



Article Copper(II) Prevents the Saccarine-Dialkylcyanamide Coupling by Forming Mononuclear (Saccharinate) (Dialkylcyanamide)copper(II) Complexes

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Abstract: The reaction in the system $Cu^{II}/sacNa(H)/NCNR_2$ (sacNa(H) = sodium saccharinate (saccharin); R = Me, Et) results in the formation of the complexes [Cu(sac)₂(NCNR₂)(H₂O)₂] (R = Me **1**, Et **2**) instead of the expected products derived from the saccharin–cyanamide coupling. Complexes **1**, **2**, and hydrate **1**·2H₂O were characterized by IR, AAS (Cu%), TGA, and also by single-crystal X-ray diffraction for **1** and **1**·2H₂O. An integrated computational study of model structure **1** in the gas phase demonstrates that the Cu–N_{cyanamide} and Cu–N_{sac} coordination bonds exhibited a single bond character, polarized toward the N atom and almost purely electrostatic, with the calculated vertical total energies for the Cu–N_{cyanamide} and Cu–N_{sac} of 43.6 and 156.4 kcal/mol, respectively. These data confirmed that the copper(II) completely blocks the nucleophilic centers of ligands via coordination, thus preventing the saccharin–cyanamide coupling.

Keywords: copper(II) complexes; saccharinate ligand; dialkylcyanamides; X-ray diffraction; computational study

1. Introduction

Saccharin (sacH), which is a common and widely used artificial sweetener [1], also finds application in diverse areas of chemistry, particularly being applied as a catalyst of a number of organic reactions (leading to, e.g., compounds of biological importance [2–5]) and a functional group protector [2,6]. SacH is also applied in the preparation of drugbased co-crystals exhibiting an improved solubility and bioavailability compared to the poorly soluble parent drugs [7].

Our recent finding in the saccharin chemistry was the observation of unusual metalfree "two saccharin–one cyanamide" coupling between sacH and NCNR₂ to grant guanidinated saccharin derivatives [8]. The distinctive feature of this transformation is its formal three-component character, while other known examples of reactivity of sacH toward multiple bond substrates includes the additions to amino alkynes [9,10], isocyanide [11], isocyanates [12], and carbodiimides [12,13]; all these examples include two-component 1:1 additions.

In light of the general interest in coordination chemistry of NCNR₂ ($R_2 = Alk_2$, Ar_2 , H/Alk, H/Ar, H/CN, etc.) and their metal-mediated and metal-catalyzed reactions (for our and other group reviews on metal-involving reactivity and coordination chemistry of cyanamides see [14–17], respectively), we now studied the reaction between sacH and NCNR₂ in the presence of a metal center, which as we assumed, should change its directionality. For these purposes, we addressed copper(II), as a kinetically labile metal center, which is commonly used in various catalytic reactions including coupling-based transformations. We observed that the introduction of copper(II) completely changed the directionality of the reaction by blocking the nucleophilic centers of both reactants



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Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). by the ligation to give $(sac)(NCNR_2)Cu^{II}$ species instead of the guanidinated saccharin derivatives.

2. Results and Discussion

2.1. Synthesis and Characterization

For the study of the Cu^{II}-involving reactions between cyanamides and saccharin, we addressed the copper salts CuCl₂·2H₂O or CuBr₂, *N*,*N*-disubstituted cyanamides NCNR₂ (R = Me, Et), and sacH or its sodium salt (sacNa). These reactions were performed in a neat NCNR₂ or NCNR₂/solvent mixture (solvent = H₂O, MeOH, EtOH) where the copper salts and saccharin(ate) are well soluble. In the systems, Cu^{II}/NCNR₂/SacNa, [Cu(sac)₂(NCNR₂)(H₂O)₂] (R = Me **1**, Et **2**) complexes were obtained and isolated as crystalline solids. The results previously reported for metal-free process "two saccharin–one cyanamide" addition products were neither isolated, nor identified by HRESI⁺-MS in the reaction mixtures, although peaks from the 1:1 addition product were detected in the HRESI⁺-MS spectra (see ESI, Supplementary Materials Figures S1 and S2). Furthermore, we optimized the synthesis conditions in order to increase the yield of complexes **1** and **2**.

Copper(II) saccharinate/dimethyl cyanamide complexes **1** and **1**·2H₂O (50–75%) were obtained by the dissolution of CuCl₂·2H₂O or CuBr₂ in NCNR₂ (R = Me, Et) at 60 °C followed by the addition of a solution of sacNa in MeOH, EtOH, or H₂O (Scheme 1). Notably, the choice of solvent affects the release of either hydrated, or anhydrous form of the complex. When the reaction proceeds in dried EtOH, complex **1** was obtained, while from undried MeOH, EtOH, or in H₂O, hydrate **1**·2H₂O was isolated. In this reaction, sacH can be used instead of sacNa, however, this treatment gives a lower yield of the product (up to 35% for **1**·2H₂O). The yield reduction can be explained by a lower reactivity of the protonated form (pK_a of sacH = 1.6 [18] in H₂O). The reason of the moderate yield of **1** and **1**·2H₂O is the formation of various unidentified by-products. IR monitoring of the filtrate from the reaction mixture verified broad bands at 1641s and 1620 m-s sh cm⁻¹ and band 2251 cm⁻¹ s, which were attributed to ν (C=O) from the saccharinate moiety of the 1:1 addition product, and Me₂NC(O)NH₂, and ν (CN)_{cyanamide} from the coordinated NCNMe₂, respectively.



Scheme 1. Generation of **1**, $1 \cdot 2H_2O(R = Me)$, and **2** (R = Et).

Upon the extension of the complexation to the other cyanamides NCNR₂ (R₂ = Et₂, C₄H₈, C₅H₁₀, C₄H₈O), we found that CuCl₂·2H₂O and CuBr₂ were almost insoluble in most of these cyanamides (R₂ = C₄H₈, C₅H₁₀, C₄H₈O). Therefore, we modified the reaction conditions, namely CuCl₂·2H₂O (or CuBr₂) was dissolved in THF and then a solution of both sacNa and NCNR₂ in MeOH (or EtOH) was added to a THF solution. Under these conditions, a lantern-like complex $[Cu_2(sac)_4(THF)_2]$ ·2THF (3·2THF) was obtained. When we attempted to replace THF in this reaction with another solvent (MeOH, EtOH, or MeCN), we obtained the complex $[Cu(sac)_2(H_2O)_4]$ ·2H₂O (from the system CuCl₂·2H₂O/NCNC₅H₁₀/sacNa). The structure of this known [19] complex $[Cu(sac)_2(H_2O)_4]$ ·2H₂O was confirmed by X-ray diffractometry (XRD; see ESI). In the case of NCNEt₂, in which CuCl₂·2H₂O and CuBr₂ demonstrated limited solubility, we suc-

ceeded in obtaining complex **2** under conditions similar to those applied for the synthesis of $1.2H_2O$.

Complexes 1, 1·2H₂O, and 3·2THF were characterized by IR, AAS (Cu%), and TGA methods and also by single-crystal X-ray diffraction. Complex 2 was characterized by IR and AAS (Cu%). The AAS (Cu%) data agree with the calculated values for the proposed formulas. In the IR spectra of 1, 1·2H₂O, and 2, the ν (C \equiv N) of the NCNR₂ ligand was observed in the range 2226–2245 cm⁻¹; these values are comparable with those observed for the homoleptic complexes [Cu(NCNR₂)₄](BF₄) (R = Me, Et; ca. 2240 cm⁻¹) [20] and the mixed-ligand copper(I) complexes [Cu(tpm)(NCNR₂)](BF₄) (R = Me, Et; ca. 2250 cm⁻¹) [21] and the clusters [Cu₄X₆O(NCNMe₂)₄] (2255–2261 cm⁻¹) [22]. In the IR spectra of all complexes, the two strong bands in the ranges 1306–1330 and 1165–1177 cm⁻¹ were attributed to ν_{sym} (SO₂) and ν_{asym} (SO₂) of the saccharinate ligands, respectively. We also attempted mass-spectrometric characterization of the obtained species, but the HRMS⁺ (ESI) spectra (in MeCN) did not display molecular ions for all complexes and only products of deep fragmentation of complexes (e.g., ions Cu(NCMe)₂⁺) were observed due to the lability of copper(II) complexes in a solution.

Complexes **1** and **2** are stable until ca. 70 °C and then decompose with the loss of the NCNR₂ ligand in the interval ca. 70–150 °C and two H₂O ligands at ca. 150–250 °C; after 250 °C, the residue undergoes decomposition of sac⁻ ligands forming yet unidentified species. Hydrate **1**·2H₂O somehow demonstrates greater stability and its decomposition starts at ca. 100 °C with loss of the crystallization water and the NCNMe₂ ligand at 100–150 °C; after 250 °C, the decomposition to yet unidentified species occurs. Complex **3**·2THF is stable until ca. 120 °C and then starts losing the solvated THF (125–260 °C), whereupon the coordinated THF (260–326 °C) is lost. After 326 °C, non-stochiometric decomposition of the sac⁻ ligands occurs.

2.2. X-ray Diffraction Studies

Single-crystal XRD studies were performed for 1, 1·2H₂O (Figure 1), and 3·2THF.



Figure 1. (a) Molecular structure of 1 with the atomic numbering. Thermal ellipsoids are given at the 50% probability level. (b) Molecular structure of $1.2H_2O$ with the atomic numbering. Thermal ellipsoids are given at the 50% probability level. The H_2O of hydration was omitted for clarity.

Complex 1 is crystallized in two forms, viz. anhydrous 1 (from dry EtOH) and dihydrate $1.2H_2O$, which was crystallized from H_2O . In both structures, the copper(II) centers are surrounded by two saccharinate, two water, and one dimethylcyanamide ligands, thus forming the complexes exhibiting a distorted square-pyramidal geometry, where the $NCNMe_2$ ligand occupies the apical position. The degree of the geometry distortion is greater for the dihydrate (geometry index [23] $\tau_5 = 0.16$ for 1 and 0.35 for $1.2H_2O$). Two saccharinate ligands are coordinated to the copper(II) center with different $\angle N$ -Cu-N angles (160.24(14)° for 1 and 174.65(15)° for 1·2H₂O), and for the $\{(H_2O)_2Cu\}$ moieties $\angle O$ -Cu-O are also different: 169.93(12)° for 1 and 153.39(19)° for 1.2H₂O. The Cu–N distances are 2.020(2) (1) and 2.011(3) Å (1.2H₂O), similar to those in some other known square-pyramidal (sac)₂Cu^{II} complexes (e.g., 1.997(4)–2.046(4) Å for [Cu(sac)₂(H₂O)(nicotinamide)]_n [24], [Cu(sac)₂(H₂O)(EtOH)(benzimidazole)] [25], and [Cu(sac)₂(H₂O)₂(2-methylpyrazine)]) [26]). The Cu–O separations exhibited values (1.963(3) and 1.971(3) for 1 and 1.995(4) and 1.971(4) Å for $1.2H_2O$ comparable with the Cu–O distances in similar (H₂O)(sac)₂Cu^{II} complexes (1.959(4)–2.3145(14) Å) [24–26]. The Cu– N_{cvanamide} bond lengths (2.152(3) Å in 1 and 2.158(4) Å in 1·2H₂O) were longer than the Cu-N_{cvanamide} bond lengths in the known copper(II) complexes featuring cyanamides, viz. the tetranuclear clusters $Cu_4Cl_6O(NCNR_2)_4$ (R = Me, [22] allyl [27]) and the solvates $Cu_4X_6O(NCNMe_2)_4 \cdot 4(arene)$ [22] (X = Cl, Br; arene = PhMe, PhCH=CH₂; 1.903(10)-1.952(6) Å) as a consequence of different geometry and composition of the complexes. The $C \equiv N$ and C–N bond lengths of the NCNMe₂ ligands (1.153(5) and 1.312(5) Å for 1 and 1.156(7) and 1.306(7) Å for $1.2H_2O$, respectively) was quite similar. In contrast, the structures of 1 and $1.2H_2O$ demonstrate $\angle Cu-N-C$ (171.6(3) and 146.8(5)°, respectively), which differently deviate from the linearity because of a noticeable contribution of the heterocumulene mesomeric form $N^{(-)}=C=N^{(+)}R_2$. The strong deviation from the linearity of the M–N–C fragment of the coordinated NCNR₂ was observed by us for iridium(III) [28], copper(I) [20], and zinc(II) [29] complexes featuring disubstituted cyanamides. This strong deviation from linearity of the M–N–C fragment distinguishes NCNR₂ ligands from NCR.

Various type hydrogen bonds were detected in the structures of **1** and $1.2H_2O$ (Figures 2 and 3). In **1**, eight-membered hydrogen bond-based cycle { $O_{carbonyl} \cdots H-O-H \cdots$ } $O_{carbonyl} \cdots H-O-H \cdots$ } is formed by three molecules of **1**. These cycles link the complexes into 1D-zigzag chains. The oxygen atoms of the SO₂ groups from weak hydrogen bonds with H-C_{arene} binding 1D-chains into a 3D-structure.



Figure 2. A fragment of crystal packing of 1 with the inter-ligand hydrogen bonds shown in dotted lines.



Figure 3. A fragment of crystal packing of $1.2H_2O$ with the interligand hydrogen bonds shown in dotted lines.

In the structure $1.2H_2O$, we identified several hydrogen bond-based patterns. One out of the two H_2O ligands forms two hydrogen bonds with two H_2O , which in turn form each hydrogen bond with the double bonded O atom of two sac⁻ ligands, and these two saccarinate ligands are connected by another coordinated H_2O . This 12-atom hydrogen bondbased cycle $\{O_{carbonyl}\cdots H-O-H\cdots O_{carbonyl}\cdots H-O(hydr)\cdots H-O-H\cdots O-H(hydr)\cdots\}$ links three molecules of 1 and two molecules of H_2O . In addition, metal-bound H_2O of each molecule is linked with the O=S moiety of the sac⁻ ligand.

Different systems of hydrogen bonding and types of molecular packing affect geometric parameters of complex 1 in the structures of 1 and $1.2H_2O$. Thus, 1 and $1.2H_2O$ differ by \angle Cu–N–C (171.6(3) and 146.8(5)°, respectively) and the degree of the square pyramidal geometry distortion.

On one hand, complexes 1 and $1.2H_2O$ represent the first examples of the structurally characterized mononuclear (NCNR₂)Cu^{II} species. Structures of cyanamide copper(II) complexes were previously represented by the clusters Cu₄Cl₆O(NCNR₂)₄ (R = Me, al-lyl) [22,27,30], and the solvates Cu₄X₆O(NCNMe₂)₄.4(arene) (X = Cl, Br; arene = PhMe, PhCH=CH₂) [22], and no single example of mononuclear (NCNR₂)Cu^{II} was known. For copper(I), there are several known structures of mononuclear complexes [Cu(NCNR₂)₄] (BF₄) [20], [Cu(tpm)(NCNR₂)](BF₄) (tpm = tris-(1,3-dimethylpyrazolyl)methane) [21], and [Cu(NCNMe₂)₂(DPEphos)](BF₄) (DPEphos = bis[2-diphenylphosphino)phenyl]-ether) [31], dinulear [Cu₂(μ_2 -Cl)₂(dppm)₂(NCNMe₂)]·2NCNMe₂, [Cu₂(μ_2 -Cl)(dppm)₂(NCNMe₂)](Cl), [Cu₂(μ_2 -X)(dppm)₂(NCNMe₂)₂](X) (X = ClO₄, NO₃), [Cu₂(dppm)₂(NCNMe₂)₃](BF₄) [32], and polymeric [CuX(NCNAllyl₂)] (X = Cl, Br, NO₃) species [33].

On the other hand, these complexes represent examples of the $(N-\operatorname{sac})_2\operatorname{Cu}^{II}$ -type complexes. Metal complexes of saccharin(ate) exhibit versatile coordination chemistry due to the existence of different coordination sites [34]. For copper(II), several types of complexes are reported, demonstrating monodentate *N*-, or *O*-coordination, and *N*,*O*-bidentate coordination modes of the sac⁻⁻ ligand [34]. The $(N-\operatorname{sac})_2\operatorname{Cu}^{II}$ moiety is rather typical for various saccharinate complexes. In relation to 1 and $1\cdot 2\operatorname{H}_2O$, the structures of pentacoordinate complexes should be emphasized (e.g., $[\operatorname{Cu}(\operatorname{sac})_2(\operatorname{H}_2O)_2(2-\operatorname{methylpyrazine})]$ [26], $[\operatorname{Cu}(\operatorname{sac})_2(\operatorname{H}_2O)(\operatorname{ethylnicotinate})_2]$ [35], $\operatorname{Cu}(\operatorname{sac})_2(\operatorname{H}_2O)(\operatorname{nicotinic}\operatorname{acid})_2$] [36], $[\operatorname{Cu}(\operatorname{sac})_2(\operatorname{H}_2O)(\operatorname{pyridazine})_2]$ [38], $[\operatorname{Cu}(\operatorname{sac})_2(\operatorname{H}_2O)(\operatorname{Py})_2]$ [39], etc). Notably, no complexes featuring the (sac)(NCR)Cu^{II} (R = Alk, Ar, NR₂) entity were reported prior to this study.

Complex 3·2THF features two THF per one $[Cu_2(THF)_2(sac)_4]$ (3) entity. Complex 3 exhibits a lantern-like structure, which is comprised by two copper(II) centers, four *N*,*O*-bridging saccharinate ligands, and two terminal THF ligands (Figure 4).



Figure 4. The molecular structure of **3**·2THF with the atomic numbering. Thermal ellipsoids are given at the 50% probability level. Solvated THF molecules were omitted for clarity.

The Cu–N (2.0246(14) and 2.0335(15) Å) and Cu–O distances (1.9567(12) and 1.9633(12) Å) for the saccharinate ligands are comparable with those of the corresponding Cu-N(2.0243(14) and 2.0329(15) Å) and Cu-O (1.9562(12) and 1.9624(12) Å) bond values in the closely related lantern-like copper(II) species bearing N,O-bridging ligands, namely $[Cu_2(Me_2NCHO)_2(C_7H_5NS)_4]$ ·2(Me_2NCHO) (C_7H_5NS-1,2-benzothiazol-3-ato) [40]. The latter complex exhibits the trans-N,O-configuration of the benzothiazolato ligands around the copper(II) center, while complex **3** exhibited the *trans-N,N/trans-O,O* geometry, thus preventing the repulsion of the SO₂ groups and the THF ligand. In 3.2THF, the Cu–Cu distance (2.7519(5) Å) was slightly longer than those in Cu₂(Me₂NCHO)₂(1,2-benzothiazol-3-ato)]·2(Me₂NCHO) (2.6816(10) Å). The Cu–O_{THF} bond lengths (2.1089(17) and 2.1023(18) Å) were in the typical Cu^{ll}–O bond range [41]. The bond length and angles for the saccharinate ligand were similar to those reported for the $[Cr_2L_2(\mu-sac)_4]$ complexes (L = THF, Py) [42,43]. In addition, 3.2THF represents a rare reported example of saccarinate-based lantern-like complexes with a core $\{M_2(Sac)_4\}$. No significant H-bonding was detected in the structures of the complexes, while weak π - π interactions between aryl···aryl rings were identified.

2.3. Theoretical Calculations

In order to obtain additional indirect evidence supporting the blocking role of the copper(II) in the saccharine/cyanamide coupling, we studied the nature of Cu-N_{cyanamide} and Cu-N_{sac} coordination bonds in 1 and carried out an integrated computational study including the full geometry optimization of the model of structure 1 in the gas phase using the appropriate experimental XRD structure as a starting point, the topological analysis of the electron density distribution (QTAIM) [44], the natural bond orbital and charge decomposition analyses (NBO [45] and CDA [46]), and calculation of the vertical total energies for the Cu-N_{cvanamide} and Cu-N_{sac} coordination bond dissociations (see ESI for all details). This approach has already been successfully used by us upon studies of bonding properties in various similar transition metal complexes [20,47–50]. The results of our computational study revealed that (i) crystal-packing strongly affects the structural characteristics of 1 in the solid state; (ii) the dialkylcyanamide copper(II) complexes featuring noticeable contribution of the heterocumulene mesomeric form; (iii) Cu-N_{cvanamide} and Cu-N_{sac} coordination bonds in 1 exhibit a single bond character, clearly polarized toward the N atom and almost purely electrostatic; (iv) the $\{M\} \leftarrow L \sigma$ -donation substantially prevails over the {M} \rightarrow L π -back-donation in both Cu–N_{cyanamide} and Cu–N_{sac} coordination bonds in 1; (v) the calculated vertical total energies (E_v) for the Cu–N_{cyanamide} and Cu–N_{sac} coordination bond dissociation in optimized equilibrium model structure 1 were 43.6 and 156.4 kcal/mol, respectively. Overall, one can conclude that the nature of Cu-N coordination bonds in **1** is similar, but the saccharinate is a stronger ligand toward the copper(II) center than the cyanamide.

3. Materials and Methods

All solvents and reactants were obtained from commercial sources and used as received. Sodium saccarinate was obtained according to the published method [51]. Atomic absorption spectrometry (AAS) was carried out on a Shimadzu AA-7000 spectrometer (Shimadzu, Japan) (spectral range 189–900 nm) using the flame emission spectroscopy method. Standard Cu samples for the calibration solutions were prepared by MERCK standard (Merck KGaA, Darmstadt, Germany) in 0.1 *M* HNO₃; calibration solutions were 0.01–100.0 mg/L. Spectral analysis of the sample solutions was carried out with 100-fold dilution. Infrared spectra (4000–400 cm⁻¹) were recorded using a Bruker FTIR TENSOR 27 (Bruker, Germany) instrument in Nujol. The thermogravimetry/differential thermal analysis was performed with a NETZSCH TG 209 F1 Libra thermoanalyzer (NETZSCH Group, Selb, Germany) and MnO₂ powder was used as the standard. The initial weights of the samples were in the range 1.1–1.8 mg. The experiments were run in an open aluminum crucible in a stream of argon at a heating rate of 10 K/min. The final temperature was 530 °C. Processing of the thermal data was performed with Proteus analysis software [52].

3.1. Synthetic Work

Synthesis of $[Cu(sac)_2(NCNR_2)(H_2O)_2]$ (1, 1·2H₂O, 2). CuCl₂·2H₂O or CuBr₂ (0.25 mmol) was dissolved in 5-fold excess of NCNR₂ (R₂ = Me₂ 1, Et₂ 2; 0.10 mL, 1.3 mmol) at room temperature (RT), whereupon a solution of sodium saccharinate (0.25 mmol) in certain solvents (2 mL, dried EtOH for 1, MeOH, EtOH, or H₂O for 1·2H₂O and MeOH or EtOH for 2) was added. The resulting mixture was left to stand for 3–5 days at RT without stirring and the bright greenish-blue prismatic crystals were precipitated. These crystals were filtered off, washed by methanol, and dried in air at RT. One- or two-fold reprecipitation from the mother liquid allowed the increased yield of 1·2H₂O (75%). The total isolated yields were 50–75%. Alternatively, 1·2H₂O was obtained from a CuX₂/saccharin mixture with excess NCNMe₂ and without solvents by keeping for 1 h at 60 °C and then at RT for 2–3 days, however, the reaction proceeds in lower yields (15–35%). A few crystals of pure 1–2 were mechanistically separated from the reaction mixture and yields were not calculated.

1. Cu-% (AAS) for $C_{17}H_{18}N_4CuO_8S_2$ found (calcd.) = 11.4% (11.8%). IR in Nujol (selected bands, cm⁻¹): 3331 m-s br v(O–H), 2261 m v(C=N), 1646, 1618, and 1587 m v(C=O) and δ (O–H), 1313 m-s v_{sym}(S=O), 1170 m v_{asym}(S=O).

 $1.2H_2O.$ Cu-% (AAS) for $C_{17}H_{22}N_4CuO_{10}S_2$ found (calcd.) = 10.7% (11.1%). IR in Nujol (selected bands, cm⁻¹) 3334 m-s br v(O–H), 2226 m v(C \equiv N), 1646, 1618, and 1566 m v(C=O) and δ (O–H), 1313 m-s ν _{sym}(S=O), 1170 m ν _{asym}(S=O).

2. Cu-% (AAS) for C₂₁H₂₂N₄CuO₈S₂ found (calcd.) = 10.9% (11.3%). IR in Nujol (selected bands, cm⁻¹) 3330 m-s br v(O–H), 2245 m v(C \equiv N), 1628 s br and 1584 m v(C=O) and δ (O–H), 1309 m-s v_{sym}(S=O), 1168 m-s v_{asym}(S=O).

Synthesis of $[Cu_2(sac)_4(THF)_2]$ ·2THF (3·2THF). CuCl₂·2H₂O or CuBr₂ (0.25 mmol) were dissolved in THF (2 mL) at RT, whereupon a solution of sodium saccarinate (0.25 mmol) and NCNR₂ (100 mkL, 1.3 mmol, R₂ = C₄H₈, C₅H₁₀, C₄H₈O) in MeOH or EtOH (2 mL in each case) was added. The resulting mixture was left to stand for five days at RT without stirring until the bright greenish-blue prismatic crystals were released. The crystals were washed by THF (1–2 mL) and dried in air at RT. The isolated yields were 40–50%.

3.2THF. Cu-% (AAS) for C₄₄H₄₈N₄Cu₂S₄O₁₆ found (calcd.) = 11.3% (11.1%). IR in Nujol (selected bands, cm⁻¹): 1640 m and 1568 m-s cm⁻¹ ν (N–C=O in sac⁻), 1330 m-s ν_{sym} (S=O), 1177 m ν_{asym} (S=O).

3.2. X-ray Structure Determinations

X-ray diffraction studies were performed at 100 K on Rigaku XtaLAB Synergy-S diffractometer (Rigaku Oxford Diffraction) (HyPix-6000HE type detector) in the case of 1·2H₂O, 3·2THF, and [Cu(sac)₂(H₂O)₄]·2H₂O and Rigaku XtaLAB SuperNova diffractometer (Agilent Technologies (Oxford Diffraction), Yarnton, Oxfordshire, UK) (HyPix-3000

type detector) in the case of **1** using Cu K α (λ = 1.54184 Å) radiation. The structures were solved with the ShelXT [53] structure solution program using Intrinsic Phasing for **1**, **1**·2H₂O, and **3**·2THF, and the Superflip [54] structure solution program using Charge Flipping for [Cu(sac)₂(H₂O)₄]·2H₂O and refined with the ShelXL [55] refinement package incorporated in the OLEX2 program package [56] using least squares minimization. Empirical absorption correction was applied in the CrysAlisPro 1.171.40.67a (Rigaku Oxford Diffraction, 2019) (for **1** and **1**·2H₂O) and 1.171.40.71a (Rigaku Oxford Diffraction, 2020) (for **3**·2THF and [Cu(sac)₂(H₂O)₄]·2H₂O)) [57] program complex using spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm. The crystallographic data and structure refinement parameters are given in Table S1. All structures have been deposited at Cambridge Crystallographic Data Center (CCDC numbers 2062446 (**1**), 2062447 (**1**·2H₂O), 2062448 (**3**·2THF), 2062451 ([Cu(sac)₂(H₂O)₄]·2H₂O)) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. (Accessed on 07 September 2021)

3.3. Computational Details

The full geometry optimization of model structure **1** was carried out at the DFT level of theory using the M06 functional [58] with the help of the Gaussian-09 program package [59]. No symmetry restrictions were applied during the geometry optimization procedure and appropriate experimental X-ray structure **1** was used as a starting point. The calculations were carried out using the multi electron fit fully relativistic energy-consistent pseudopotential MDF10 of the Stuttgart/Cologne group that described 10 core electrons and the appropriate contracted basis set for the copper atom [60]) and the 6-31G(d) basis sets for other atoms. The Hessian matrix was calculated analytically for the optimized model structure **1** in order to prove the location of correct minima on the potential energy surface (no imaginary frequencies). The topological analysis of the electron density distribution with the help of the "atoms in molecules" method developed by Bader (QTAIM) [44] and charge decomposition analysis developed by Dapprich and Frenking (CDA) [46] were carried out by using the Multiwfn program (version 3.7) [61]. The Cartesian atomic coordinates for optimized equilibrium model structure **1** are presented in Table S2, ESI, and as the attached xyz-file.

4. Conclusions

In this study, we demonstrate that in the system Cu^{II}/SacNa(H)/NCNR₂, copper(II) forms complexes with saccharinate and disubstituted cyanamides. The directionality of the reaction is completely different from that observed for the metal-free reaction between saccharin and NCNR₂; the latter results in the formation of guanidinated saccharins [8].

We succeeded in the isolation and characterization of the $[Cu(sac)_2(NCNR_2)(H_2O)_2]$ (R = Me, Et) complexes, which represent the first example of structurally characterized mononuclear (cyanamide)Cu^{II} species. The experimental X-ray structure of 1 was used as a starting point for an integrated computational study of model structure 1 in the gas phase. As can be inferred from inspection of the obtained theoretical data, Cu–N_{cyanamide} and Cu–N_{sac} coordination bonds in 1 exhibited a single bond character, clearly polarized toward the N atom and predominately electrostatic, but the saccharinate was a better ligand toward the copper(II) center than the cyanamide (the calculated vertical total energies for the Cu–N_{cyanamide} and Cu–N_{sac} were 43.6 and 156.4 kcal/mol, respectively). All these data confirmed the role of the copper(II) in the change of the directionality of the reaction between saccharin and NCNR₂. The copper(II) completely blocks the nucleophilic centers of ligands via coordination, thus preventing the saccharin–cyanamide coupling.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/inorganics9090069/s1, crystal data and structure refinement, experimental spectra, and TG/dTG curves, other experimental data, and cartesian atomic coordinates. The CIF and the checkCIF output files.

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