Activation of the Tertiary Carboxamide C–N Bond in Werner Complexes: A Classical Structure–Function Relationship**

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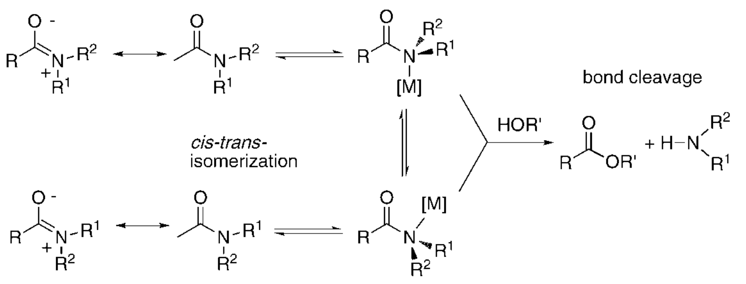
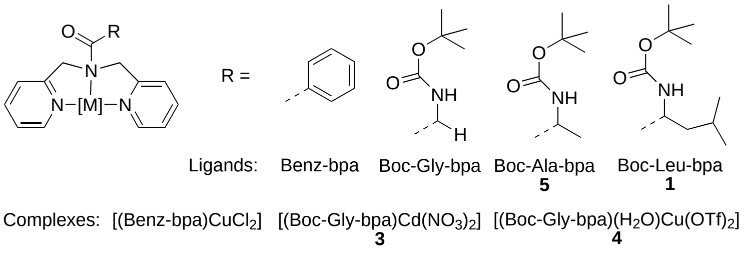
Dedicated to Professor Karl Wieghardt
on the occasion of his 60th birthday



Scheme 1. The reactivity of N-coordinated tertiary carboxamides.



Scheme 2. Ligands and complexes used.

Tertiary carboxamides, $RC(O)NR_2$, are fascinating reactive building blocks in organic and biological compounds.[1] The *cis–trans* isomerization about peptidyl–prolyl C–N bonds is a key step in many protein folding processes. Enzymes trigger this important biological switch but simple metal salts also catalyze amide isomerizations. Metal complexes have therefore attracted interest as potential synthetic peptide-folding reagents.[2] Another biologically relevant reaction of tertiary amides, the C–N bond hydrolysis of penicillins and cephalosporines, is also accelerated by metal ions.[3]

Coordination of a metal ion to the neutral amide nitrogen atom has been proposed to explain both *cis–trans* isomerization and C–N bond cleavage (Scheme 1).[1,3,4] However, despite the generality and importance of their reactions very little is known about the structures of N-coordinated tertiary amides. Only two Werner complexes have been characterized to date,[4,5] and the number of organometallic and urea derivatives is small as well.[6]

More data are clearly necessary to explain the occurrence of *cis–trans* isomerization or solvolytic bond cleavage in Werner complexes with nitrogen-bound tertiary amides. With the structural study presented herein we are, for the first time, able to compare a family of compounds which reveal a classical structure–function relationship. Scheme 2 summarizes the relevant compounds. New are Boc-Leu-bpa (**1**), $[(\text{Boc-Ala-bpa})CuCl_2]$ (**2**), $[(\text{Boc-Gly-bpa})Cd(NO_3)_2]$ (**3**), and $[(\text{Boc-Gly-bpa})(H_2O)Cu(OTf)_2]$ (**4**, $OTf = CF_3SO_3$, Boc = *t*-butyloxycarbonyl, bpa = *N,N*-bis(pyridin-2-ylmethyl)amine). We have recently reported the ligand Boc-Ala-bpa (**5**) and its $Cd(NO_3)_2$ complex **6**.[5] Lectka and co-workers have published the structure of $[(\text{Benz-bpa})CuCl_2]$ (Benz = benzyl).[4]

Figure 1 contains ORTEP plots of **1**-**4**.[7] The structures confirm that the amide nitrogen atom is bound to the metal center in all complexes. Figure 2 illustrates that a significant distortion of the amide geometry results. A quantitative

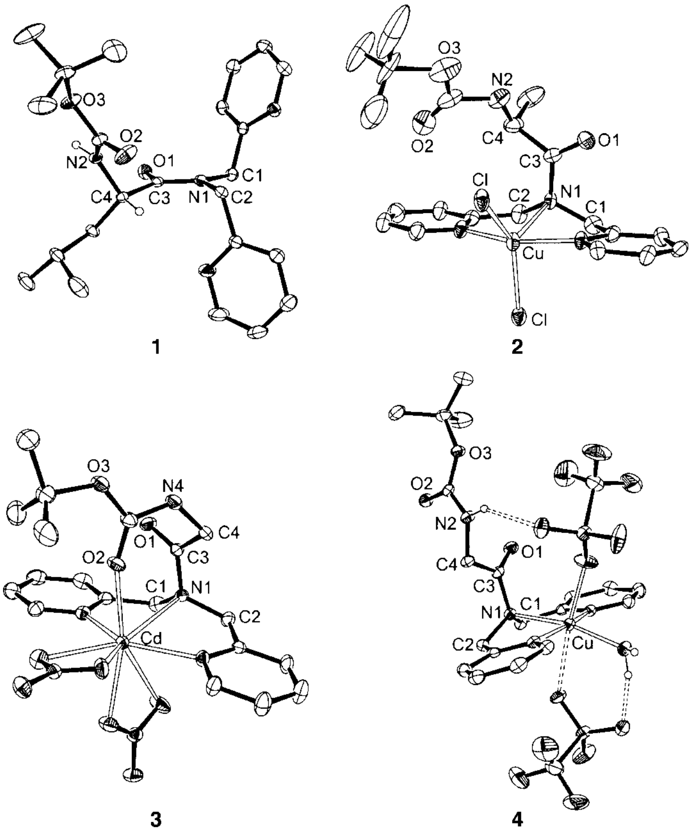


Figure 1. ORTEP plots (thermal ellipsoids set to 30 % probability) of **1**–**4**.

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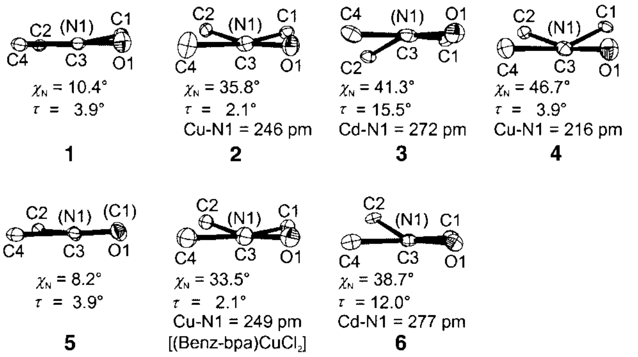

Figure 2. The tertiary amide moieties in **1**–**6**, and [(Benz-bpa)CuCl$_2$] viewed along the C3→N1 axis.

measure for the observed deplanarization is provided by the Winkler-Dunitz parameters χ_N and τ. The parameter χ_N is a measure of the pyramidalization at the N1 atom, and reflects the degree of sp^3 hybridization induced by metal coordination; this value ranges from 0° in a perfectly planar amide to a maximum of 60°. The parameter τ is the twist angle between the O1-C4 and the C1-C2-axis which has a maximum of 90°. Both values are calculated from the torsion angles defined by C1, C2, C3, C4, O1, and N1.[8] Our series shows a steady increase of χ_N from **1** to **4**. The free ligand **1** ($\chi_N = 10.4°$) is practically undistorted, but coordination of CuCl$_2$ in **2** causes a significant distortion ($\chi_N = 35.8°$) of the planar to near-pyramidal. The value of χ_N is even larger in the Cd(NO$_3$)$_2$ derivative **3** ($\chi_N = 41.3°$) and reaches a maximum of 46.7° in the Cu(OTf)$_2$ complex **4**. The known structures of **5**, [(Benz-bpa)CuCl$_2$],[4] and **6** nicely confirm this trend.

It is evident that the distortion increases with the Lewis acidity of the coordinated metal center. This is also reflected by the Cu–N bond distances which are 246 and 249 pm in the dichloro compounds and only 216 pm in the triflato complex. Thus, the activation of the tertiary amide moiety strongly depends on the coligands and on the metal ion. This variability is characteristic for Werner type complexes and does not occur in related organometallic compounds.

The differences are revealed by a plot of χ_N versus τ (Figure 3). This graph contains the data of all known complexes with an N-coordinated RC(O)NR$_2$ moiety and includes some examples of purely organic cations (C(O)NR$_3^+$) for comparison.[9] The data of the ligands **1** and **5** serve as standards for undistorted amides. It is evident from Figure 3 that the χ_N values are very similar and always close to the maximum of 60° in organometallic compounds,[6a–g] organic cations,[9] and in a urea complex.[6h] The twist angles, τ, are scattered over the whole range from about 0° to about 90°. This range is a clear indication of completely sp^3-hybridized nitrogen atoms and covalent M–N bonds. In marked contrast, χ_N values are smaller and more scattered in classical coordination complexes. The corresponding twist angles are small and do not differ much from those of the undistorted ligands. Thus, the M–N bonds in Werner complexes are apparently more electrostatic with distorted sp^2-hybridized nitrogen atoms. Such a binding mode explains the strong dependence of χ_N on the acidity of the metal center and should allow for a fine tuning of the C–N bond activation.

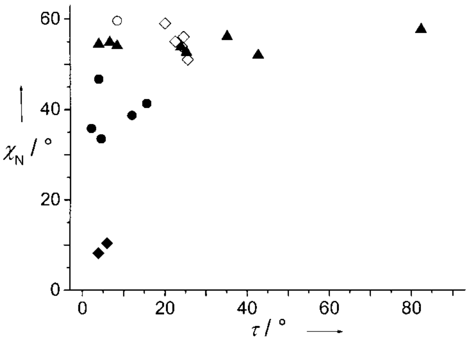

Figure 3. Plot of pyramidalizations, χ_N, versus twist angles, τ, for Werner type tertiary amide (●) and urea (○) complexes, organometallic compounds (▲), free ligands **1** and **5** (◆), and four selected organic cations RC(O)NR$_3^+$) (◇).

This explanation is in agreement with the observed reactivity of different metal-tertiary carboxamide complexes. Lectka and co-workers reported that Cu(OTf)$_2$ is an efficient *cis–trans*-isomerization catalyst, whereas CuCl$_2$ shows only very low activity.[2] We studied the effect of triflate and chloride ions on the isomerization rates of zinc complexes of **5** by temperature-dependent ^{1}H NMR spectroscopic measurements in acetone.[10] At 25 °C, rate constants of $k = 1400\,\mathrm{s}^{-1}$ ($\Delta H^{\neq} = 11.4 \pm 0.3\,\mathrm{kcal\,mol^{-1}}$; $\Delta S^{\neq} = -6.3 \pm 1.0\,\mathrm{cal\,K^{-1}\,mol^{-1}}$) for the triflate salt, and $k = 285\,\mathrm{s}^{-1}$ ($\Delta H^{\neq} = 13.2 \pm 0.3\,\mathrm{kcal\,mol^{-1}}$; $\Delta S^{\neq} = -3.0 \pm 0.9\,\mathrm{cal\,K^{-1}\,mol^{-1}}$) for the chloro complex have been determined. These results clearly indicate that chloride ions significantly reduce the ability of a metal center to induce *cis–trans* isomerization.

One would assume that C–N bond cleavage occurs only in strongly activated complexes. Thus, addition of Cu(ClO$_4$)$_2$ or Cu(OTf)$_2$ induces methanolysis whereas the corresponding Cd(NO$_3$)$_2$ complexes only isomerize.[5] This result is in complete agreement with the structures of **3**, **6**, and **4**. The case of CuCl$_2$ is more complicated. We have observed the solvolysis of all ligands in MeOH/CH$_2$Cl$_2$ mixtures. The rates are comparable to those observed with Cu(OTf)$_2$. However, according to the structures of [(Benz-bpa)CuCl$_2$] and **2**, one would not expect bond cleavage to be feasible. The apparent contradiction is caused by an initial exchange of coordinated chloride for methanol. This exchange is evident from an induction period observed in kinetic electron paramagnetic resonance (EPR) and UV/Vis experiments. In addition, we were able to crystallize a product which contains a [(bpa)LCuCl]$^+$ cation in the complex salt [(bpa)CuCl]$_2$-[CuCl$_4$].[11] Exchange or removal of chloro ligands from [LCuCl$_2$] makes the metal center more Lewis acidic. Thus, the structure–reactivity relationship discussed above remains valid.

The proposed structure–function relationship may help us to a better understanding of the organic and biological chemistry of tertiary carboxamides. Interesting new insight is expected from the experiments which will be designed to test its validity for a broad range of metal ions and ligands.

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[1] *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science* (Eds.: A. Greenberg, C. M. Breneman, J. F. Liebman), Wiley-VCH, Weinheim, **2000**, p. 47.

[2] C. Cox, T. Lectka, *Acc. Chem. Res.* **2000**, *33*, 849.

[3] M. I. Page, *Acc. Chem. Res.* **1984**, *17*, 144; b) E. C. Constable, *Metals and Ligand Reactivity*, VCH, Weinheim, **1996**, p. 56.

[4] C. Cox, D. Ferraris, N. N. Murthy, T. Lectka, *J. Am. Chem. Soc.* **1996**, *118*, 5332.

[5] N. Niklas, F. Hampel, G. Liehr, A. Zahl, R. Alsfasser, *Chem. Eur. J.* **2001**, *7*, 5135.

[6] a) J.-C. Wang, C.-H. Sun, T. J. Chow, L.-K. Liu, *Acta Crystallogr. Sect. C* **1991**, *47*, 2459; b) F. Muller, G. van Koten, K. Vrieze, B. Krijnan, C. H. Stam, *J. Chem. Soc. Chem. Commun.* **1986**, 150; c) F. Muller, G. van Koten, M. J. A. Kraakman, K. Vrieze, D. Heijdenrijk, M. C. Zoutberg, *Organometallics* **1989**, *8*, 1331; d) F. Muller, G. van Koten, K. Vrieze, D. Heijdenrijk, *Organometallics* **1989**, *8*, 33; e) L. H. Polm, G. van Koten, K. Vrieze, C. H. Stam, W. C. J. van Tunen, *J. Chem. Soc. Chem. Commun.* **1983**, 1177; f) O. C. P. Beers, J. G. P. Delis, W. P. Mul, K. Vrieze, C. J. Elsevier, W. J. J. Smeets, A. L. Spek, *Inorg. Chem.* **1993**, *32*, 3640; g) Z. Chen, L. Luo, S. P. Nolan, J. L. Petersen, M. L. Trudell, *J. Organomet. Chem.* **1997**, *533*, 25; h) P. Maslak, J. J. Sczepanski, M. Parvez, *J. Am. Chem. Soc.* **1991**, *113*, 1062.

[7] Synthesis: The ligands Boc-Gly-bpa and Boc-Leu-bpa, as well as the complexes **2**, **3**, and **4**, were prepared analogously to the procedures in reference [5]. The copper complexes were synthesized in dry CH_3CN. Cadmium complexes were prepared in methanol. All complexes were purified by recrystallization from solvent mixtures. Yields and analytical data: Boc-Gly-bpa: 62%, field-desorption (FD)-MS ($CHCl_3$) m/z (%) = 357 (100) [M^+]. **1**: 54%, FD-MS ($CHCl_3$) m/z (%) = 413 [M^+]. **2**: 68%; elemental analysis calcd (%) for $C_{20}H_{26}Cl_2CuN_4O_3$: C 47.58, H 5.19, N 11.10; found: C 47.45, H 5.32, N 10.85. **3**: 44%; elemental analysis calcd (%) for $C_{19}H_{24}CdN_6O_9$: C 38.49, H 4.08, N 14.18; found: C 38.90, H 4.58, N 14.15. **4**: 67%; elemental analysis calcd (%) for $C_{21}H_{26}CuF_6N_4O_{10}S_2$: C 34.26, H 3.56, N 7.61; found: C 34.13, H 3.54, N 7.46. X-ray crystallography**:** Intensity data: $Mo_{K\alpha}$, $\lambda = 0.71073$ Å; Siemens P4 diffractometer (**1**, **3**, **4**; ω scans, 6° min^{-1}, $T = 200$ K); Nonius Kappa CCD area detector (**2**, $T = 173$ K). Absorption corrections: Empirical ψ scans (**1**, **3**, and **4**), or SCALEPACK (**2**; Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307). Structure solution and refinement: direct methods and full-matrix least-squares on F^2 (**1**, **3**, **4**: SHELXTL NT 5.10, Bruker AXS, **1998**; **2**: SHELXS-97 and SHELXL-97, G. M. Sheldrick, University of Göttingen, Göttingen (Germany), **1997**). Non-H-atoms: anisotropically refined. H-atoms: localized in the density map (isotropically refined), or calculated (riding mode). Details: CCDC-182767 (**1**), CCDC-184027 (**2**), CCDC-182768 (**3**), and CCDC-182769 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk). **1**: $C_{23}H_{32}N_4O_3$; colorless needles from CH_2Cl_2/Et_2O; monoclinic, $P2_1$; $a = 10.185(1)$, $b = 10.174(1)$, $c = 11.597(1)$ Å; $\beta = 100.42(1)°$; $Z = 2$; $V = 1181.9(2)$ Å^3; Θ range = 1.79–28.5°; reflections coll./unique = 6640/6010; data/restr./param. = 6010/1/368; $R1$ [$I > 2\sigma(I)$] = 0.0497, $wR2 = 0.1253$ (all data); largest diff. peak/hole = 0.300/−0.175 e Å^{-3}. **2**: $C_{21}H_{29}Cl_4N_4O_{3.5}$; blue plates from CH_2Cl_2; 4 independent molecules+4 CH_2Cl_2+2 H_2O; monoclinic, $P2_1$; $a = 16.960(1)$, $b = 13.284(1)$, $c = 26.564(1)$ Å; $\beta = 101.60(1)°$; $Z = 8$; $V = 5862.4(2)$ Å^3; Θ range = 2.19–24.11°; reflections coll./unique = 18137/18137; data/restr./param. = 18137/16/1192; $R1$ [$I > 2\sigma(I)$] = 0.0708, $wR2 = 0.2029$ (all data); diff. peak/hole = 1.385/−0.703 e Å^{-3}. **3**: $C_{19}H_{24}CdN_6O_9 \cdot 2\,CH_2Cl_2$; colorless plates from CH_2Cl_2/MeOH/Et_2O; monoclinic, $C2/c$; $a = 22.364(3)$, $b = 16.962(2)$, $c = 17.266(2)$ Å; $\beta = 110.75(1)°$; $Z = 8$; $V = 6125(1)$ Å^3; Θ range = 1.76–27.0°; reflections coll./unique = 8932/6684; data/restr./param. = 6684/9/471; $R1$ [$I > 2\sigma(I)$] = 0.0564, $wR2 = 0.1153$ (all data); diff. peak/hole = 0.557/−0.668 e Å^{-3}. **4**: $C_{21}H_{26}CuF_6N_4O_{10}S_2 \cdot CH_2Cl_2$; blue needles from CH_2Cl_2; monoclinic, $P2_1/c$; $a = 12.296(1)$, $b = 15.165(3)$, $c = 18.470(3)$ Å; $\beta = 104.83(1)°$; $Z = 4$; $V = 3329.4(9)$ Å^3; Θ range = 1.76–27.01°; reflections coll./unique = 8915/7260; data/restr./param. = 7260/1/434; $R1$ [$I > 2\sigma(I)$] = 0.0519, $wR2 = 0.1381$ (all data); diff. peak/hole = 0.486/−0.533 e Å^{-3}.

[8] F. K. Winkler, J. D. Dunitz, *J. Mol. Biol.* **1971**, *59*, 169.

[9] a) E. Chelain, R. Goumont, L. Hamon, A. Parlier, M. Rudler, H. Rudler, J.-C. Daran, J. Vaissermann, *J. Am. Chem. Soc.* **1992**, *114*, 8088; b) M. Rosoff, M. Rudler, J. Vaissermann, *J. Am. Chem. Soc.* **1992**, *114*, 8088; c) J. A. King, Jr., G. L. Bryant, Jr., *Acta Crystallogr. Sect. C* **1991**, *47*, 2249.

[10] Temperature-dependent ^1H NMR spectra of the complexes [(Boc-Ala-bpa)$(H_2O)_2$Zn](OTf)$_2$ and [(Boc-Ala-bpa)ZnCl]$_2$[ZnCl$_4$] were measured in dry [D$_6$]acetone. Details of the method are described in reference [5].

[11] N. Niklas, F. W. Heinemann, unpublished results. Cleavage experiments were performed using solutions of the respective pure metal complex in methanol/dichloromethane (1:0, 4:1, 3:2, 1:1) mixtures assuring pseudo-first-order conditions.