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Dynamics of the alkyne → copper(ı) 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), interactions were used to assemble the four-component nanorotor ROT-1 that exhibited a highly dynamic alkyne \rightarrow copper(ı) 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 → 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 walkers 22 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 → copper(1) interaction. 31,32 Specifically, we designed a four-component supramolecular assembly and nanorotor based

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.

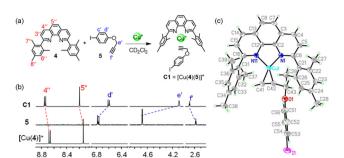
For our study, we decided to use the phenanthrolineappended zinc(II) porphyrin ligands 1 or 2 as stator. Bulky aryl groups³³ at the 2,9-position of the phenanthroline phenAr₂ are essential to avoid the unwanted formation of the corresponding homoleptic Cu⁺ complexes. 34-36 In order to design rotator 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 $C1 = [Cu(4)(5)]^{-1}$ (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

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

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Fig. 2 (a) Formation of model complex C1. (b) Partial 1 H 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(phenAr₂)]⁺ 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 CD_2Cl_2 (Fig. 3a). Two characteristic multiplets for the CH_2 -units of DABCO in the negative region of the 1H NMR indicated quantitative formation of the hetero-sandwich complex (Fig. 3b). 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(i)-loaded phenanthroline stations (Fig. 3c and d).

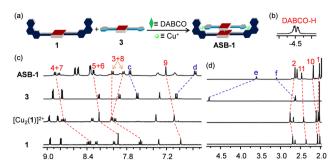


Fig. 3 (a) Cartoon representation of the four-component self-assembly leading to the formation of **ASB-1**. (b) DABCO-H signal of **ASB-1** in 1 H NMR (CD₂Cl₂, 400 MHz, 298 K). Partial 1 H NMR (CD₂Cl₂, 400 MHz, 298 K) of **1**, [Cu₂(**1**)] $^{2+}$, **3** and **ASB-1** showing the (c) aromatic and (d) 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(CH₃CN)₄]PF₆ in a 1:1:1:1 ratio in CD₂Cl₂ 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

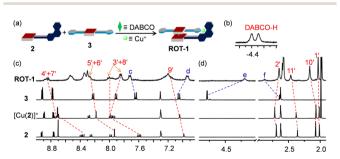


Fig. 4 (a) Cartoon representation of the self-assembly of rotor **ROT-1** from four components. (b) $(CH_2)_{DABCO}$ signal of **ROT-1** in the 1H NMR $(CD_2Cl_2, 400 \text{ MHz})$. Partial 1H NMR $(CD_2Cl_2, 400 \text{ MHz})$. Partial 1H NMR $(CD_2Cl_2, 400 \text{ MHz})$, 298 K) of 2, $[Cu(2)]^+$, 3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

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ASB-1⊸ 0.02 kHz 0.45 kHz -50 °C -40 °C 1.2 kHz -25 °C 5 kHz 0 °C 40 kHz

Fig. 5 (a) Partial ¹H NMR (CD₂Cl₂, 400 MHz, 298 K) of **3**, **ROT-1** and **ASB-**1. (b) VT-1H NMR (CD₂Cl₂, 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.

5.0 40 5.0 4.0

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 CD₂Cl₂ (Fig. 6a). To accelerate the reaction, 1 μL 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	$\Delta H^{\ddagger}/\mathrm{kJ} \mathrm{mol}^{-1}$	$\Delta S^{\ddagger}/J \text{ K}^{-1} \text{ mol}^{-1}$	$\Delta G_{298}^{\ddagger}/\mathrm{kJ} \mathrm{mol}^{-1}$
ROT-1	240	44.0 ± 0.2	5.0 ± 0.7	42.5
ROT-2	77	50.1 ± 0.4	16.7 ± 0.6	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.

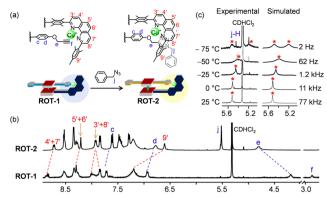


Fig. 6 (a) In situ transformation of ROT-1 to ROT-2 upon addition of 2.0 equiv. of benzyl azide. (b) Partial ¹H NMR (CD₂Cl₂, 400 MHz, 298 K) of ROT-1 and ROT-2. (c) VT-1H NMR (CD₂Cl₂, 600 MHz) of ROT-2 showing splitting of the proton signal j-H (1:1 ratio) and the corresponding rotational frequency at 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

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Conflicts of interest

There are no conflicts to declare.

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