16.85. Found: C, 24.44; H, 6.18; N, 16.76%. ESI-MS: $m/z = 358.18, 358.14$ expected for $[(\text{cyclamAc})\text{Co}^{\text{III}}(\text{N}_3)]^+$.

Synthesis of metal–triazolate complexes

Synthesis of $\{(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2]\}\text{ClO}_4$. To 10 mg $[(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}(\text{N}_3)]\text{ClO}_4$ (0.02 mmol) dissolved in chloroform were added 14 μL of dimethyl acetylenedicarboxylate (0.11 mmol). The solution was stirred for 6 h and the formation of the triazolate product was followed by FT-IR. The product was precipitated in hexane, filtered, and dried under vacuum. X-Ray quality crystals were obtained by slow diffusion of hexane into a dichloromethane solution at 4 °C. Yield: 91%. FTIR (NaCl, cm^{-1}): 2955, 2870, 1726 ($\nu(\text{C=O})$), 1480 ($\nu(\text{N=N})$), 1441, 1328, 1270 ($\nu(\text{C-O})$), 1202, 1171, 1090, 964, 826, 806, 778, 750, 623. UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 636 (88), 514 (149), 386 (731). Anal. Calc. for $\text{C}_{20}\text{H}_{38}\text{ClNiN}_7\text{O}_8 \cdot 0.5\text{C}_6\text{H}_{14}$ (MW 641.79): C, 43.04; H, 7.07; N, 15.28. Found: C, 43.01; H, 6.93; N, 15.34%. ESI-MS: $m/z = 498.30, 498.23$ expected for $\{(\text{Me}_4\text{cyclam})\text{Ni}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2]\}^+$.

Synthesis of $\{(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2]\}\text{ClO}_4$. To 10 mg $[(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}(\text{N}_3)]\text{ClO}_4$ (0.02 mmol) dissolved in chloroform were added 14 μL of dimethyl acetylenedicarboxylate (0.11 mmol). The solution was stirred for 10 h and the formation of the triazolate product was followed by FT-IR. The product complex was precipitated in hexane, filtered, and dried under vacuum. X-ray quality crystals were obtained by slow diffusion of hexane into a dichloromethane solution at room temperature. Yield: 84%. FTIR (NaCl, cm^{-1}): 2961, 2923, 2861, 2064, 1728 ($\nu(\text{C=O})$), 1479 ($\nu(\text{N=N})$), 1454, 1302, 1261, 1226 ($\nu(\text{C-O})$), 1170, 1090, 1042, 1019, 960, 842, 822, 806, 779, 732, 623 cm^{-1} . UV-Vis recorded in MeCN, $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$): 552 (30), 483 (43), 325 (sh). Anal. Calc. for $\text{C}_{20}\text{H}_{38}\text{ClCo-N}_7\text{O}_8 \cdot 2\text{H}_2\text{O}$ (MW 616.97): C, 38.83; H, 6.67; N, 15.44. Found: C, 38.42; H, 6.39; N, 15.35%. ESI-MS: $m/z = 499.16, 499.23$ expected for $\{(\text{Me}_4\text{cyclam})\text{Co}^{\text{II}}[\text{N}_3\text{C}_2(\text{CO}_2\text{Me})_2]\}^+$.

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