Inorg. Chem. **2004**, *43*, 4663–4673

The Activation of Tertiary Carboxamides in Metal Complexes: An Experimental and Theoretical Study on the Methanolysis of Acylated Bispicolylamine Copper(II) Complexes

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Received March 12, 2004

It is a well-established concept that the C–N bond cleavage of carboxamide functions is facilitated by the coordination of a metal ion to the carbonyl oxygen atom. In contrast, the alternative C–N bond activation by coordination of a neutral tertiary carboxamide nitrogen atom has not been studied. We present the first results on the effect of nitrogen pyramidalization in N-coordinated metal complexes on the methanolysis of tertiary carboxamide groups. An analysis of the reactions products obtained from the methanol cleavage of $[(N\text{-Acyl-bpa})Cu]^{2+}$ (bpa = *N*,*N*-bispicolylamine) complexes is presented together with experimental and high-level theoretically calculated structures. The strong effect of different anions on the amide pyramidalization and subsequent C–N-bond cleavage is evaluated. We show that dichloro complexes $[(N\text{-Acyl-bpa})CuCl_2]$ have much less activated amide groups than the corresponding triflate species. They should therefore be less reactive. However, $[(N\text{-Acyl-bpa})CuCl_2]$ complexes dissociate in solution to give cationic monochloro complexes $[(N\text{-Acyl-bpa})Cu(S)Cl]^+$ (S = solvent molecule). Theoretical calculations show that the amide pyramidalization in the monochloro complexes is equal to that in the corresponding $CF_3SO_3^-$ salts. Consequently, chloro and triflato complexes are cleaved with similar rates and efficiencies. Parallels to and differences in the reactivity of purely organic distorted amides are discussed.

Introduction

The metal-induced cleavage of carboxamides is a well-established reaction. Its importance in hydrolytic enzymes[1] inspired sophisticated biomimetic applications such as the site-selective cleavage of peptides by synthetic palladium complexes.[2] In all well understood cases, the amide bond is activated by coordination of the amide carbonyl oxygen atom to the metal center. However, the coordination of an electrically neutral nitrogen atom in metal complexes of tertiary carboxamides is an alternative that has gained little attention. This mode of coordination should result in sp^3 hybridization at the N-atom and concomitant weakening of the amide-resonance stabilization, which should lead to a weakening of the C−N bond. This mechanism has been proposed[3] but until now there has been no way to study it, even though a comparison with the well-known oxygen activation would be of fundamental interest for a better understanding of carboxamide coordination chemistry. The lack of information has a simple reason. For a long time N-coordinated tertiary carboxamides could only be found in the literature as hypothetical intermediates needed to rationalize the metal-mediated cleavage of strained amides such as penicillins,[3] or enhanced *cis*−*trans*-isomerization rates about the C−N bond in the presence of metal ions such as Ag^+.[4] These suggestions were controversial since other

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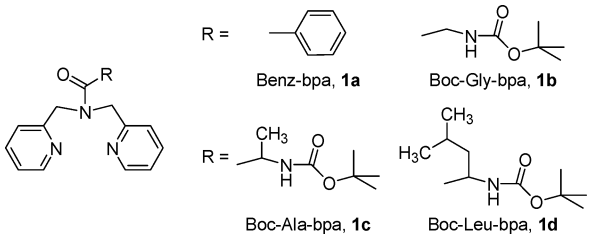
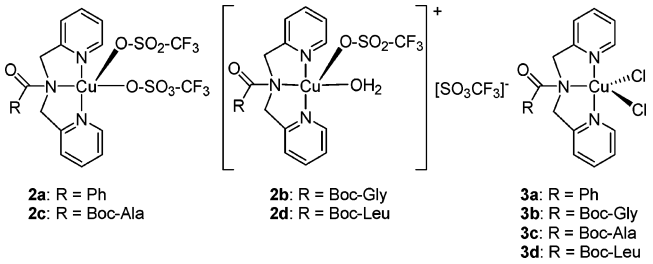
10.1021/ic0496774 CCC: $27.50
Published on Web 07/01/2004

Scheme 1. Structures of Ligands **1a**−**d**



Scheme 2. Structures of Copper(II) Complexes **2a**−**d** and **3a**−**d**



authors categorically ruled out the possible coordination of a nondeprotonated amide nitrogen atom because of the more favorable binding mode to the more basic carbonyl oxygen.[5] More than 30 years ago, Houghton and Puttner[6] studied the methanolysis of *N*,*N*-bispicolylamide derivatives in the presence of $CuCl_2$. The idea was to use the thermodynamically stable bispicolylamine (bpa) copper(II) complexes as leaving groups in acylation reactions.[7] However, neither the nature of the actual reactive species nor the structures of the products were reported. Only in 1996 Lectka et al. were able to crystallize the benzoyl substituted derivative [(Benz-bpa)-$CuCl_2$], which provided the first example of an N-bound tertiary carboxamide in a Werner-type complex.[8] Over the last three years, we have synthesized and characterized a larger number of these unusual compounds and shown that they contain pyramidal amide groups that are significantly to strongly activated.[9] This allows us to study the detailed mechanism of nucleophilic amide cleavage reactions for the first time. In particular, it was not possible to explain why $CuCl_2$ and $Cu(CF_3SO_3)_2$ are similarly well suited to promote the C−N bond methanolysis in acylated bpa derivatives based solely on our structural data. Complexes of the latter have much more strongly activated amide groups. We have therefore combined an experimental evaluation of the structures of these complexes and their products with kinetic data and the first theoretical calculations designed to determine the relevant species during the $CuCl_2$ and $Cu(CF_3SO_3)_2$ mediated cleavages of acylated bpa derivatives.

Results and Discussion

Synthesis and Reactivity Studies. Scheme 1 shows the ligands Benz-bpa (**1a**),[8,9] Boc-Gly-bpa (**1b**), Boc-Ala-bpa (**1c**),[9] and Boc-Leu-bpa (**1d**) which were synthesized from bispicolylamine and the appropriate carboxylic acid according to the DCC/HOBt coupling method (DCC, dicyclohexylcabodiimide; HOBt, *N*-hydroxybenzotriazole).[10]

Copper complexes of **1a**−**d** are readily obtained by reaction of the appropriate ligand with $Cu(CF_3SO_3)_2$ or $CuCl_2 \cdot 2H_2O$ in acetonitrile. Scheme 2 illustrates the resulting compounds. The analytically pure triflate salts **2a**−**d** precipitated from dichloromethane−ether solvent mixtures. C,H,N-elemental analysis data indicate that samples of [(Benz-bpa)$Cu(CF_3SO_3)_2$] (**2a**) and [(Boc-Ala-bpa)-$Cu(CF_3SO_3)_2$] (**2c**) do not always contain a coordinated water molecule.[9] In analogy to a $Cu(NO_3)_2$ complex of bpa,[11] as well as a $Cu(CF_3SO_3)_2$ complex of a diethylenetriamine derivative,[12] we assume square-pyramidal structures with two coordinated triflate anions, one in an axial position and one in an equatorial position. This is analogous to the square-pyramidal amino acid derivatives **2b** and **2d** which have an equatorial aqua and an axial triflato ligand. A crystal structure was obtained for the glycine derivative **2b**. The similarity of **2d** is indicated by spectroscopic and analytical data.

The $CuCl_2$ complexes **3a**−**d** were synthesized and stored in the dark since prolonged exposure to light resulted in decomposition, presumably due to the formation of chlorocuprate salts as was indicated by elemental analysis data of the yellow-orange products. It is shown below that chlorocuprate(II) ions are easily formed in the investigated system. We have also observed a similar behavior in related complexes.[13] All compounds precipitate from the reaction mixtures upon standing. We have crystallized and solved the structure of **3c**. The structure of **3a** was determined by Lectka et al.[8] Crystals were also obtained for the leucine derivative **3d**, but the X-ray diffraction data were not of publishable quality yet nevertheless confirmed a structure similar to **3a** and **3c**.

All the copper complexes readily undergo methanolysis of their C−N-bonds to yield the methyl ester of the acyl substituent and complexes of the $[(bpa)Cu]^{2+}$ fragment. We have studied four selected reactions on a preparative scale quantitatively. They are summarized in Scheme 3.

The ligand Boc-Ala-bpa (**1c**) was reacted with $Cu(CF_3SO_3)_2$ in pure methanol to give the bpa complex $[(bpa)Cu(H_2O)][CF_3SO_3]_2$ (**4**) and Boc-Ala-OMe. Although we were not able to crystallize **4**, spectroscopic and analytical data indicate that its structure is similar to that of the Jahn−Teller distorted octahedral perchlorate derivative $[(bpa)Cu(CH_3OH)][ClO_4]_2$.[9] The two compounds have similar ESR parameters (120 K;

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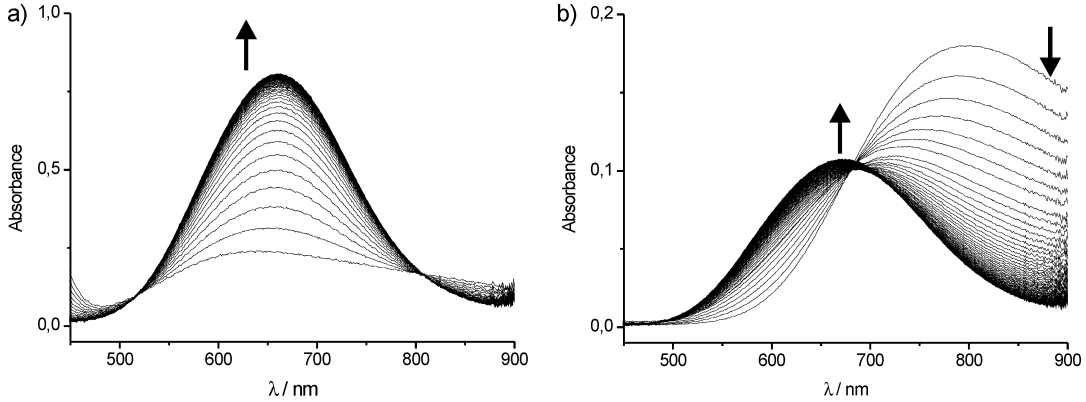
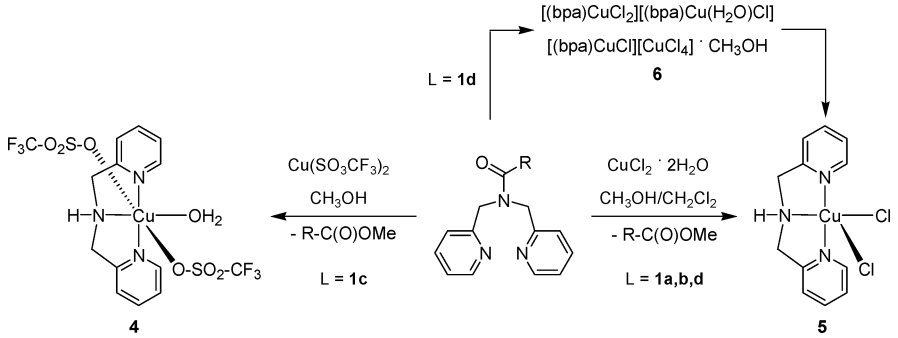


Figure 1. (a) UV−vis spectra obtained during the methanolysis of **2a** (10^{-2} M in methanol); (b) UV−vis spectra obtained during the methanolysis of **3a** (10^{-3} M in CH_3OH/CH_2Cl_2 4:1).

Scheme 3. Preparative Studies on Amide Methanolysis Reactions



4, $g_{||} = 2.26$, $A_{||} = 187 \times 10^{-4}$ cm^{-1}, $g_{\perp} = 2.07$; ClO_4^- salt, $g_{||} = 2.26$, $A_{||} = 186 \times 10^{-4}$ cm^{-1}, $g_{\perp} = 2.07$) and d−d-absorption bands (**4**, $\lambda_{max} = 661$ nm, $\epsilon = 88$ M^{-1} cm^{-1}; ClO_4^- salt, $\lambda_{max} = 660$ nm, $\epsilon = 89$ M^{-1} cm^{-1}) in methanol.

More interesting and revealing are the products formed upon cleavage of the chloro complexes. Mixing the ligands **1a**, **1b**, or **1d** with $CuCl_2 \cdot 2H_2O$ in methanol resulted in the immediate precipitation of the corresponding complexes **3a**, **3b**, and **3d**. In the case of **1d**, it was possible to dissolve the complex by addition of methanol. The reaction of **1d** in pure methanol provided the best conditions for a quantitative preparation of [(bpa)$CuCl_2$] (**5**). Crystals of **5** were obtained, and the structure is described below. The alanine derivative **1c** also gave **5** from pure methanol solutions. In the case of **1a**, **1b**, and **1d**, the complexes dissolved upon addition of an equal volume of CH_2Cl_2 to methanol suspensions and were subsequently cleaved. Prolonged standing of the solutions always produced the dark blue complex [(bpa)-$CuCl_2$] (**5**). However, upon ether diffusion into the reaction mixtures we were able to isolate a green byproduct together with small amounts of the starting material and **5** after a few hours. An X-ray structural analysis of this material revealed the composition {[(bpa)$CuCl_2$][(bpa)Cu(H_2O)Cl]-[Cu(bpa)Cl][$CuCl_4$]·CH_3OH} (**6**). This was confirmed by C,H,N-elemental analysis data and density measurements on single crystals. The result is important because it provides evidence for the formation of free copper(II)−chloro species and monocationic $LCuCl^+$ complexes in the course of the reactions.

In order to compare the different reactivities of the copper complexes, the methanolysis of **2a**−**d** and **3a**−**d** was followed by UV−vis spectroscopy. Starting materials in these studies were the analytically pure isolated complexes. Addition of 180 μL of aqueous phosphate buffer (pH 7; 0.1 M) to 100 mL of the reaction mixtures assured comparable water contents and the scavenging of potentially catalytic trace amounts acid or base. Under these conditions, all results were perfectly reproducible. The triflate salts were studied in methanol solutions (10^{-2} M Cu^{2+}) whereas 4:1 methanol/dichloromethane mixtures were used in the case of the chloro complexes (10^{-3} M Cu^{2+}) because of their low solubility in CH_3OH. Figure 1 shows two typical experiments. Although the data of **2a** seem to show two perfect isosbestic points, we were not able to fit the kinetic traces to a rate law. Preliminary ESR data indicate that this is most probably due to partial dissociation and other dynamic processes of the complex. However, it is evident that the chloro complexes and the triflate salts are both cleaved within ca. 8 h. This is surprising since the structural data discussed below clearly indicate that the dichloro species should have much less activated amide groups than their triflate analogues. On the basis of the structure of **6**, we reasoned that monochloro complexes could be the actual reactive species. We have therefore performed a theoretical study to confirm that the amide group in $[(Ac\text{-}bpa)CuCl]^+$ is significantly more distorted than in the dichloro complex.

X-ray Structural Analyses

[(Boc-Gly-bpa)Cu(H_2O)(CF_3SO_3)](CF_3SO_3) (2b). The structure of the complex **2b** is shown in Figure 2. It consists of the distorted square-pyramidal cation [(Boc-Gly-bpa)Cu-(H_2O)(CF_3SO_3)]$^+$ and a loosely bound triflate ion (*d*(Cu−

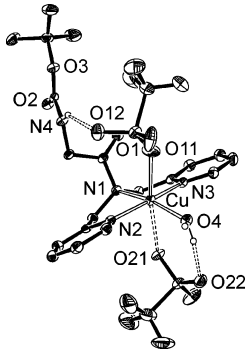


Figure 2. ORTEP plot (30% ellipsoids) of the R_P enantiomer of **2b**. Selected bond lengths and angles are listed in Table 1.

Table 1. Selected Bond Lengths (Å) and Angles (deg) of the Tertiary Amide Complexes **2b and 3c**,[a] and the Calculated Structures [(Ac-bpa)$CuCl_2$] and [(Ac-bpa)$CuCl(CH_3OH)$]$^+$

	2b·CH_2Cl_2	**3c**·0.5H_2O·CH_2Cl_2 (S,R_P)	**3c**·0.5H_2O·CH_2Cl_2 (S,S_P)	[(Ac-bpa)-$CuCl_2$]	[(Ac-bpa)Cu-$Cl(CH_3OH)$]$^+$
Cu−N1	2.164(3)	2.460(7)	2.437(6)	2.627	2.222
Cu−N2	1.952(3)	1.991(7)	1.960(7)	2.058	2.018
Cu−N3	1.948(3)	1.982(7)	1.968(7)	2.074	2.045
Cu−O4	2.027(2)				
Cu−Cl1		2.227(2)	2.227(2)	2.286	2.239
Cu−Cl2		2.269(2)	2.269(2)	2.262	
Cu−O11	2.209(3)			2.363	
Cu−O21	2.623(3)				
N1−Cu−N2	82.8(2)	78.5(3)	78.0(2)	74.98	81.12
N1−Cu−N3	83.5(2)	78.5(2)	78.9(3)	75.87	81.13
N1−Cu−O4	165.4(2)				
N1−Cu−Cl1		119.9(2)	120.1(2)	91.57	169.66
N1−Cu−Cl2		103.7(2)	101.9(2)	116.18	
N1−Cu−O11	101.8(2)			91.93	
N2−Cu−N3	165.2(2)	157.0(3)	156.9(3)	150.39	162.21
N2−Cu−O4	98.1(2)				
N2−Cu−Cl1		95.2(2)	96.2(2)	94.20	99.15
N2−Cu−Cl2		93.4(2)	92.7(2)	95.40	
N2−Cu−O11	99.4(2)			94.55	
N3−Cu−O4	93.8(2)				
N3−Cu−Cl1		96.0(2)	96.0(2)	91.70	98.10
N3−Cu−Cl2		92.2(2)	92.2(2)	92.74	
N3−Cu−O11	89.0(2)			87.22	
O4−Cu−O11	92.5(2)				
O11−Cu−O21	172.2(2)				
Cl1−Cu−Cl2		136.5(1)	138.0(1)	152.14	
Cl1−Cu−O11				98.34	
N4···O12	2.925(4)				
O4···O22	2.756(4)				

[a] Standard deviations in parentheses.

O34) = 2.62 Å). A chirality plane is defined by the amide RC(O)−NR_2 group, and the crystals are racemic with an equal distribution of the R_P and S_P enantiomers. Most important is the coordination of the tertiary amide nitrogen atom N1 at a distance of 2.16 Å to the copper(II) center. This is only ca. 0.10−0.15 Å longer than the typical copper to secondary amine contacts in common bpa derivatives[14,15] but more than 0.3 Å shorter than the corresponding distances in **3a**[8] and **3c** (see below). However, the tertiary amide function is a weak donor, and this results in a rather unusual feature. The apical triflate anion is only 2.21 Å (Cu−O31) away from the coordination center. Distances of more than 2.4 Å are common in typical Jahn−Teller distorted octahedral complexes, and only a few examples are known where d(Cu−O) is between 2.3 and 2.4 Å.[16] Shorter Cu−O(triflate) distances than in **2b** have only been reported for trigonal-bipyramidal[17] and tetrahedral[18] complexes, or in compounds were a triflato ligand is located in an equatorial position of a square-pyramid. The latter case has been observed by Holm et al. in a diethylenetriamine complex.[12] Interestingly, the authors find an axial Cu−triflate bond of 2.21 Å, similar to that in **2b**. Thus, the poor equatorial electron donation from the N-bound amide function in **2b**, or from the triflate ion in Holm's complex, is compensated by an unusually strong axial copper to triflate bond.

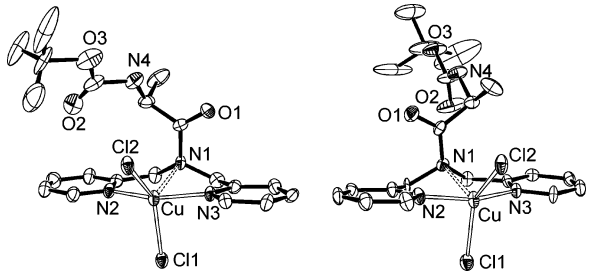


Figure 3. ORTEP plots (30% ellipsoids) of the structures of (S,R_P)-**3c** (left) and (S,S_P)-**3c** (right). Selected bond lengths and angles are listed in Table 1.

[(Boc-Ala-bpa)$CuCl_2$] (3c). Compound **3c** crystallizes in the noncentrosymmetric space group $P2_1$ with 4 independent molecules per asymmetric unit. Their relevant geometric parameters are very similar with one exception. The chiral amino acid moiety in combination with the chirality plane defined by the amide group gives rise to the formation of diastereomers. Three molecules are in the (S,S_P) conformation whereas one is in the (S,R_P) form. Both isomers are shown in Figure 3, and bond parameters are given for both forms. A comparison of the structure of **3c** with those of the closely related complexes **3a**, which were reported by Lectka et al.,[8] and the preliminary data obtained for **3d** confirm that all dichloro complexes are very similar. Their characteristic features are two almost equal Cu−Cl distances, as well as weak copper−amide bonds ca. 0.3 Å longer than in **2b** and ca. 0.5 Å longer than the copper to secondary amine bond in common bpa complexes. The following discussion therefore applies to all known derivatives. However, it is interesting to note that the leucine derivative **3d** crystallizes exclusively in the (S,S_P) conformation.

The geometry of the first coordination sphere of **3c** is interesting. At first sight, the overall geometry may be

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classified as distorted trigonal-bipyramidal with the two pyridine donor ligands in the axial positions. However, the Cu−N(amide) distance (2.46 Å/*S*,*S*$_P$; 2.44 Å/*S*,*R*$_P$) is longer than the sum of the van der Waals radius of nitrogen (1.6 Å) and the ionic radius of 5-coordinate Cu^{2+} (0.79 Å).[19] Furthermore, the Cu−N(amide) distance is ca. 0.2 Å longer than the longest Cu−Cl contact (2.27 Å). It is therefore more appropriate to describe the structure as monocapped distorted tetrahedral. Only weak electrostatic interactions are active between the amide nitrogen atom and the metal ion. This interpretation is further supported by the theoretical results described below. It is also consistent with the 2 Cu−Cl distances in **3c**, which differ by only ca. 0.04 Å (2.23 Å/2.27 Å). The similar Cu−Cl bond lengths and the long Cu−N distance are in marked contrast to observations in most of the known $CuCl_2$ complexes with substituted bpa ligands.[14,15,20,21] These compounds usually have an idealized basal plane defined by the shortest Cu−ligand contacts and formed by only one chloro ligand and three bpa nitrogen atoms. The remaining second Cu−Cl contact is the longest metal−ligand bond. Depending on their trigonality index[22] the geometries can be characterized as square-pyramidal ($\tau < 0.2$, Δ(Cu−Cl) = 0.21−0.46 Å) or trigonally distorted square-pyramidal ($\tau > 0.2$, Δ(Cu−Cl) = 0.07−0.26 Å). The only exception is a N-pyridine substituted complex in which Δ(Cu−Cl) = 0.07 Å and the Cu−N(amine) bond is 0.013 longer than the longest Cu−Cl bond.[23] However, this difference is much smaller than in the tertiary amide complexes, putting the compound closer to the common bpa derivatives.

[(bpa)CuCl$_2$] (5). The methanol cleavage of **3a**−**d** finally resulted in the formation of complex **5**. This compound has been known for quite some time, and considering the widespread application of bpa derivatives in copper(II) coordination chemistry, it is somewhat surprising that its structure has only been reported in December 2003.[24] The literature data show some interesting differences from our results which are most probably due to the crystallization conditions. We have obtained crystals from methanol whereas Choi et al. have used a water/acetonitrile mixture. An ORTEP plot of our structure is shown in Figure 4. The compound is square-pyramidal with an equatorial *d*(Cu−Cl) of 2.23 Å, and a typical elongated axial *d*(Cu−Cl) of 2.64 Å. A trigonality index τ of 0.05 is calculated, close to the ideal value of 0 for square-pyramidal complexes.[22] Choi et al. have reported a slightly more trigonally distorted structure with τ = 0.12 and correspondingly different Cu−Cl distances of 2.25 and 2.41 Å. Particularly notable is the large effect of the slight trigonal distortion on the axial bond which differs by more than 0.2 Å in the two structures. Almost ideally square-pyramidal geometries were also found in other $CuCl_2$ complexes of bpa-derived ligands.[20,21b] However, structures with trigonally distorted coordination spheres (τ_{sqp} = 0; τ_{tbpy} = 1; $\tau_{observed}$ = 0.18−0.66) are also commonly observed.[14,15,21] The relevant geometric parameters of the $[(bpa)Cu]^{2+}$ fragment in **5** are in good agreement with those in the structurally related complex $[(bpa)Cu(CH_3OH)](ClO_4)_2$.[9a]

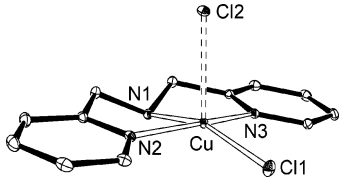

Figure 4. ORTEP plot (30% ellipsoids) of the structure of **5**. Selected bond lengths (Å) and angles are listed in Table 2.

Table 2. Selected Bond Lengths (Å) and Angles (deg) of the bpa Complexes **5** and **6**[a]

		6·CH_3OH		
	5	A	B	C
Cu−N1	2.007(2)	1.994(8)	1.996(5)	1.987(5)
Cu−N2	2.013(2)	1.996(5)	1.989(5)	2.007(4)
Cu−N3	2.022(2)	1.996(5)	1.989(5)	2.007(4)
Cu−Cl1	2.233(1)	2.266(2)	2.27(2)	2.219(2)
Cu−Cl1a			2.32(2)	
Cu−Cl2	2.609(1)	2.658(2)		
Cu−O11			2.507(7)	
N1−Cu−N2	81.4(1)	82.4(2)	83.2(2)	81.9(2)
N1−Cu−N3	81.7(5)	82.4(2)	83.2(2)	81.9(2)
N1−Cu−Cl1	159.6(1)	167.4(5)	166.3(5)	179.0(2)
N1−Cu−Cl1a			170.5(7)	
N1−Cu−Cl2	93.4(1)	88.4(1)		
N1−Cu−O11			80.8(2)	
N2−Cu−N3	162.8(1)	164.4(3)	165.3(3)	163.3(2)
N2−Cu−Cl1	97.5(1)	97.1(2)	108.9 (3)	98.2(2)
N2−Cu−Cl1a			106.1(3)	
N2−Cu−Cl2	90.9(1)	91.4(2)		
N2−Cu−O11			91.5(2)	
N3−Cu−Cl1	97.1(1)	97.1(2)	108.9 (3)	98.2(2)
N3−Cu−Cl1a			106.1(3)	
N3−Cu−Cl2	93.7(1)	91.4(2)		
N3−Cu−O11			91.5(2)	
Cl1−Cu−Cl2	107.0(1)	104.2(1)		
Cl1−Cu−O11			92.4(4)	
Cl1a-Cu−O11			101.2(4)	

[a] Standard deviations in parentheses.

{**[(bpa)CuCl$_2$][(bpa)Cu(H$_2$O)Cl][Cu(bpa)Cl][CuCl$_4$]·CH$_3$OH**} **(6).** Compound **6** was obtained as an intermediate product in the methanolysis of **3a**, **3b**, and **3d**. It contains three different chloro complexes of the $[(bpa)Cu]^{2+}$ fragment and a tetrachlorocuprate(II) dianion. The structure of [(bpa)-$CuCl_2$] in **6** is identical within the experimental errors to that of **5**. The square-pyramidal complex $[(bpa)Cu(H_2O)Cl]^+$ and the square-planar complex $[Cu(bpa)Cl]^+$ are shown in Figure 5. These components have structures similar to those of related complexes described by Mascharak et al.[25] Only the axial Cu−H_2O distance of 2.51 Å in our compound is notably longer than the reported Cu−methanol and

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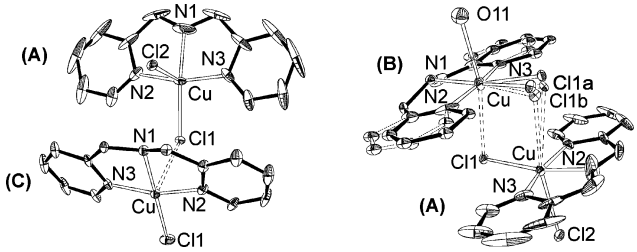

Figure 5. ORTEP plots (30% ellipsoids) of the structures of the components $[(bpa)CuCl_2]$ (A), $[(bpa)Cu(H_2O)Cl]^+$ (B), and $[(bpa)CuCl]^+$ (C) in **6**. Selected bond lengths and angles are listed in Table 2.

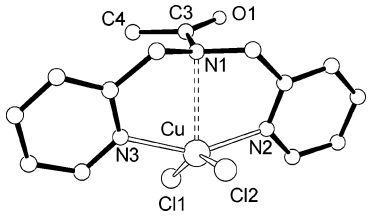

Figure 6. Ball and stick plot of the calculated structure of $[(Ac\text{-}bpa)CuCl_2]$. Selected bond lengths and angles are listed in Table 1.

−ethanol contacts of 2.33 and 2.32 Å, respectively. The tetrachlorocuprate(II) ion has a typical distorted tetrahedral structure[26] and is disordered about a crystallographic mirror plane. It should be noted that the $[(bpa)Cu(H_2O)Cl]^+$ cation and the solvent molecule in **6** are also severely disordered. This has prompted us to confirm the constitution not only by C,H,N-elemental analysis, but also by a determination of the crystal density. These data confirm the structural assignments. The importance of the structure of **6** lies not so much in the geometric details but rather in the fact that it indicates the presence of monochloro complexes and free chlorocopper(II) complexes in the reaction mixtures.

Calculated Structures

$[(Ac\text{-}bpa)CuCl_2]$. Since this study represents the first attempt to model N-bound tertiary amide complexes, our first aim was to validate the calculations by comparison of theoretical and crystallographic results. In order to reduce the number of geometric parameters, the acyl substituents in **1a**−**d** were replaced by an acetyl group in the model ligand Ac-bpa. The first calculated structure is that of the complex $[(Ac\text{-}bpa)CuCl_2]$. The result is shown in Figure 6. Remarkably good agreement with the experimental structures of **3a**, **3c**, and **3d** is evident. The longest distance is found between the Cu(II) center and the amide-nitrogen atom. With 2.627 Å it is clearly outside the range of a covalent interaction. Consequently, the flattened tetrahedral N_2Cl_2-geometry is even more pronounced than that in **3c**. This Jahn−Teller distorted geometry is frequently observed in tetracoordinate copper(II) complexes containing two nitrogen and two chloro ligands[27] and is consistent with a "2 + 1" binding mode of the acylated bpa-ligand. This coordination mode is rare in copper(II) complexes with tri- and polydentate amine ligands. A comparable situation was described by Reedijk et al. for a sterically hindered copper complex of the hexadentate EDTB (EDTB = *N*,*N*,*N*′,*N*′-tetrakis[(2-benzimidazolyl)methyl]-1,2-ethanediamine).[28]

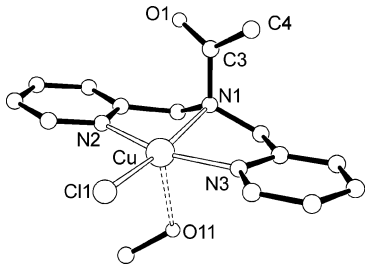

Figure 7. Ball and stick plot of the calculated structure of $[(Ac\text{-}bpa)CuCl(CH_3OH)]^+$. Selected bond lengths and angles are listed in Table 1.

$[(Ac\text{-}bpa)CuCl(CH_3OH)]^+$. The X-ray structural analysis of the mixed salt **6** revealed that monochloro complexes may be involved in the methanol cleavage reactions of **3a**−**d**. We reasoned that they could be the actual reactive species, since the dichloro complexes show only a rather small activation of their amide functions. Our aim was to compare the calculated structure of an N-bound tertiary amide in the monochloro complex $[(Ac\text{-}bpa)CuCl(CH_3OH)]^+$ with the structure of the strongly activated triflate salt **2b**. It turned out that the two structures are strikingly similar. An ORTEP representation of $[(Ac\text{-}bpa)CuCl(CH_3OH)]^+$ is shown in Figure 7. The coordination geometry is square-pyramidal with Cl^-, the two pyridine donors, and the tertiary amide nitrogen atom in the basal plane. Most important, the Cu−N^{amide} distance of 2.22 Å is only slightly longer than that in **2b** (2.164 Å). The Cu−Cl bond length is 2.24 Å. The methanol is weakly bound at a distance of 2.363 Å in the apical position. It is interesting to note the close relationship between $[(Ac\text{-}bpa)CuCl(CH_3OH)]^+$ and **2b**, and the cleavage products **5**, $[(bpa)CuCl]^+$ in **6** and $[(bpa)Cu(H_2O)](ClO_4)_2$[9a] which have similar coordination geometries. Only a shortening of one Cu−N distance from ca. 2.2 (Cu−N^{amide}) to ca. 2.0 Å (Cu−N^{amine}) is required when [(bpa)CuL] acts as a leaving group.

Activation of the Amide Group. In order to understand the C−N bond solvolysis, it is necessary to consider the activation of the amide group in the complexes **2a**−**d** and **3a**−**d**, as well as in the calculated structures of $[(Ac\text{-}bpa)CuCl_2]$ and $[(Ac\text{-}bpa)CuCl(CH_3OH)]$. Figure 8 contains an illustration of the first coordination spheres. It shows that the dichloro complexes are characterized by a weak, noncovalent copper to amide nitrogen contact (Figure 8a). Their monocapped distorted tetrahedral N_2Cl_2 coordination sphere is distinctly different from the distorted trigonal-bipyramidal geometry in related bpa complexes without a tertiary carboxamide unit (Figure 8b).[14,15,21] It is interesting to compare our dichloro complexes with copper complexes of

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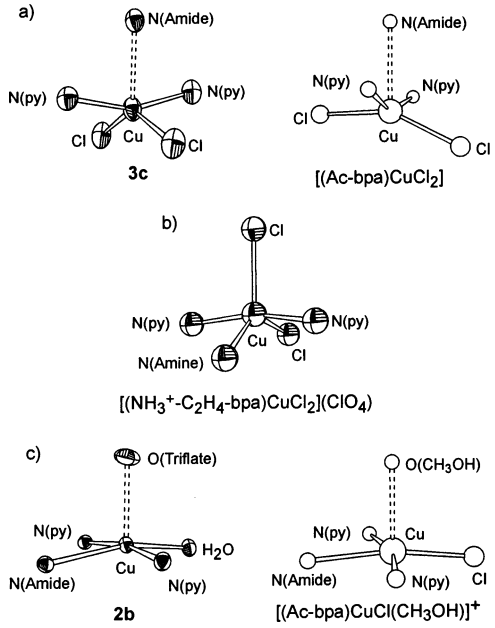

Figure 8. First coordination sphere of (a) the monocapped distorted-tetrahedral complexes **3c** (X-ray), [(Ac-bpa)$CuCl_2$] (calculated), (b) the distorted trigonal-bipyramidal complex *N*-(2-aminoethyl)bis(2-picolyl)-amino-dichlorocopper(II)-hydroperchlorate,[15] and (c) the square-pyramidal complexes **2b** (X-ray) and [(Ac-bpa)CuCl(CH_3OH)] (calculated).

a monoacylated triazacylononane ligand which was recently reported by Houser et al.[29] The tertiary amide function in these compounds does not bind to the metal center, and the triazacyclononane binds in a bidentate ethylenediamine fashion. Due to the ligand geometry, the amide nitrogen points away from the metal center and is not activated. Schindler et al. have reported an amide substituted copper complex of bpa which contains the neutral nitrogen atom in the apical position of a square pyramid, 2.64 Å away from the central copper ion.[30] The authors reported a small deplanarization of the amide moiety as a consequence of weak electrostatic interactions, but the effect is much smaller than in our complexes. Our ligands keep the nitrogen atom in a position that enforces electrostatic interactions. As a consequence, a significant pyramidalization of the amide group is observed in **3a**−**d** although less pronounced than in the structures of the square pyramidal triflato complex **2b** and the monochloro complex [(Ac-bpa)CuCl(CH_3OH)]$^+$, which contain a strongly bound tertiary amide function (Figure 8c).

The geometry of the amide moiety is best described by the pyramidalization χ_N at the nitrogen atom.[31] The parameter χ_N reflects the degree of sp^3 hybridization as a consequence of metal-ion coordination. It is conveniently calculated from the C−N−C−O and C−N−C−C torsion angles of the amide group and increases from 0° (sp^2 hybridization) to 60° (sp^3 hybridization) when N is completely pyramidal. This corresponds to a significant activation of the amide function by loss of resonance stabilization. Figure 9 shows the R_2N−C(O)R groups in the two calculated and two experimental structures. The agreement between experiment and theory is very good. It is evident that the dichloro-complexes (χ_N = ca. 30°) are significantly less distorted than the monochloro- and triflato-derivatives (χ_N = ca. 45°). Concomitant with a higher degree of sp^3 pyramidalization and loss of resonance stabilization is a lengthening of the C−N bond from ca. 1.39 to ca. 1.44 Å. For comparison, the free ligands **1c** and **1d** have shorter C−N distances of ca. 1.35 Å and χ_N-values of 10.4° and 8.2°.[9] These data are typical for unperturbed tertiary amide groups.

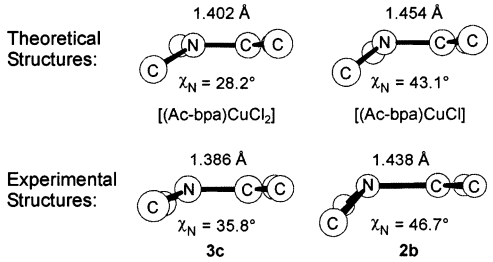

Figure 9. Distortion of the formally planar amide function in the calculated structures of [(Ac-bpa)$CuCl_2$] and [(Ac-bpa)CuCl(CH_3OH)], as well as in the crystal structures of **2b** and **3c**.

The C−O bond distances are less useful for a quantitative evaluation of structural effects than the C−N distances.[32] However, the carbonyl stretching frequencies are highly sensitive measures for the degree of resonance in an amide function. This has been extensively exploited in studies on purely organic distorted amides which show nice correlations between the C−N bond lengths and the CO stretching vibration.[33] In metal complexes, N-coordination results in higher, and O-coordination in lower, frequencies compared to the free amide ligand. For the dichloro-complex **3c**, we observe a value of 1690 cm^{-1} whereas the triflato-complex **2b** exhibits a band at 1756 cm^{-1}. The free ligand resonances are at 1674 (**1c**) and 1660 (**1b**) cm^{-1}, respectively. Thus, the χ_N values correspond to the magnitude of the high frequency shift which is most pronounced in the highly distorted derivative **2b**. The complexes for which no crystallographic information is available clearly fall into the same ranges, confirming the similarity of their structures. It is interesting to compare our data with those of the most twisted organic amide, a 1-aza-2-adamantanone reported by Kirby et al.[34] This compound has a C−N bond length of 1.475 Å and an IR-stretching frequency of 1732 cm^{-1}. The authors have shown that it behaves like an aminoketone rather than an amide. This is enforced by a large twist angle τ of ca. 90° which completely removes the amide resonance. The twist angle τ is the angle between the C(N)−C(N) axis and the O(C)−C(C) axis and ranges from 0° in a planar amide

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to 90° in a completely distorted amide function. Generally, a geometrically enforced large twist angle is the means of activation in purely organic carboxamides.[32] We have shown that N-coordination of a metal ion to a tertiary amide has the same activating effect but does not require any steric strain in the amide. The significantly enhanced nucleophilic cleavage lability of the C−N bond is common to both Werner-type complexes and twisted amides. However, whereas numerous experimental[35] and theoretical[36] studies have dealt with the C−N-bond hydrolysis in organic compounds, we are only at the beginning of understanding the corresponding reactivity of metal complexes. A major obstacle is the inherent lability of N-coordinated tertiary carboxamides. We have shown earlier that the ligands **1a**−**d** do not form stable copper(II) complexes in aqueous solutions at pH values below ca. 9[37] and that addition of propylamine is sufficient to extract the metal ion from acylated bpa ligands.[9a] The formation of tetrachlorocuprates in the present study provides evidence for a dissociation in methanol solutions. Theoretical studies are therefore important to gain insight into the actual reactive species in solution. The first results are presented in this paper. We were able to show that the formation of monochloro complexes $LCuCl^+$ nicely explains the similar reactivity of triflato and chloro complexes in methanolysis reactions.

Conclusions

The activation of tertiary carboxamides by coordination of their electrically neutral nitrogen atom to a metal center was postulated 30 years ago as a means of promoting the nucleophilic C−N bond cleavage in acylated $[(R-C(O)bpa)Cu]^{2+}$ complexes.[6] Our present paper provides the first detailed structural investigation of such complexes and their reaction products. Theoretical studies were performed to gain a better understanding of the reactive species in solution. The importance of ligand dissociation and exchange processes in reactions of N-bound tertiary carboxamides is evident. We were able to show that the coordination properties of a neutral amide nitrogen atom can range from covalent binding with strong activation to weak electrostatic interactions. This depends on the co-ligands, triflate and chloride in our study. Our results further suggest that metal coordination may have similar effects on an amide function to steric strain in purely organic compounds. With our work, we are beginning to answer what are perhaps some of the last open questions in the coordination chemistry of the amide group.

Experimental Section

General Methods. Spectra were recorded with the following instruments. ^{1}H NMR: Bruker Avance DPX 300. All chemical shifts are referenced to TMS as internal standard, with high-frequency shifts recorded as positive. UV−vis spectra: Varian Cary 1G spectrophotometer. IR (KBr): Mattson Polaris FTIR. Elemental analysis: Carlo Erba elemental analyzer model 1106. FD- and FAB-MS: Varian MAT 212.

All complexes were prepared and stored under an atmosphere of dry nitrogen. Absolute solvents were purchased from Fluka and stored under nitrogen. Solvents were used without further purification. The water used for extractions was bidistilled. All other reagents were of commercially available reagent grade quality. Amino acid derivatives were purchased from Bachem and copper(II) triflate from Acros. All other chemicals were from Aldrich. Bis[(2-pyridyl)methyl]amine (bpa) was prepared according to literature procedures.[38]

Chromatographic separations were achieved on flash columns under nitrogen pressure. The stationary phase was silica (Merck Type 9385, 230−400 mesh, 60 Å) from Aldrich. CH_3OH/CH_2Cl_2 mixtures were used as eluents. Technical grade dichloromethane was used which was purified by rotary evaporation. Methanol was of p.a. quality. The separation was optimized and followed by TLC (silica).

The synthesis of the ligand Boc-Ala-bpa (**1c**) and its methanolysis in the presence of $Cu(CF_3SO_3)_2$, as well as the synthesis of complex **2c**, were published previously.[9a] The ligands **1a**,[8] **1b**, and **1d**[9b] were reported in short communications but without experimental details. Their syntheses are described below.

Ligands. A general method was used for the DCC/HOBt coupling, but the following workup conditions differed significantly for each compound.

DCC/HOBt Coupling (General Method). A THF solution containing equimolar amounts of the carboxylic acid component, bpa, and 1.2 equiv of hydroxybenzotriazol (HOBt) was cooled to −10 °C in an ice/salt bath. *N*,*N*′-Dicyclohexylcarbodiimid (DCC, 1.2 equiv) was dissolved in a small volume of THF and added in one portion to the solution. The mixture was stirred at −10 °C over a period of 1 h and then allowed to warm to room temperature. Stirring was continued overnight. The suspension was filtered off and washed several times with small amounts of cold (4 °C) THF. The combined filtrates were evaporated to dryness. The following workup is described separately for each compound.

PhC(O)-bpa (1a). The amounts of each reagent follow: benzoic acid (5.00 g, 40.9 mmol), bpa (8.15 g, 40.9 mmol), HOBt (6.65 g, 49.1 mmol), DCC (10.14 g, 49.1 mmol), THF (50 mL). The crude product was dissolved in CH_2Cl_2 (100 mL) and washed 3 times with 100 mL of a 0.5 M $NaHCO_3$-solution, and finally washed with 100 mL of water. The organic phase was dried over $MgSO_4$, filtered and rotary-evaporated to dryness. Flash column chromatography using 20:1 CH_2Cl_2/CH_3OH as the eluent yielded the ligand as the third fraction ($R_f = 0.45$). Compound **1a** was isolated as a light yellow solid which was recrystallized from warm $(C_2H_5)_2O$ in an ultrasound bath. Colorless needles precipitated after a short period of standing at room temperature; these were filtered off and dried under vacuum (9.25 g, 30.5 mmol, 75%).

MS (FD, $CHCl_3$): $m/z = 608$ $[2M]^+$, 304 $[M]^+$. IR (KBr, $[cm^{-1}]$): $\nu = 1634$ ($\nu_{C=O}$, amide), 1590 ($\nu_{C=N}$). ^{1}H NMR (300 MHz, $CDCl_3$, [ppm]): $\delta = 4.69$ (s, 2H; py-CH_2), 4.89 (s, 2H; py-CH_2), 7.19 (m, 3H; 2 × H5-py, H4-Ph), 7.32−7.45 (m, 4H; 2 × H3-py, H3-Ph, H5-Ph), 7.56 (m, 2H; H2-Ph, H6-Ph), 7.67 (m, 2H; 2 × H4-py), 8.55 (m, 2H; 2 × H6-py).

Boc-Gly bpa (1b). The amounts of each reagent follow: Boc-Gly-OH (5.00 g, 28.5 mmol), bpa (5.68 g, 28.5 mmol), HOBt (4.63

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g, 34.4 mmol), DCC (7.07 g, 34.4 mmol), THF (100 mL). The crude product was dissolved in 100 mL of CH_2Cl_2 (100 mL) and washed 3 times with citric acid (50 mL, 0.05 M), 1 time with H_2O (50 mL), 3 times with $NaHCO_3$ (0.5 M, 50 mL), and 1 time with H_2O (100 mL). The organic phase was dried over $MgSO_4$, filtered, and rotary-evaporated to dryness. Purification was achieved by flash column chromatography using 15:1 CH_2Cl_2/CH_3OH as the eluent. Several small yellow and brown fractions eluted first which were followed by ligand **1b** in a broad, light-yellow band ($R_f = 0.5$). Rotary-evaporation of the solvent and drying under vacuum yielded **1b** as a light-yellow, viscous oil (6.89 g, 19.3 mmol, 68%).

MS (FD, $CHCl_3$): $m/z = 714$ $[2M]^+$, 357 $[M]^+$. IR (KBr, film, $[cm^{-1}]$): $\nu = 3421$ (ν_{N-H}), 3320 (ν_{N-H}), 1711 ($\nu_{C=O}$, urethane), 1660 ($\nu_{C=O}$, amide), 1592 ($\nu_{C=N}$). ^1H NMR (300 MHz, $CDCl_3$, [ppm]): $\delta = 1.43$ (s, 9H; $C(CH_3)_3$), 4.18 (d, $^3J(^{\alpha}CH_2,NH) = 5.5$ Hz, 2H; $^{\alpha}CH_2$), 4.64 (s, 2H; py-CH_2), 4.77 (s, 2H; py-CH_2), 5.59 (s, br, 1H; NH), 7.15−7.29 (m, 4H; 2 × H3-py, 2 × H5-py), 7.64 (m, 2H; 2 × H4-py), 8.50 (d, ^3J(H6,H5) = 6.5 Hz, 1H; H6-py), 8.56 (d, ^3J(H6,H5) = 4.5 Hz, 1H; H6-py).

Boc-Leu-bpa (1d). The amounts of each reagent follow: Boc-Leu-OH (5.00 g, 20.1 mmol), bpa (3.99 g, 20.1 mmol), HOBt (3.25 g, 24.1 mmol), DCC (4.97 g, 24.1 mmol), THF (100 mL). The crude product was dissolved in CH_2Cl_2 (100 mL) and washed 3 times with citric acid (100 mL, 0.05 M), 1 time with saturated NaCl (100 mL), 3 times with $NaHCO_3$ (0.5 M, 100 mL), and 1 time with saturated NaCl (100 mL). The organic phase was dried over $MgSO_4$ and filtered and the volume reduced to ca. one-third. Residual DCH was filtered off, the solvent removed by rotary evaporation and the residual dried under vacuum. The crude product was recrystallized several times from $(C_2H_5)_2O$. This was achieved by dissolving the solid in large amounts of ether with heating and subsequent storage at −20 °C. The resulting colorless product **1d** was isolated by filtration and dried under vacuum (4.47 g, 10.8 mmol, 54%).

MS (FD, $CHCl_3$): $m/z = 826$ $[2M]^+$, 413 $[M]^+$. IR (KBr, $[cm^{-1}]$): $\nu = 3384$ (ν_{N-H}), 3180 (ν_{N-H}), 1700 ($\nu_{C=O}$, urethane), 1640 ($\nu_{C=O}$, amide), 1593 ($\nu_{C=N}$). ^1H NMR (300 MHz, $CDCl_3$, [ppm]): $\delta = 0.80$, 0.86 (2 × d, $^3J(CH_3, {}^{\gamma}CH) = 6.4$ Hz, $^3J(CH_3, {}^{\gamma}CH) = 6.6$ Hz, 6H; $^{\gamma}CH(CH_3)_2$), 1.43−1.57 (m, 2H; $^{\beta}CH_2$), 1.43 (s, 9H; $C(CH_3)_3$), 1.61−1.70 (m, 1H; $^{\gamma}CH$), 4.64−4.76 (m, 3H; 2 × py-CH^AH^B, $^{\alpha}CH$), 4.85 (d, $^2J(CH^A, H^B) = 15.4$ Hz, 1H; py-CH^AH^B), 5.50 (d, $^2J(CH^A, H^B) = 17.4$ Hz, 1H; py-CH^AH^B), 5.19 (d, $^3J(NH, CH^{\alpha}) = 9.0$ Hz, 1H; NH), 7.14−7.28 (m, 4H; 2 × H3-py, 2 × H5-py), 7.63 (m, 2H; 2 × H4-py), 8.50 (d, ^3J(H6, H5) = 4.2 Hz, 1H; H6-py), 8.56 (d, ^3J(H6, H5) = 4.6 Hz, 1H; H6-py).

$[LCu(CF_3SO_3)_2]$-Complexes: General Method. An equimolar amount of $Cu(CF_3SO_3)_2$ was added to an acetonitrile solution of the ligand. The resulting dark-blue solution was stirred overnight and all solvent removed under vacuum.

$[Cu(PhC(O)\text{-}bpa)(CF_3SO_3)_2]$ (2a). The amounts of each reagent follow: Benz-bpa (**1a**) (301 mg, 0.99 mmol), $Cu(CF_3SO_3)_2$ (358 mg, 0.99 mmol), CH_3CN (10 mL). The crude product was dissolved in 10 mL of CH_2Cl_2. Within several minutes, the solid product **2a** precipitated. The resulting suspension was left overnight at 4 °C. After filtration and drying under vacuum, pure **2a** was obtained as a turquoise powder (606 mg, 0.91 mmol, 92%).

Anal. (%) Calcd for $C_{21}CuF_6H_{17}N_3O_7S_2$ (665.04 g/mol): C 37.93, H 2.58, N 6.32. Found: C 37.75, H 2.71, N 6.13. MS (FAB, NBA): $m/z = 515$ $[Cu(PhC(O)\text{-}bpa)(CF_3SO_3)]^+$, 366 $[Cu(PhC(O)\text{-}bpa)]^+$, 304 $[PhC(O)\text{-}bpa]^+$. IR (KBr, $[cm^{-1}]$): $\nu = 1701$ ($\nu_{C=O}$, amide), 1678 (sh), 1615 ($\nu_{C=N}$), 1318 (ν_{SO_3}), 1281 (ν_{SO_3}), 1246 (ν_{CF_3}), 1230 (ν_{CF_3}), 1165 (ν_{CF_3}), 1032 (ν_{SO_3}). UV−vis (CH_3CN, λ [nm] (ϵ)): 632 (58).

$[Cu(Boc\text{-}Gly\text{-}bpa)(H_2O)(CF_3SO_3)_2]$ (2b). The amounts of each reagent follow: Boc-Gly bpa (**1b**) (863 mg, 2.42 mmol), $Cu(CF_3SO_3)_2$ (875 mg, 2.42 mmol), CH_3CN (20 mL). The blue crude product was treated with CH_2Cl_2 until it was mostly dissolved. The green solution was filtered and left for crystallization. A microcrystalline solid precipitated which was filtered off and washed with CH_2Cl_2 until the filtrate remained colorless. This procedure afforded **2b** as a pure, dark-blue solid which was readily soluble in CH_3CN but not longer in CH_2Cl_2 (1.201 g, 1.63 mmol, 67%). X-ray quality crystals were obtained from a highly dilute CH_2Cl_2 solution. Blue needles of **2b**·CH_2Cl_2 crystallized upon standing at RT for several days.

Anal. (%) Calcd for $C_{21}CuF_6H_{26}N_4O_{10}S_2$ (736.12 g/mol): C 34.26, H 3.56, N 7.61. Found: C 34.13, H 3.54, N 7.46. MS (FAB, NBA): $m/z = 568$ $[Cu(Boc\text{-}Gly\text{-}bpa)(CF_3SO_3)]^+$, 512 $[(Cu(Boc\text{-}Gly\text{-}bpa)(CF_3SO_3)) - H_2C{=}C(CH_3)_2]^+$, 419 $[Cu(Boc\text{-}Gly\text{-}bpa)]^+$, 319 $[(Cu(Boc\text{-}Gly\ bpa)) - (CH_3)_3CCOO]^+$. IR (KBr, $[cm^{-1}]$): $\nu = 3414$ (br, ν_{O-H}, H_2O), 1756 ($\nu_{C=O}$, amide), 1701 ($\nu_{C=O}$, urethane), 1667 (sh), 1615 ($\nu_{C=N}$), 1289 (ν_{SO_3}), 1244 (ν_{CF_3}), 1167 (ν_{CF_3}), 1032 (ν_{SO_3}). UV−vis (CH_3CN, λ [nm] (ϵ)): 648 (62).

$[Cu(Boc\text{-}Leu\text{-}bpa)(H_2O)(CF_3SO_3)_2]$ (2d). The amounts of each reagent follow: Boc-Leu-bpa (**1d**) (349 mg, 0.85 mmol), $Cu(CF_3SO_3)_2$ (307 mg, 0.85 mmol), CH_3CN (10 mL). The crude product was dissoved in 10 mL of CH_2Cl_2. Slow diffusion of $(C_2H_5)_2O$ to this solution resulted in separation of a blue oil. The mother liquor was decanted off and the oil dried under vacuum. This afforded pure **2d** as a dark-blue to turquoise solid foam. (506 mg, 0.64 mmol, 75%).

Anal. (%) Calcd for $C_{25}CuF_6H_{34}N_4O_{10}S_2$ (792.23 g/mol): C 37.87, H 4.33, N 7.07. Found: C 37.90, H 4.66, N 7.00. MS (FAB, NBA): $m/z = 624$ $[Cu(Boc\text{-}Leu\text{-}bpa)(CF_3SO_3)]^+$, 475 $[Cu(Boc\text{-}Leu\text{-}bpa)]^+$, 375 $[(Cu(Boc\text{-}Leu\text{-}bpa)) - (CH_3)_3CCOO]^+$. IR (KBr, $[cm^{-1}]$): $\nu = 3420$ (br, ν_{O-H}, H_2O), 1747 ($\nu_{C=O}$, amide), 1698 (sh), 1660 ($\nu_{C=O}$, urethane), 1614 ($\nu_{C=N}$), 1283 (ν_{SO_3}), 1252 (ν_{CF_3}), 1166 (ν_{CF_3}), 1031 (ν_{SO_3}). UV−vis (CH_3CN, λ [nm] (ϵ)): 664 (66).

$[LCuCl_2]$ Complexes: General Method. Because of their light sensitivity the dichloro copper(II) complexes **3a**−**d** were synthesized and stored in the dark. Equimolar quantities of $CuCl_2 \cdot 2H_2O$ and the respective ligand were reacted in acetonitrile.

$[Cu(PhC(O)\text{-}bpa)(Cl)_2]$ (3a). The amounts of each reagent follow: Benz-bpa (**1a**) (704 mg, 2.32 mmol), $CuCl_2 \cdot 2H_2O$ (396 mg, 2.32 mmol), CH_3CN (15 mL). Precipitation of the product from the reaction mixture started after several minutes of stirring. The suspension was stirred overnight and thereafter stored for 24 h at −20 °C. Filtration, repeated washing with small amounts of acetonitrile, and drying under vacuum afforded **3a** as a turquoise powder (825 mg, 1.88 mmol, 81%).

Anal. (%) Calcd for $C_{19}Cl_2CuH_{17}N_3O$ (437.81 g/mol): C 52.13, H 3.91, N 9.60. Found: C 52.57, H 3.99, N 9.48. MS (FAB, NBA): $m/z = 401$ $[Cu(PhC(O)\text{-}bpa)(Cl)]^+$, 366 $[Cu(PhC(O)\text{-}bpa)]^+$, 304 $[PhC(O)\text{-}bpa]^+$. IR (KBr, $[cm^{-1}]$): $\nu = 1673$ ($\nu_{C=O}$, amide), 1608 ($\nu_{C=N}$). UV−vis (CH_2Cl_2, λ [nm] (ϵ)): 789 (293).

$[Cu(Boc\text{-}Gly\text{-}bpa)(Cl)_2]$ (3b). The amounts of each reagent follow: Boc-Gly bpa (**1b**) (605 mg, 1.70 mmol), $CuCl_2 \cdot 2H_2O$ (290 mg, 1.70 mmol), CH_3CN (15 mL). A light blue solid precipitated after several minutes. Stirring was continued overnight and the resulting suspension stored for 24 h at −20 °C. Product **3b** was filtered off and dried under vacuum to yield a light-blue powder (714 mg, 1.45 mmol, 85%).

Anal. (%) Calcd for $C_{19}Cl_2CuH_{24}N_4O_3$ (490.87 g/mol): C 46.49, H 4.93, N 11.41. Found: C 46.80, H 5.12, N 11.31. MS (FAB, NBA): $m/z = 454$ $[Cu(Boc\text{-}Gly\text{-}bpa)(Cl)]^+$, 419 $[Cu(Boc\text{-}Gly\text{-}bpa)]^+$, 356 $[Boc\text{-}Gly\text{-}bpa]^+$. IR (KBr, $[cm^{-1}]$): $\nu = 3441$ (ν_{N-H}),

Table 3. Crystallographic Data for **2b**, **3c**, **5**, **5**·$2H_2O$, and **6**

	2b·CH_2Cl_2	**3c**·$0.5H_2O$·CH_2Cl_2	**5**	**5**·$2H_2O$	**6**·CH_3OH
formula	$C_{22}H_{28}Cl_2CuF_6N_4O_{10}S_2$	$C_{21}H_{29}Cl_4CuN_4O_{3.50}$	$C_{12}H_{13}Cl_2CuN_3$	$C_{12}H_{17}Cl_2CuN_3O_2$	$C_{37}H_{45}Cl_{18}Cu_4N_9O_2$
fw	821.04	598.82	336.69	369.73	1185.58
cryst size [mm^3]	0.96 × 0.28 × 0.12	0.40 × 0.30 × 0.10	0.29 × 0.29 × 0.17	0.23 × 0.09 × 0.07	0.29 × 0.29 × 24
T [K]	200(2)	173(2)	100(2)	100(2)	100(2)
cryst syst	monoclinic	monoclinic	monoclinic	orthorhombic	orthorhombic
space group	$P2_1/c$	$P2_1$	$P2_1/n$	$Pbca$	$Pnma$
a [Å]	12.296(1)	16.9604(3)	6.5320(1)	15.6476(3)	22.3994(4)
b [Å]	15.165(3)	13.2836(2)	13.2558(2)	6.5115(2)	15.3804(3)
c [Å]	18.470(3)	26.5637(5)	15.4821(2)	30.6818(6)	13.2115(2)
α [deg]	90	90	90	90	90
β [deg]	104.83(1)	101.6030(10)	98.985(2)	90	90
γ [deg]	90	90	90	90	90
V [$Å^3$]	3329.4(9)	5862.37(18)	1324.10(3)	3126.2(2)	4551.5(2)
Z	4	8	4	8	4
D_{calcd} [Mg/m^3]	1.638	1.357	1.674	1.571	1.730 (D_{obsd} = 1.735)
μ [mm^{-1}]	1.031	1.139	2.036	1.742	2.359
θ-range [deg]	1.76−27.01	2.19−24.11	3.35−34.00	3.45−28.00	3.82−27.10
measured reflns	8915	18137	33908	20895	33601
indep reflns	7260 (R_{int} = 0.0452)	18137 (R_{int} = 0.0000)	5390 (R_{int} = 0.0580)	3780 (R_{int} = 0.1221)	5149 (R_{int} = 0.0487)
obsd reflns[a]	4082	13565	3887	1864	4296
params	434	1192	202	181	363
GOF on F^2	1.022	1.350	1.030	0.942	1.162
R-value[a]	R1 = 0.0519	R1 = 0.0708	R1 = 0.0325	R1 = 0.0489	R1 = 0.0616
R-value (all data)	wR2 = 0.1381	wR2 = 0.2029	wR2 = 0.0717	wR2 = 0.0996	wR2 = 0.1269
max/min [e $Å^{-3}$]	0.486/−0.533	1.385/−0.703	0.471/−0.611	455/−812	1.041/−0.905

[a] [$I > 2\sigma(I)$].

3344 (ν_{N-H}), 1722 + 1674 ($\nu_{C=O}$, amide + urethane), 1607 ($\nu_{C=N}$). UV−vis (CH_2Cl_2, λ [nm] (ϵ)): 771 (281).

[Cu(Boc-Ala-bpa)(Cl)$_2$] (3c). The amounts of each reagent follow: Boc-Ala-bpa (**1c**) (387 mg, 1.04 mmol), $CuCl_2$·$2H_2O$ (179 mg, 1.04 mmol), CH_3CN (10 mL). The reaction solution was stirred overnight. The solvent was removed and the remaining crude product dissolved in CH_2Cl_2. Slow diffusion of ether into this solution resulted in the precipitation of **3c** as a microcrystalline, blue solid within several days. The product was filtered off and dried under vacuum (357 mg; 0.71 mmol, 68%). Crystals for an X-ray structure analysis were obtained when ether was allowed to diffuse slowly into a solution of analytically pure **3c** in CH_2Cl_2. Blue plates of **3c**·$^1/_2H_2O$·CH_2Cl_2 crystallized after several days at room temperature.

Anal. (%) Calcd for $C_{20}Cl_2CuH_{26}N_4O_3$ (504.90 g/mol): C 47.58, H 5.19, N 11.10. Found: C 47.45, H 5.32, N 10.85. MS (FAB, NBA): m/z = 468 [Cu(Boc-Ala-bpa)(Cl)]$^+$, 433 [Cu(Boc-Ala-bpa)]$^+$, 371 [Boc-Ala-bpa]$^+$. IR (KBr, [cm^{-1}]): ν = 3436 (ν_{N-H}), 3363 (ν_{N-H}), 1690 ($\nu_{C=O}$, amide + urethane), 1609 ($\nu_{C=N}$). UV−vis (CH_2Cl_2, λ [nm] (ϵ)): 803 (288).

[Cu(Boc-Leu-bpa)(Cl)$_2$] (3d). The amounts of each reagent follow: Boc-Leu-bpa (**1d**) (539 mg, 1.31 mmol), $CuCl_2$·$2H_2O$ (223 mg, 1.31 mmol), CH_3CN (15 mL). The blue reaction mixture turned green after a short period of time. The solution was stirred overnight and the solvent removed by rotary evaporation leaving a mixture of blue, green, and brown solids. The crude product was dissolved in CH_2Cl_2 and the solution filtered to remove insoluble material. Slow diffusion of ether into the filtrate for several days resulted in the crystallization of light-green plates of **3d** which were isolated by filtration and dried under vacuum (557 mg, 1.02 mmol, 78%). Green crystalline plates of **3d**·CH_2Cl_2 were obtained by ether diffusion into a solution of pure **3d** in CH_2Cl_2. The X-ray structure was of poor quality which was mostly due to a severe disordering of the Boc protecting group. However, the similarity of the first coordination sphere to that of **3a** and **3c** was confirmed.

Anal. (%) Calcd for $C_{23}Cl_2CuH_{32}N_4O_3$ (546.98 g/mol): C 50.51, H 5.90, N 10.24. Found: C 50.02, H 5.91, N 10.09. MS (FAB, NBA): m/z = 510 [Cu(Boc-Leu-bpa)(Cl)]$^+$, 475 [Cu(Boc-Leu-bpa)]$^+$, 454 [(Cu(Boc-Leu-bpa)(Cl)) − H_2C=$C(CH_3)_2$]$^+$, 413 [Boc-Leu-bpa]$^+$, 375 [(Cu(Boc-Leu-bpa)) − $(CH_3)_3CCOO$]$^+$. IR (KBr, [cm^{-1}]): ν = 3450 (ν_{N-H}), 3389 (ν_{N-H}), 1682 ($\nu_{C=O}$, amide + urethane), 1610 ($\nu_{C=N}$). UV−vis (CH_2Cl_2, λ [nm] (ϵ)): 807 (303).

Methanolysis of 1d in the Presence of $CuCl_2$·H_2O. [Cu(bpa)Cl$_2$] (5). Addition of $CuCl_2$·$2H_2O$ (77 mg, 0.45 mmol) to a solution of Boc-Leu-bpa (**1d**) (187 mg, 0.45 mmol) in CH_3OH (5 mL) was followed by immediate precipitation of [Cu(Boc-Leu-bpa)$(Cl)_2$] (**3d**). The precipitate redissolved upon addition of methanol (ca. 15 mL). The resulting turquoise solution was stirred in the dark at room temperature for 3 days. After reduction of the volume to ca. one-half and storage of the solution at −20 °C for several days, product **5** precipitated as a dark-blue solid which was isolated and dried under vacuum (81 mg, 0.24 mmol, 53%). Slow diffusion of $(C_2H_5)_2O$ to the reaction mixture at room temperature yielded dark-blue prisms which were suitable for an X-ray structure analysis. The compound was also crystallized by slow evaporation of water from an aqueous solution. This modification yielded a structure with different crystal parameters due to the presence of two noncoordinating solvent H_2O molecules in the unit cell.

Anal. (%) Calcd for $C_{12}Cl_2Cu\ H_{13}N_3$ (331.71 g/mol): C 43.19, H 3.93, N 12.59. Found: C 43.33, H 3.97, N 12.43. MS (FAB, NBA): m/z = 631 $[Cu_2(bpa)_2Cl_3]^+$, 297 [Cu(bpa)Cl]$^+$, 262 [Cu(bpa)]$^+$. IR (KBr, [cm^{-1}]): ν = 3070 (ν_{N-H}), 1606 ($\nu_{C=N}$). UV−vis (CH_3OH, λ [nm] (ϵ)): 673 (118).

[Cu(bpa)Cl$_2$][Cu(bpa)(H$_2$O)Cl][Cu(bpa)Cl][CuCl$_4$]·CH$_3$OH (6). $CuCl_2$·$2H_2O$ (148 mg, 0.87 mmol) was added to a solution of Boc-Leu-bpa (**1d**) (358 mg, 0.87 mmol) in CH_3OH (10 mL). The precipitated [Cu(Boc-Leu-bpa)$(Cl)_2$] (**3d**) redissolved upon addition of CH_2Cl_2 (ca. 10 mL), and the solution stirred for several hours. A sample of ca. 5 mL was separated and set for slow diffusion of $(C_2H_5)_2O$. Dark-green X-ray quality crystals of **6** were obtained within 24 h. The compound was insoluble in CH_3CN, CH_2Cl_2, and CH_3OH which prevented its investigation in solution. Drying of the compound under vacuum resulted in quantitative loss of methanol from the crystals. Anal. (%) Calcd for $C_{36}Cl_8Cu_4H_{41}N_9O$ (1153.57 g/mol): C 37.48, H 3.58, N 10.93. Found: C 37.53, H

3.38, N 10.78. MS (FAB, NBA): m/z = 631 $[Cu_2(bpa)_2Cl_3]^+$, 297 $[Cu(bpa)Cl]^+$, 262 $[Cu(bpa)]^+$. IR (KBr, [cm^{-1}]): ν = 1609 ($\nu_{C=N}$).

Theoretical Calculations. All calculations used the Gaussian 98[39] suite of programs. Geometries were fully optimized without constraints using the Becke 3-parameter hybrid functional[40] in conjunction with the Lee−Yang−Parr correlation functional[41] (B3LYP).[42] The Schaefer−Horn−Ahlrichs split-valence basis set[43] was used with an additional set of polarization functions[44] for all calculations. Stationary points were characterized by calculation of their normal vibrations within the harmonic approximation. All structures reported here are minima.

X-ray Crystallography. A summary of the crystallographic parameters for all compounds is given in Table 3. Intensity data (Mo Kα, λ = 0.71073 Å) were collected on a Siemens P4 diffractometer (**3c**; ω-scans, 6°/min) and on a Nonius Kappa CCD area detector (**2b**, **5**, **5**·2H_2O, **6**). Absorption corrections were made numerically from crystal faces (**5**·2H_2O),[45] or using empirical ψ-scans (**2b**),[46] or with the program SORTAV (**5**, **6**),[47] or SCALEPACK (**3c**).[48] All structures were solved by direct methods and refined using full-matrix least-squares on F^2 using the program packages SHELXTL NT 5.10 (**2b**, **5**, **5**·2H_2O, **6**)[49] and SHELXS-97/SHELXL-97 (**3c**).[50] Non-H-atoms were anisotropically refined. H-atoms were localized in the density map and isotropically refined, or fixed in geometrically calculated positions (riding mode). Details have been deposited at the Cambridge Crystallographic Data Centre as supplementary publications CCDC nos. 182769 (**2b**), 184027 (**3c**), 231941 (**5**), 231942 (**5**·2H_2O), and 231943 (**6**). Copies are available free of charge from CCDC, 12 Union Road, Cambridge CB2 1 EZ (U.K.) [Fax: (+44)1223-336033. E-mail: deposit@ccdc.cam.ac.uk.]

Supporting Information Available: Crystallograhic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

IC0496774

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