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An Efficient Computational Model to Predict Protonation at the Amide Nitrogen and Reactivity along the C–N Rotational Pathway

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Abstract

N-protonation of amides is critical in numerous biological processes, including amide bonds proteolysis and protein folding, as well as in organic synthesis as a method to activate amide bonds towards unconventional reactivity. A computational model enabling prediction of protonation at the amide bond nitrogen atom along the C–N rotational pathway is reported. Notably, this study provides a blueprint for the rational design and application of amides with a controlled degree of rotation in synthetic chemistry and biology.

The amide bond is one of the most important functional groups in chemistry and biology.¹ The $n_N \rightarrow \pi^*_{C=O}$ conjugation and the resulting planarity controls the vast majority of chemico-physical properties of amides (Fig. 1).² In contrast to planar amides, distorted amides have received much less attention³ despite their profound implications for structure,⁴ reactivity⁵ and wide significance in biology and medicinal chemistry⁶ (amide bond proteolysis,^{6a} isomerization of cis-trans peptides,^{6b} protein splicing,^{6c} β -lactam antibiotics,^{6d} conformational preferences of peptides,^{6e} generation of new pharmacophores and lead structures^{6f}). More fundamentally, non-planar amides that are characterized by ground-state distortion provide crucial insight into the amide bond resonance, including the long-standing question of structural factors governing the O- vs. N-protonation switch.⁷ N-protonation of amides is critical in numerous biological processes, including amide bonds proteolysis⁸ and protein folding,⁹ as well as in organic synthesis as a method to activate amide bonds towards unconventional reactivity.^{10,11} N-protonation results in disruption of the amide bond resonance, which has been used to catalyze isomerization of amides¹² and promote reactions of C–N bonds adjacent to the carbonyl group.^{10,11} At present, the structural factors that govern the N- vs. O-protonation aptitude are poorly understood.

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Herein, we present an efficient computational model that allows to predict the likelihood that a given amide can be protonated at the nitrogen atom, and disclose how one may predict the reactive properties of amides along the C–N rotational pathway from simple calculation of structural properties. This approach makes the amide bond distortion models developed by Greenberg¹³ generally applicable to accurately predict the reactive properties of amide linkages.^{1–12} We expect that these findings will enable synthetic and medicinal chemists to utilize amides with a controlled degree of rotation as versatile intermediates and target lead structures in organic synthesis.^{14,15}

We designed a model series of amides in which the overall sum of carbon atoms forming the core scaffold is between five and ten (Scheme 1). These compounds are based on the highly promising one-carbon bridged 1-azabicyclo scaffold (Fig 1c).^{10,11} The compounds have been selected on the basis of their synthetic accessibility and distortion range of amide bonds. The conceptual advantage of using one-carbon bridged twisted amides (cf. two-carbon or larger bridge analogues)^{13a,b} stems from their better hydrolytic profile,¹⁶ their successful use as a platform for discovery of new reactivity of amide bonds,^{10,11} and accessibility of diverse ring systems that span the whole spectrum of the amide bond distortion.¹⁷ Crucially, our approach determines the relationship between distortion and energetic parameters in readily-accessible amide models that (i) are non-planar in the ground-state conformation;^{1–5} and (ii) have already been synthesized in a laboratory environment and validated experimentally (cf. two-carbon or larger bridge analogues).^{13a,b} As a key design element, we hypothesized that mapping the amide bond distortion along energetic parameters of amide bonds *over sufficiently large distortion range* would allow for elucidating the role of strain and the $n_N \rightarrow \pi^*_{C=O}$ delocalization on the N-protonation of amide linkages.

We first established geometric changes that occur upon the amide bond rotation in the series.¹⁸ Total energies as well as selected structural parameters are listed in Table 1. The results validate the use of small- and medium-sized one-carbon bridged twisted amides^{10,11} as models for a systematic study of geometric changes that occur during the amide bond rotation.^{1–12} The selected set covers the whole spectrum of the amide bond distortion geometries. The twist angle changes from essentially planar to fully perpendicular ($\tau = 11.32\text{--}90.0^\circ$), while the pyramidalization at nitrogen varies from essentially sp^2 to fully sp^3 hybridized nitrogen ($\chi_N = 5.99\text{--}71.44^\circ$). In contrast, the pyramidalization at carbon remains relatively unchanged ($\chi_C = 0.0\text{--}15.42^\circ$) with the carbonyl carbon essentially planar in the series, which is consistent with previous observations regarding amide bond distortion.^{3,4} In agreement with the amide bond distortion parameters, the length of the N–C(O) bond varies between 1.474 Å and 1.365 Å, while the length of the C=O bond is between 1.201 Å and 1.233 Å.

The approach verifies structural changes that occur with the N–C(O) bond rotation as a function of the twist angle and the pyramidalization at nitrogen. *Most importantly, a plot of N–C(O) bond length versus the sum of twist angles and nitrogen pyramidalization ($\Sigma\tau + \chi_N$) gives an excellent linear correlation over the observed range of amide bond geometries ($R^2 = 0.97$, Fig. 2). Plots of N–C(O) bond length versus twist angle ($R^2 = 0.87$) and nitrogen pyramidalization ($R^2 = 0.88$) give scattered correlations in the series (not shown). In*

agreement with the classical resonance,^{1,2,7c} disruption of the $n_N \rightarrow \pi^*_{C=O}$ delocalization results in a significant lengthening of the N–C(O) bond, while the C=O bond experiences minor shortening.

Importantly, the results demonstrate that description of the amide bond distortion by additive twist angle/pyramidalization at nitrogen parameters (i.e. the sum of twist and nitrogen pyramidalization angles ($\Sigma\tau+\chi_N$)) provides a more accurate representation of the geometric properties than the twist angle or the pyramidalization at nitrogen alone. Previous studies demonstrated that 1-azabicyclo[3.3.1]nonan-2-one (X-ray of a phenyl analogue: $\tau = 20.8^\circ$; $\chi_N = 48.8^\circ$; $\chi_C = 5.9^\circ$; $\Sigma\tau+\chi_N = 69.6^\circ$)^{10c} and derivatives of one-carbon bridged amides containing the [4.3.1] ring system (X-ray of an aryl analogue: $\tau = 42.8^\circ$; $\chi_N = 34.1^\circ$; $\chi_C = 16.5^\circ$; $\Sigma\tau+\chi_N = 76.9^\circ$)^{10b} feature amide bonds that are predominantly protonated at nitrogen.^{10,11} It was thus proposed that a twist angle of as low as approx. 40–50° may be sufficient to promote N-protonation of amide bonds.^{10a–c} Additionally, earlier reports by Brown demonstrated that extended 2-quinuclidone analogues favor N-alkylation ([3.2.2] amide ring system, X-ray: $\tau = 33.2^\circ$; $\chi_N = 52.8^\circ$; $\chi_C = 11.0^\circ$; $\Sigma\tau+\chi_N = 86.0^\circ$) or O-alkylation ([3.3.2] ring system, X-ray: $\tau = 15.3^\circ$; $\chi_N = 38.6^\circ$; $\chi_C = 4.3^\circ$; $\Sigma\tau+\chi_N = 53.9^\circ$);^{3a} detailed experimental results not disclosed. The additive ($\Sigma\tau+\chi_N$) parameter normalizes these results and reveals that a ($\Sigma\tau+\chi_N$) value of 60–70° appears to be close to a barrier between N- vs. O-protonation of amides. Note that this value is much lower than the distortion that would correspond to a fully perpendicular amide bond ($\Sigma\tau+\chi_N = 150.0^\circ$), which has been proposed to be required for N-protonation.^{11a–c,3} In addition, these structural features indicate that an increase of the amide bond distortion results in a significant lengthening of the N–C(O) bond, while the C=O bond remains relatively unchanged, providing a strong support for the classical resonance.^{1,2,7c}

Having validated our model, we addressed the key question of structural factors governing the O- vs. N-protonation switch in amides. As predicted by the resonance, planar amides undergo protonation at oxygen (formamide: O- vs. N-protonation is favored by ca. 11.5 kcal/mol).^{1,2} O-protonation of planar amides shortens the N–C(O) bond and significantly reinforces the double bond character of amides (RE of O-protonated amides of ca. 40 kcal/mol).¹⁹

Table 2 lists proton affinities (PA) and differences between N- and O-protonation affinities (PA) in the series of studied lactams.^{13a,b} *Most importantly, there is an excellent linear correlation between proton affinity difference and the sum of twist and pyramidalization at nitrogen angles ($R^2 = 0.98$, Fig. 3),* which can be compared with the correlation between proton affinity difference and twist angles ($R^2 = 0.90$) and the correlation between proton affinity difference and pyramidalization at nitrogen angles ($R^2 = 0.86$). This finding validates the use of additive descriptors of the geometric transformations of amide bonds to predict reactive properties of non-planar amides (vide supra). Importantly, this equation provides a very useful tool to predict N- vs. O-protonation sites of amides as only a single determination of the amide bond geometry is required from the X-ray crystallography or calculations to provide a reliable prediction of PA.^{1,2} Since our calculations have already shown that ($\Sigma\tau+\chi_N$) can be correlated with the N–C(O) bond lengths (vide supra), this can be used in conjunction with amide bond distortion parameters to accurately predict PA in

one-carbon bridged amides.²⁰ Overall, this finding provides a compelling argument to the long-standing question of structural factors governing the O- vs. N-protonation switch in non-planar lactams, and determines that ($\Sigma\tau+\chi_N$) of ca. 50-60° should be sufficient to promote N-protonation of amides.^{1,3-5,10,11,13} The N- vs. O-cross-over point in the studied series of lactams is located around the geometry region defined by the [5.4.1] ring system.

In conclusion, we have presented an efficient model enabling to predict the likelihood that a given amide can be protonated at the nitrogen atom. This study provides a compelling answer to the long-standing question of structural factors governing the N- vs. O-protonation switch in non-planar amides.^{1,2,10,11,13} The ($\Sigma\tau+\chi_N$) value of around 50-60° appears to be close to a barrier between N- vs. O-protonation of amides. This is much lower than the distortion that would correspond to a fully perpendicular amide bond ($\Sigma\tau+\chi_N = 150.0^\circ$), which has been proposed to be required for efficient N-protonation. Given the availability of distorted amides in moderate distortion range,³⁻⁵ our data suggest that a wide range of amide analogues can be readily applied for probing the unconventional reactivity of amide bonds via N-protonation, including in biological contexts. We expect that the understanding provided for the amide bond protonation will enable the rational application of non-planar amides with a controlled-degree of rotation in organic synthesis and medicinal chemistry. Further studies on the effect of functional groups on the N-/O-protonation aptitude of non-planar amides are ongoing and these results will be reported shortly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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18. Ab initio molecular orbital calculations were carried out at the readily accessible and practical MP2/6-311++G(d,p) level. This method has been shown to be accurate in predicting properties and resonance energies of amides^{2c,13a} (e.g. resonance energy, N,N-dimethyl-acetamide: experimental value of 16.8±1.3 kcal/mol; calculated value of 16.4 kcal/mol). This method was further verified by obtaining good correlations between the calculated structures and available X-ray structures in the series (see the Electronic Supplementary Information, ESI, for details).
19. Only few examples of N-protonated amides have been reported to date. For lead references, see: Cox C, Wack H, Lectka T. *Angew Chem, Int Ed*. 1999; 38:798. (b) Ref. 11b.
20. A plot of PA to ($\Sigma\tau+\chi_N$) for larger bridge 2-quinuclidone analogues reported by Greenberg^{13b} gives a linear correlation ($R^2 = 0.94$), with a cross-over point around the [3.3.1] derivative ($(\Sigma\tau+\chi_N) = 71.8^\circ$).^{13b} Note that in the studied series of amides, τ gives a more reliable prediction of PA than χ_N if these parameters are used separately.

A. Amide bond resonance

B. General methods to achieve non-planarity of amide bonds

C. Restricting conformation of non-planar amides as bridged lactams

Fig. 1.

(a) Resonance description of amides. (b) Geometric changes resulting in non-planarity. (c) Conformational restriction of amides.

Fig. 2. Correlation of N–C(O) bond length [Å] to the sum of twist and pyramidalization at nitrogen angles ($\Sigma\tau + \chi_N$).

Fig. 3.
Correlation of ΔPA to the sum of twist and pyramidalization at nitrogen angles ($\Sigma\tau+\chi_N$).

Scheme 1.

Structures of model lactams calculated in the current study.

Table 1

Energies and Selected Geometric Parameters^a

Amide	$-E_T$ (corr) [au]	N-C(O) [Å]	C=O [Å]	τ [deg]	χ_N [deg]
A	362.90686	1.474	1.201	90.00	71.44
B	402.08837	1.447	1.209	65.40	63.10
C	441.25388	1.446	1.212	90.00	53.20
D	402.07156	1.422	1.207	38.23	57.48
E	441.26376	1.401	1.218	36.90	47.69
F	480.42708	1.391	1.225	41.78	36.01
G	519.59194	1.409	1.223	47.52	41.78
H	480.44070	1.381	1.223	21.97	32.11
I	519.59957	1.372	1.230	25.53	17.39
J	519.60699	1.365	1.228	11.32	5.99
K	558.75395	1.378	1.231	37.94	14.10
L	558.77041	1.367	1.233	18.84	12.19

^aComputed using MP2/6-311++G(d,p) level. See ESI for full details.

Table 2
Proton Affinities and Differences in Proton Affinities^a

Entry	Amide	N _{PA} [kcal/mol]	O _{PA} [kcal/mol]	PA [kcal/mol]
1	A	223.9	186.4	37.5
2	B	224.6	200.9	23.7
3	C	227.9	202.6	25.4
4	D	218.7	204.6	14.2
5	E	219.1	211.5	7.7
6	F	220.7	216.4	4.3
7	G	225.5	215.0	10.6
8	H	211.8	217.0	-5.3
9	I	215.2	219.7	-4.5
10	J	206.0	218.8	-12.8
11	K	220.7	219.8	0.9
12	L	209.2	222.0	-12.8

^a Computed using MP2/6-311++G(d,p) level. See ESI for full details.