ChemComm



View Article Online

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Cite this: Chem. Commun., 2022, 58, 13019

Received 12th August 2022, Accepted 28th October 2022

DOI: 10.1039/d2cc04497h

rsc.li/chemcomm

Dynamics of the alkyne \rightarrow copper(I) interaction and its use in a heteroleptic four-component catalytic rotor[†]

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The HETPYNE (HETeroleptic Phenanthroline and alkYNE metal) and DABCO (zinc porphyrin)₂ interactions were used to assemble the four-component nanorotor ROT-1 that exhibited a highly dynamic alkyne \rightarrow copper(I) dissociation (k_{298} = 240 kHz) at 298 K. Quantitative click reaction transformed ROT-1 into the new rotor ROT-2 (k_{298} = 77 kHz) with a triazole \rightarrow copper(I) linkage thus opening perspectives for bioorthogonal click strategies to biohybrid machinery.

Inspired by nanomechanical motions¹ in biological machines,^{2–4} scientists have developed an enormous interest in the development of artificial molecular devices.^{5–8} Among them, molecular motors,^{9–11} rotors,¹² shuttles,^{13–15} tweezers,^{16–18} turnstiles,¹⁹ muscles,²⁰ elevators,²¹ pumps,¹⁰ walkers²² *etc.*^{5–8} are well studied. Though numerous examples of artificial covalent molecular devices are known in the literature,^{5–8} evolution toward multicomponent artificial machineries still represents a major challenge due to the limited amount of dynamic orthogonality in hetero-assemblies.^{23,24}

For designing artificial multicomponent rotors, orthogonal dynamic interactions are a key requirement.²⁵ To the best of our knowledge, all literature known dynamic interactions that have been used to construct artificial multicomponent rotors are derived from H-bonding or *N*,*O*-donor¹⁹ metal interactions.²⁶⁻³⁰ Clearly, development of any new dynamic interaction will open further opportunities. Here, we demonstrate for the first time a supramolecular assembly and a rotor built on the dynamic alkyne \rightarrow copper(i) interaction.^{31,32} Specifically, we designed a four-component supramolecular assembly and nanorotor based

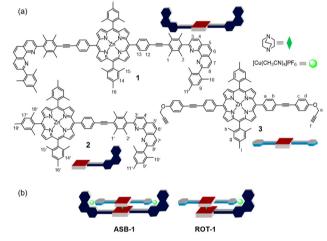


Fig. 1 (a) Chemical structure and cartoon representation of the ligands 1,
2, 3 and DABCO. (b) Cartoon representation of the four-component assembly ASB-1 and nanorotor ROT-1.

on the heteroleptic Cu⁺-phenanthroline alkyne (HETPYNE: HETeroleptic Phenanthroline and alkYNE metal) complexation (Fig. 1). Addition of stoichiometric quantities of azide to the rotor afforded the new class of a Cu⁺-triazole rotor through an *in situ* copper(I) catalysed click reaction.

For our study, we decided to use the phenanthrolineappended zinc(π) porphyrin ligands 1 or 2 as stator. Bulky aryl groups³³ at the 2,9-position of the phenanthroline phenAr₂ are essential to avoid the unwanted formation of the corresponding homoleptic Cu⁺ complexes.^{34–36} In order to design rotator 3, we performed a few model experiments to evaluate the binding of a terminal ethynyl group to [Cu(phenAr₂)]⁺. Mixing of 4, 5 and [Cu(CH₃CN)₄]PF₆ in 1:1:1 ratio (2.5 mM each) in CD₂Cl₂ accomplished quantitative formation of C1 = [Cu(4)(5)]⁺ (Fig. 2a). In the ¹H NMR, a downfield shift of all phenanthroline protons indicated binding of 5 to [Cu(4)]⁺, for instance, proton 4"-H shifted from 8.67 to 8.74 ppm and 5"-H from

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[†] Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, spectral data, NMR titration, and VT⁻¹H-NMR kinetics. CCDC 2199510. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2cc04497h

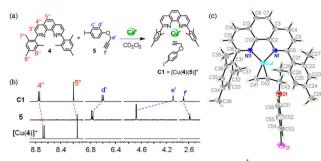


Fig. 2 (a) Formation of model complex C1. (b) Partial ¹H NMR (400 MHz, 298 K) of $[Cu(4)]^+$, 5 and C1 in CD_2Cl_2 (2.5 mM). (c) X-ray crystal structure of complex C1. Carbons are shown in light grey; H, light green; N, blue; O, red; Cu⁺, cyan and I, violet.

8.14 to 8.20 ppm (Fig. 2b). In contrast, protons d'-H (from 6.77 to 6.60 ppm) and e'-H (from 4.68 to 4.09 ppm) of the ethynyl ligand 5 shifted upfield upon its complexation to $[Cu(4)]^+$, due to the shielding of these protons by the π -ring current of the mesityl groups. On the other hand, despite being in the shielding region of a strong π -electron cloud, the downfield shift of proton f'-H (from 5 to C1: 2.58 to 2.68 ppm) validated the ethynyl binding to the Cu⁺ center. Single crystal X-ray analysis of C1 revealed a triclinic crystal system with the space group P1 (ESI,† Fig. S27). Importantly, it clearly demonstrated the side-on binding of Cu⁺ to both ethynyl carbons whereas there was no binding visible between oxygen and Cu⁺ center (Fig. 2c). The solid state structure disclosed the bond lengths of Cu(1)-C(41), Cu(1)-C(42), Cu(1)-N(11) and Cu(1)-N(1) to be 1.958(5) Å, 1.969(4) Å, 2.002(3) Å and 2.013(3) Å, respectively. The angle between the planes defined by N(1)-Cu(1)-N(11) and C(41)-Cu(1)-C(42) was determined as 16°. This geometry around the copper(1) center is not very common. From an NMR titration, the binding constant of 5 to $[Cu(4)]^+$ was determined as log $K = 2.81 \pm 0.16$ (ESI,[†] Fig. S26). We propose to denote the heteroleptic complexation motif between a $[Cu(phenAr_2)]^+$ and an alkyne as HETPYNE interaction (vide supra).

After establishing the HETPYNE motif, the zinc(II) porphyrin **3** with two ethynyl terminals was designed. To synthesize ligand **3**, we first reacted 5,15-di(4-iodophenyl)-10,20-dimesityl zinc(II) porphyrin and 4-ethynylphenol under Sonogashira coupling conditions providing the corresponding diphenol. In the final step, a Williamson ether synthesis between the phenol-substituted zinc(II) porphyrin and propargyl bromide in presence of base furnished ligand **3** in 85% yield. Protons e-H of **3** appear in the ¹H NMR well separated from other proton signals and should serve as good indicator of any binding.

As expected from the model studies, the four-component self-assembly **ASB-1** was quantitatively afforded by mixing DABCO, ligands **1** & **3**, and $[Cu(CH_3CN)_4]PF_6$ in a 1:1:1:2 ratio in CD₂Cl₂ (Fig. 3a). Two characteristic multiplets for the CH₂-units of DABCO in the negative region of the ¹H NMR indicated quantitative formation of the hetero-sandwich complex (Fig. 3b).³⁷ Significant changes at all phenanthroline protons in the ¹H NMR upon moving from $[Cu_2(1)]^{2+}$ to **ASB-1** supported the binding of **3** to the copper(1)-loaded phenanthroline stations (Fig. 3c and d).

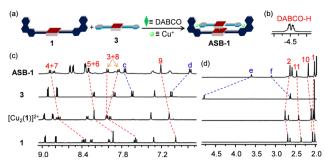


Fig. 3 (a) Cartoon representation of the four-component self-assembly leading to the formation of **ASB-1**. (b) DABCO-H signal of **ASB-1** in ¹H NMR (CD₂Cl₂, 400 MHz, 298 K). Partial ¹H NMR (CD₂Cl₂, 400 MHz, 298 K) of **1**, $[Cu_2(1)]^{2+}$, **3** and **ASB-1** showing the (c) aromatic and (d) aliphatic region.

Downfield shift of proton f-H from 2.64 to 3.10 ppm in **ASB-1** attested the terminal ethynyl binding of 3 at the Cu⁺ center of **1** (Fig. 3d). Drastic upfield shifts of proton signal e-H from 4.79 to 3.60 ppm and of d-H from 7.05 to 6.77 ppm along with a downfield shift of proton signal c-H from 7.64 to 7.75 ppm validated the formation of the HETPYNE complex. Furthermore, a single peak in the ESI-MS at m/z = 1489.1 confirmed formation of the hetero-assembly (ESI,† Fig. S23) and a single diffusion trace in the ¹H-DOSY NMR representing structure **ASB-1** excluded the presence of other undesired assemblies (ESI,† Fig. S20).

The clean formation of the heteroleptic sandwich complex encouraged us to test the HETPYNE motif as a dynamic interaction in a multicomponent rotor. To assemble the rotor, we selected zinc(II) porphyrin 2 containing just one phenanthroline station as stator and ligand 3 as rotator. Dissolving the ligands 2, 3, DABCO and $[Cu(CH_3CN)_4]PF_6$ in a 1:1:1:1 ratio in CD_2Cl_2 quantitatively furnished rotor **ROT-1** irrespective of the sequence of addition (Fig. 4a). As in **ASB-1**, two broad signals in the negative region corresponding to DABCO and significant shifts of all phenanthroline protons in the ¹H NMR validated formation of the heteroassembly (Fig. 4b–d). Upfield shifts of rotator proton signals e-H from 4.79 to 4.19 ppm along with downfield shift of f-H from 2.64 to 2.88 ppm authenticated the rotor structure (Fig. 4c and d). Its formation was further confirmed by DOSY NMR and ESI-MS data (ESI,† Fig. S21 and S24).

A single set of ¹H NMR signals for protons c-H, d-H, e-H and f-H of **ROT-1** suggested fast rotation of the rotor on the NMR

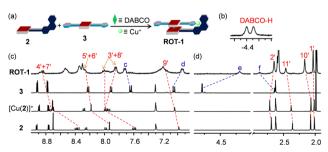


Fig. 4 (a) Cartoon representation of the self-assembly of rotor **ROT-1** from four components. (b) $(CH_2)_{DABCO}$ signal of **ROT-1** in the ¹H NMR $(CD_2Cl_2, 400 \text{ MHz})$. Partial ¹H NMR $(CD_2Cl_2, 400 \text{ MHz}, 298 \text{ K})$ of **2**, $[Cu(2)]^+$, **3** and **ROT-1** in the (c) aromatic and (d) aliphatic region.

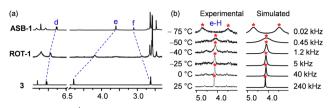


Fig. 5 (a) Partial ¹H NMR (CD_2Cl_2 , 400 MHz, 298 K) of 3, ROT-1 and ASB-1. (b) VT-¹H NMR (CD_2Cl_2 , 600 MHz) of ROT-1 exhibiting the splitting of proton signal e-H into a 1:1 set and the corresponding rotational frequency at different temperatures.

time scale (Fig. 4c and d). Comparison of the ¹H NMR spectra of the free rotator 3, ROT-1 and ASB-1 showed that the proton signals d-H, e-H and f-H of rotor ROT-1 appeared approximately in the averaged position of those of free 3 and ASB-1 (Fig. 5a). Variable temperature (VT) ¹H NMR of **ROT-1** was thus performed to evaluate its dynamic behavior. Upon lowering the temperature, the sharp singlet at 4.19 ppm corresponding to proton e-H broadened and split into two singlets in a 1:1 ratio at -75 °C with a coalescence temperature around -50 °C (Fig. 5b). The upfield signal at 3.50 ppm was assigned to the HETPYNE-complexed proton e-H and the downfield signal at 4.71 ppm is ascribed to proton e-H at the uncomplexed arm. The rotational frequency of the rotor at different temperatures was evaluated using winDNMR-based spectral simulations.³⁸ The activation data for the rotation was derived from the Eyring plot (Table 1 and ESI,† Fig. S18). The rotational frequency turned out to be 240 kHz at 25 °C and $\Delta G_{298}^{\ddagger}$ = 42.5 kJ mol⁻¹.

After the clean formation of rotor ROT-1, our next target was the in situ rotor-to-rotor transformation. The presence of a copper(1) ion and terminal alkynes in the rotor suggested a conversion of ROT-1 to a triazole rotor through an in situ click reaction. For this purpose, 2.0 equiv. of benzyl azide was added to **ROT-1** in CD_2Cl_2 (Fig. 6a). To accelerate the reaction, 1 μ L of Et₃N was added. After 24 h of heating at 40 °C, the solvent was evaporated to remove NEt₃ and the residue was redissolved in CD₂Cl₂. ¹H NMR showed quantitative formation of ROT-2 and a disappearance of the proton signal f-H (Fig. 6b). Upon moving from ROT-1 to ROT-2, characteristic shifts for all phenanthroline protons were observed. The downfield shift of proton signal e-H (from 4.19 to 4.81 ppm), upfield shifts of proton signals d-H (from 6.93 to 6.78 ppm) and c-H (from 7.72 ppm to 7.61 ppm) along with the appearance of a new singlet at 5.52 ppm (j-H) corroborated the formation of ROT-2. The broad signal of the DABCO protons at -4.39 ppm confirmed the

 Table 1
 Exchange frequencies of ROT-1 and ROT-2 along with their activation parameters^a

Rotor	k_{298}/kHz	$\Delta H^{\ddagger}/kJ mol^{-1}$	$\Delta S^{\ddagger}/J~\mathrm{K}^{-1}~\mathrm{mol}^{-1}$	$\Delta G_{298}^{\ddagger}/\mathrm{kJ}~\mathrm{mol}^{-1}$
ROT-1 ROT-2		$\begin{array}{c} 44.0\pm0.2\\ 50.1\pm0.4\end{array}$	$\begin{array}{c} 5.0\pm0.7\\ 16.7\pm0.6\end{array}$	42.5 45.2

^{*a*} The higher ΔH^{\ddagger} for **ROT-2** than **ROT-1** reflects the stronger binding constant of a triazole to [Cu(4)]⁺ (see triazole 6 in ESI, Fig. S27). As often seen in enthalpy–entropy compensation, strong binding leads to higher positive activation entropy.

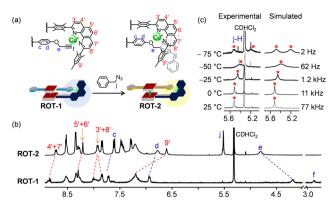


Fig. 6 (a) *In situ* transformation of **ROT-1** to **ROT-2** upon addition of 2.0 equiv. of benzyl azide. (b) Partial ¹H NMR (CD_2CI_2 , 400 MHz, 298 K) of **ROT-1** and **ROT-2**. (c) VT⁻¹H NMR (CD_2CI_2 , 600 MHz) of **ROT-2** showing splitting of the proton signal j-H (1:1 ratio) and the corresponding rotational frequency at different temperatures.

intactness of the assembly (ESI,† Fig. S15). **ROT-2** was further characterized by ESI-MS and DOSY NMR data (ESI,† Fig. S25 and S22).

A single set of ¹H NMR signals for protons c-H, d-H, e-H and j-H of **ROT-2** indicated a fast rotation on the NMR time scale. Upon performing the VT ¹H NMR the proton signal for j-H split into two singlets in 1:1 ratio at -75 °C (Fig. 6c). Rotational frequencies at different temperature along with activation parameters were calculated (Fig. 6c and Table 1). The facile transformation of the self-catalyzing rotor **ROT-1** to rotor **ROT-2** opens interesting perspectives to generate biohybrid materials *via* bioorthogonal click reactions.³⁹

In conclusion, we have synthesized a four-component heterosandwich complex and a four-component rotor based on the dynamic $[Cu(phenAr_2)(alkyne)]^+$ motif. Though alkyne \rightarrow copper(1) interactions are well known in the literature,⁴⁰ for the first time its high dynamics has been determined and used to assemble a high-speed multicomponent rotor. The utility of this dynamic orthogonal motif in supramolecular rotors opens new venues for molecular machines. Furthermore, a successful quantitative transformation of the Cu⁺-alkyne rotor to a new Cu⁺-triazole rotor was achieved through *in situ* click reaction. It is expected that thermal self-catalyzing rotors will find their way into diverse applications, *e.g.*, in catalysis,^{35,41} biohybrid materials *via* bioorthogonal functionalization⁴² and elsewhere.⁴³

We are indebted to the Deutsche Forschungsgemeinschaft for continued support under Schm 647/22-1 (No 491092614). We thank Dr Paululat for measuring the VT-¹H NMR.

Conflicts of interest

There are no conflicts to declare.

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