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Pyramidalization/twisting of the amide functional group *via* remote steric congestion triggered by metal coordination[†]

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For decades, the planarity of the amide functional group has garnered sustained interest in organic chemistry, enticing chemists to deform its usually characteristic high-fidelity plane. As opposed to the construction of amides that are distorted by imposing rigid covalent bond assemblies, we demonstrate herein the deformation of the amide plane through increased steric bulk in the periphery of the amide moiety, which is induced by coordination to metal cations. A crystallographic analysis revealed that the thus obtained amides exhibit significant pyramidalization and twisting upon coordination to the metals, while the amide functional group remained intact. The observed deformation, which should be attributed to through-space interactions, substantially enhanced the solvolytic cleavage of the amide, providing compelling evidence that temporary crowding in the periphery of the amide functional group may be used to control the reactivity of amides.

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Introduction

The amide bond is characterized by its thermodynamic stability and kinetic tolerance toward hydrolytic cleavage, which arises from conjugation via the planar O-C-N array.1 Under neutral conditions in aqueous solution at ambient temperature, nonactivated amide bonds have a half-life of ca. 100 years.² This high stability is usually attributed to the resonance interaction between the n_N and $\pi^*_{C=0}$ orbitals, which occurs most efficiently in a planar geometry with a shortened and stronger C-N bond. Therefore, amide bonds are commonly used as a robust structural motif (e.g. in synthetic polymers), and the hydrolysis of the amide bond in a practical timescale requires general harsh conditions (e.g. high or low pH at elevated temperatures). The deformation of the co-planarity of the amide bond represents an intuitive strategy to lower its robustness, which was initially proposed by Lukeš in 1938, who presented a model of strained "twisted amides" with a nitrogen atom at the bridgehead position.3 The longstanding pursuit toward twisted amides led to the identification of extreme examples of fullycharacterized and highly distorted amides (A-C),^{4,5} which exhibited twist angles (τ) and pyramidalization (χ_N) values at the nitrogen, defined by Winkler and Dunitz,⁶ of ca. 90° and 60°, respectively (Fig. 1a). The prime importance of the resonance interaction for stabilizing the amide bond manifests in the case

of **B**, which lacks an amide resonance, and exhibits a remarkably short half-life of <15 s in water.^{5d} Besides these extreme examples, a number of amides that exhibit unusual τ and χ_N values have been reported, typically using covalently distorted bridged lactam architectures.^{1,7,8} These structurally intriguing bonds may not only be of fundamental academic interest, but also of significant applied importance in life science, considering that amides constitute the primary backbone of proteins.



Fig. 1 (a) Extreme examples of highly distorted amides in a covalent framework, (b) deformation/activation of amides *via* the coordination of the amide nitrogen to metals, and (c) the distortion of the amide induced by peripheral steric constraints upon the coordination to metal cations.

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Indeed, the involvement of distorted amides has been invoked for enzymatic transformations.^{1,9} In this context, we were interested in distorting the amide planarity using an external trigger; more specifically, instead of constructing covalently assembled distorted amides, we aimed at inducing the amide deformation via temporary non-covalent interactions. Although several reports link the deformation and activation (e.g. hydrolysis and E/Z isomerization) of amides to the coordination of the amide nitrogen to metal cations (Fig. 1b),^{10,11} substantial amide deformation without direct coordination of the amide nitrogen or oxygen has, to the best of our knowledge, not yet been reported. Herein, we show that it is possible to induce significant pyramidalization and twisting of the amide functional group by remote steric congestion upon the coordination of the substituents attached to the amide nitrogen to a metal cation (Fig. 1c). A crystallographic analysis revealed that the substantial deformation of the amide planarity occurs without direct coordination of the amide. Peripheral crowding being a viable strategy to weaken the amide linkage is supported by the observed rapid solvolysis of the thus obtained distorted amides.12

Results and discussion

We began our study by designing a suitable amide with metalcoordination sites that may be able to create a steric bias upon the addition of appropriate metal cations. As the metal coordination should be orthogonal to the amide functional group, we selected a combination of azophilic metals and nitrogenbased bidentate coordination sites. Fig. 2a shows the generic structure of amide 1 with a 3-substituted-2-hydrazonopyridine moiety, which contains an amide $\left(N_{Am}\right)$ and an adjacent imine (hydrazone of benzophenone; N_{Im}) functional group. It should be noted that 1 prefers a planar amide structure, which is achieved by tilting the pyridine ring and the imine along the C(pyridine)-N_{Am} and N_{Am}-N_{Im} single bonds, respectively (Fig. 2a, I). Conversely, we anticipated that the addition of azophilic cations (M) should induce a bidentate chelation through N_{Im} and N_{Pv} , thus affording a rigid and planar 5-membered cycle. This conformational change should provoke



 $B^2 = Me$

Ρĥ

1b: $\mathbb{R}^1 = (E)$ -1-propen-1-yl **1c**: $\mathbb{R}^1 = (E)$ -1-propen-1-yl

Ēh

 $R^2 = 2,6-Me_2C_6H_3$

both the bulky benzophenone imine and the R^2 group on the pyridine ring to swing close to the amide, thus compromising the amide planarity *via* through-space steric bias (Fig. 2a, II). With this blueprint in hand, we set out to synthesize three derivatives, which contain R^2 groups of varying steric bulk: H (1a), Me (1b), and 2,6-dimethylphenyl (1c) (Fig. 2b).¹³ While 1b and 1c were synthesized as (*E*)-crotonyl amides, 1a was based on a *p*-fluorocinnamoyl amide in order to increase its crystallinity.

The coordination of **1a** to azophilic Pd²⁺ cations, which favor a square-planar coordination mode, afforded in aprotic solvents the corresponding complexes. The formation of these complexes, which are thermodynamically stable under anhydrous conditions at ambient temperature, was monitored using ¹H and ¹³C NMR spectroscopy. The NMR analysis revealed that 1a/Pd (1a : Pd = 1 : 1) and $(1a)_2/Pd$ (1a : Pd = 2 : 1) complexes were formed depending on the ratio of 1a and $[Pd(CH_3CN)_4]$ - $(BF_4)_2$ (Fig. 3). In CD₃CN, a 1:1 mixture of 1a and [Pd(CH₃- $CN_4(BF_4)_2$ favored the formation of 1a/Pd. The observed NOE signals between He and Hd are consistent with the anticipated coordination mode via N_{py} and N_{Im}, in which the amide nitrogen NAm is left uncoordinated (Fig. 3a and b).14 The characteristic downfield shift of the β -olefinic proton H_f upon complexation implied an increased polarization of the C=O bond via distortion of the amide moiety. The formation of the homoleptic complex (1a)₂/Pd from bidentate coordination via N_{pv} and N_{Im} induced similar spectral changes in the ¹H and ¹³C NMR spectra, together with diagnostic NOE signals between the two 1a fragments (H_a and H_i; Fig. 3c). For $(1a)_2/Pd$, the observed downfield shift of H_f was even more pronounced, which was tentatively ascribed to the deshielding effect of the phenyl group on the opposite 1a/Pd fragment (Fig. 3b and c and 4d; vide infra). Unfortunately, the chemical shifts in the ¹³C NMR spectra were not straightforward to interpret (Fig. 3d-f); in contrast to the rather subtle changes to the resonances for the amide carbonyl (C_{Am}) moiety, the signal for the imino carbonyl (C_{Im}) fragment experienced a substantial downfield shift. In the Ph group-rich environment of these complexes, the downfield shift of the amide carbonyl via distortion and the imino carbonyl via direct coordination might be increased and decreased, respectively, by shielding and deshielding effects from nearby multiple bonds (vide infra).

The distortion of the amide plane in 1a by peripheral crowding was further examined via single-crystal X-ray diffraction analysis (Fig. 4a and d). Single crystals of amide 1a and its Pd complex (1a)₂/Pd were obtained from acetone/hexane, and their solid-state structures are shown in Fig. 4a and d, while selected bond lengths and distortion parameters are summarized in Table 1. In 1a, the pyridyl and the hydrazine group occupy the far side of the amide group in order to minimize steric repulsion. The amide group exhibited a negligible twist angle ($\tau = 3.0^{\circ}$), whereas partial pyramidalization was observed for the amide nitrogen ($\chi_{\rm N} = 19.6^{\circ}$). In stark contrast, the complex $(1a)_2/Pd$ exhibited a significant pyramidalization ($\chi_N =$ 54.1°) of the amide nitrogen, and the expected bidentate coordination via Npy and NIm was confirmed. The pyramidalization of the amide nitrogen, in combination with a twisting of the amide ($\tau = 12.1^{\circ}$) resulted in a diminished amide conjugation,

 $Ar = 4 - FC_6H_4$ Ph

 $B^{2} = H$

1a: R¹ = (E)-β-4-F-styryl

(a)

(b)



Fig. 3 NMR analysis of **1a** and its Pd^{2+} complexes in CD_3CN . (a and d) ¹H and ¹³C NMR spectra of **1a**. (b and e) ¹H and ¹³C NMR spectra of a 1 : 1 mixture of **1a** and $[Pd(CH_3CN)_4](BF_4)_2$. (c and f) ¹H and ¹³C NMR spectra of a 2 : 1 mixture of **1a** and $[Pd(CH_3CN)_4](BF_4)_2$.



Fig. 4 Crystal structures of amides 1a-c (a-c) and of their Pd complexes $(1a)_2$ /Pd, $(1b)_2$ /Pd, and $(1c)_2$ /Pd (d-f). For the Pd complexes, hydrogen atoms and BF₄⁻ anions are omitted for clarity. In (d)–(f), the amide fragments are highlighted. Color code: white = hydrogen, gray = carbon, blue = nitrogen, red = oxygen, sky blue = fluorine, and pink = palladium. In (e) and (f), characteristic NOE signals between protons observed in the NMR analysis in solution are highlighted.

(cc)

Table 1	Selected ¹	³ C NMR	shifts and	structural	parameters	for the c	rystal stru	ctures of 1	la–c and	l their P	d complexes	(1a) ₂ /Pc	d-(1c)2	/Pc
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	¹³ C NMR	^a [ppm]		Distortion parameters ^b					
	C _{Am}	C _{Im}	$N-C_{Am}(=0)$	C _{Am} =0	Pd-N _{Im}	Pd-N _{Py}	χ_{N}	$\chi_{\rm C}$	τ
1a	166.2	170.5	1.386(1)	1.227(1)			19.6°	1.8°	1.8°
(1a) ₂ /Pd	169.4	189.6	1.425(6)	1.212(6)	2.003(5)	2.024(4)	54.1°	1.4°	12.2°
1b	168.1	161.9	1.394(3)	1.224(3)			28.3°	2.7°	4.1°
(1b) ₂ /Pd	169.0	189.8	1.421(7)	1.216(6)	1.996(3)	2.022(4)	56.3°	3.1°	19.3°
1c	163.8	169.8	1.407(3)	1.213(4)			43.8°	4.3°	19.2°
$(\mathbf{1c})_2/\mathrm{Pd}$	171.0	187.9	1.444(9)	1.211(9)	2.019(5)	2.018(5)	51.9°	0.5°	4.3°

^{*a*} Chemical shifts in CD₃CN. ^{*b*} χ_N , χ_C , and τ denote the pyramidalization of the amide nitrogen atom, the carbonyl carbon atom, and the twist angle, respectively.⁶

which is consistent with the observed decreased $C_{Am}=O$ and increased N– $C_{Am}(=O)$ bond lengths (Table 1). It should be noted here that the pyramidalization and twisting do not originate from the direct coordination to the amide functional group, but from the steric congestion in the periphery of the amide functional group.^{10b,d} Similar to other covalently assembled distorted amides, the pyramidalization of the carbonyl carbon (χ_C) was negligible for both **1a** and (**1a**)₂/Pd. The unusual downfield shift of the imino carbonyl (C_{Im}) resonance in the ¹³C NMR spectrum may arise from the deshielding effects of the amide C=O bond in close proximity (Fig. 3d and f, and Table 1). Similarly, the orientation of the Ph groups in (**1a**)₂/Pd most likely influences the chemical shift of the amide carbonyl carbon (C_{Am}) and the β -olefinic hydrogen H_f (Fig. 3c, e and f and Table 1).

The crystallographic analysis of amides 1b and 1c as well as of their Pd²⁺ complexes revealed an identical coordination mode via N_{pv} and N_{Im}, as well as distortion of the amide moiety (Fig. 4b, c, e and f).¹⁵ Although the free amides 1b and 1c showed only a moderate pyramidalization of the amide nitrogen (χ_N), presumably due to the increased steric demand of R^2 (1a: $R^2 = H$, 1b: $R^2 = Me$, 1c: $R^2 = 2$,6-dimethylphenyl), the pyramidalization was significantly enhanced upon coordination to Pd2+. The elongated CAm=O and compressed N-C_{Am}(=O) bonds suggest a diminished amide conjugation (Table 1). It should also be noted that all three complexes show $\gamma_{\rm N}$ values beyond 50°. Similar spectral (¹H and ¹³C NMR) patterns were observed upon complexation of 1b and 1c. More importantly, characteristic NOE signals were observed between the two amide fragments in $(1b)_2/Pd$ and $(1c)_2/Pd$, which provides compelling evidence for significant N-pyramidalization in solution (Fig. 4e and f).¹⁶ For 1c, some anomalies were observed: while 1a and 1b are E-amides in their free form and afford homoleptic complexes $(1)_2$ /Pd with Z-amides, the structural behavior of **1c** is antipodal. Moreover, the twist angle (τ) decreased upon the coordination of 1c to Pd^{2+} , whereas the planarity of the amide moiety was substantially disrupted by considerable pyramidalization. For amide 1c, a 1 : 1 Pd complex (1c/Pd) could be isolated, which exhibited an identical coordination mode with amide distortion ($\chi_{\rm N} = 57.5^{\circ}$),¹⁷ thus supporting the structure that was assigned to 1a/Pd (Fig. 3b and e) on the basis of the NMR analysis.

The sterically driven distortion of the amide moieties led to a substantially enhanced rate of solvolytic cleavage under neutral and ambient conditions.^{10a,c,d,f-i} Amides 1a-c exhibited high levels of stability toward hydrolytic cleavage under such conditions, and no methanolysis was detected in CD₃OD. However, in the presence of [Pd(CH₃CN)₄](BF₄)₂, 1a-c were rapidly converted to the corresponding CD₃ esters 2 and 3 under otherwise identical conditions (Fig. 5). Considering the aforementioned NMR and crystallographic analyses, this reactivity should be interpreted in terms of an electrophilic activation of the amide moiety in solution, which is most likely caused by a diminished amide conjugation in response to peripheral steric congestion.18 In contrast, amide 1d, which lacks the pyridine unit for chelating complexation with Pd²⁺, did not produce any detectable quantity of the corresponding ester, thus further supporting the importance of the peripheral congestion. While $(1c)_2/Pd$ exhibited a small twist angle ($\tau =$ 4.3°), the methanolysis rate for 1c was significantly increased, suggesting that the pyramidalization of the amide nitrogen atom is predominantly responsible for the electrophilic



Fig. 5 Methanolysis of 1a-d in the presence of 1 equiv. of $[Pd(CH_3-CN)_4](BF_4)_2$ at 27 $^\circ C$ monitored using 1H NMR spectroscopy.



Fig. 6 Crystal structure of $(1a)_2/Zn$ with selected structural parameters. Hydrogen atoms are omitted for clarity. Color code: gray = carbon, blue = nitrogen, red = oxygen, sky blue = fluorine, yellow = sulfur, and purple = zinc.

activation. The chelating unit liberated by the methanolysis was found to strongly bind to Pd^{2+} , and the slow association/ dissociation kinetics of these amides and Pd^{2+} prevented a catalytic methanolysis.^{17,19} As is evident from the averaged ¹H NMR spectrum, Zn^{2+} showed faster complexation kinetics in comparison,¹⁷ which allows the methanolysis to proceed catalytically, converting amide **1a** to CD₃ ester **2** in a 92% yield using 5 mol% of Zn(OTf)₂ (eqn (1)).²⁰ The crystallographic analysis of (**1a**)₂/Zn revealed a coordination *via* N_{Py} and N_{Im}, which corroborates that a sterically driven amide activation should also be operative in the case of complexation with Zn²⁺ (Fig. 6).²¹



Conclusions

In conclusion, we demonstrated that peripheral steric constraint may induce the pyramidalization and twisting of the amide functional group. The results summarized herein represent proof-of-concept that the distortion of the amide moiety can be induced in an indirect and temporary fashion, which stands in contrast to the previously reported permanent distortion by covalent bonds or to the temporary distortion via the direct coordination of the amide functional group. The crystallographic analysis of the Pd²⁺ and Zn²⁺ complexes of 1 revealed the presence of distorted amides in the solid state, and the observed coordination patterns, as well as the pyramidalization of the amide nitrogen were confirmed in solution via NMR analysis. The distortion of the amide moiety in solution was further supported by the enhanced solvolysis rates in the presence of metal cations. Further studies to transfer the present results to the chemoselective activation of simple

amides *via* peripheral crowding are currently under way and will be reported in due course.

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- 20 No methanolysis was detected for TfOH (10 equiv.) in $\rm CD_3OD.$
- 21 Crystal structures with different structural parameters were found in the unit cell. For full structural data, see ESI.†