# Tröger's Base Twisted Amides: High Amide Bond Twist and N-/O-Protonation Aptitude

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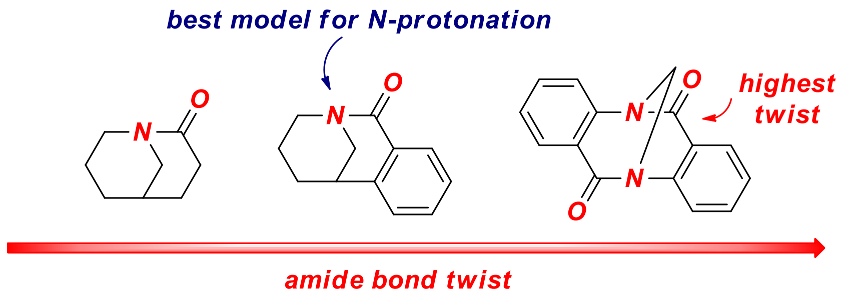
## Abstract



■ Tröger's base twisted amides: highly twisted bridged lactams

Tröger’s base twisted amides have emerged as attractive scaffolds to readily achieve substantial non-planarity of the amide bond in a bicyclic lactam framework. Herein, we report structures and proton affinities of a diverse set of Tröger’s base twisted amides and compare them with related non-planar bridged lactams. The data demonstrate that Tröger’s base twisted amides embedded in a [3.3.1] scaffold are among the most twisted bridged lactams prepared to date. Intriguingly, while these amides also favor N-protonation, our data show that the best model for probing N-protonation aptitude in the series of non-planar amides are less twisted benzofused 1-azabicyclo[3.3.1]nonan-2-one derivatives. This work (1) provides the understanding for future design of non-planar bridged lactams to directly access N-protonated amide bonds, (2) validates the use of the additive Winkler-Dunitz distortion parameter, and (3) emphasizes the importance of peripheral modification to modulate properties of non-planar amides.

## 1. Introduction

Twisted bridged lactams represent one of the most effective and wide-ranging methods to freeze the otherwise unstable conformations of the non-planar amide bond (Figure 1A).[1–6] While 2-quinuclidone[7] and 1-aza-2-adamantanone[8] ring systems have been impressively applied to achieve full distortion of the amide bond, only very limited scaffolds have been prepared that enforce substantial non-planarity of the amide bond other than these two now classic ring systems.[9,10]

Stimulated by our interest in the properties of non-planar cyclic[11] and acyclic[12] amides, we were attracted by the recently reported examples of Tröger's base twisted amides[13,14] as models for a substantial twist of the amide bond. In 2012, Wärnmark and co-workers[13] demonstrated that direct oxidation of the venerable Tröger's base scaffold[15] can be used to afford a twisted bis-amide with a remarkable twist of the amide bond (Figure 1B, $\tau = 41.0°$, $\chi_N = 57.9°$, N–C(O) = 1.430 Å, C=O = 1.210 Å). In 2017, Cvengroš and co-workers[14] reported the synthesis of an extended Tröger's base twisted amide using one-step oxidation of the ethano-Tröger's base[16] (Figure 1B, $\tau = 29.8°$, $\chi_N = 45.5°$, N–C(O) = 1.401 Å, C=O = 1.215 Å). Since the Tröger's base twisted amides reported by Wärnmark and Cvengroš (1) represent rare examples of significantly twisted amides with the additive Winkler-Dunitz parameter[17] approaching 100° ($(\tau+\chi_N) = 98.9°$ and 75.3°, respectively), and in addition, (2) are prepared by a more facile and faster approach[13,14] that related twisted amides,[3,9,10] a better understanding of the structures and energetics could facilitate the design of novel twisted amides of both theoretical and practical synthetic interest.[1–6,18–22] In this manuscript, we report a computational investigation into the structures and proton affinities of a diverse set of Tröger's base twisted amides and compare them with related non-planar bridged lactams.

Notable features of our findings include: (1) we demonstrate that Tröger's base twisted amides are significantly more twisted than related 1-azabicyclo[3.3.1]nonan-2-one derivatives; (2) Tröger's base twisted amides favor protonation at the nitrogen atom, however, our study shows that these compounds are less efficient in probing N-protonation aptitude of non-planar amides than related 1-

azabicyclo[3.3.1]nonan-2-one derivatives; (3) the study validates the use of the additive Winkler-Dunitz parameter. Collectively, the data provide the understanding for future design of non-planar bridged lactams to directly access N-protonated amide bonds, and will facilitate experimental efforts in predicting twist of non-planar amides that are energetically close to the N-/O-protonation cross-over point.

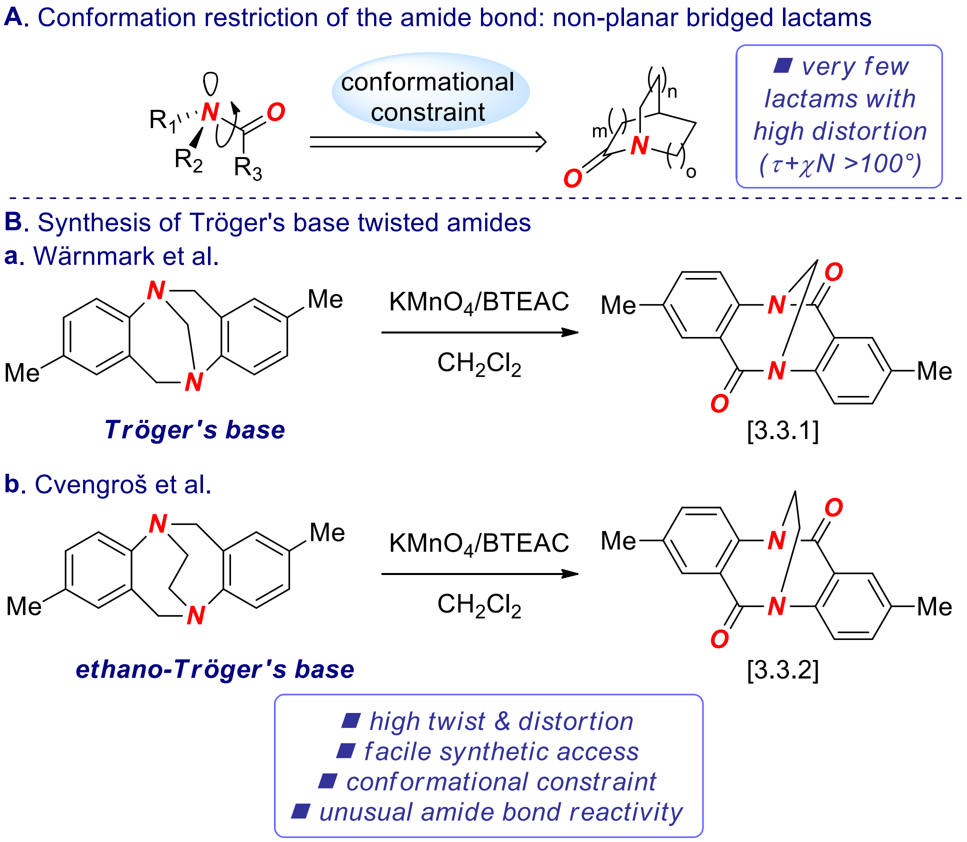


**Figure 1.** (a) Conformational restriction of the amide bond. (b) Tröger's base twisted amides.

## 2. Results and Discussion

Twisted amides selected for the study are shown in Figure 2. These amides have been selected on the basis of their synthetic accessibility and distortion range of the amide bond. Structure and energetics of 1-azabicyclo[3.3.1]nonan-2-one (**1**) have been studied in the classic computational studies on bridged lactams by Greenberg and co-workers,[18,9b] and this amide has been shown to be almost equi-energetic with respect to N-/O-protonation (ΔPA = -1.9 kcal/mol, 6-31G* level) (Figure 2A). Benzofused 1-azabicyclo[3.3.1]nonan-2-one derivative (**2**) has been used by us to demonstrate N-alkylation and the subsequent σ N–C bond cleavage of bridged lactams.[11a] Methyl-truncated Tröger's base twisted amides **3** and **4** are analogues of the amides reported by Wärnmark and Cvengroš, respectively.[13,14] Amides **5** and **6** are Tröger's base analogous of **3** and **4** lacking benzene rings, while twisted urea **7** was selected on the basis of the potential bridgehead oxidation in the course of synthesis of **3**. Note that related bridgehead iminium ions are well-known.[3a] Our study demonstrates that this compound would be fully twisted, and therefore likely unstable under the reaction conditions employed in the synthesis of **3**.

Furthermore, we selected substituted analogues of Tröger's base twisted amides **3** and **4** as an additional class of amides (Figure 2B). We hypothesized that detailed information about structures and energetics of representative analogues bearing strongly electron-withdrawing and electron-donating groups at the conjugating positions on the aromatic-rings would provide insights into the future design of Tröger's base twisted amide ring systems.

B3LYP/6-311++G(d,p) was selected to conduct geometry optimization as a result of excellent reproducibility of literature data and method practicality.[12c,22c] Extensive studies have showed that this level is accurate in predicting geometries and energetics of non-planar amides. The method was further verified by obtaining good correlations between the calculated and X-ray structures in the study. Note that structures of the parent Tröger base twisted amides in the series have been reported.[13,14] Previous studies have shown that the combination of structural and computational approach gives the best estimate of the structural and energetic properties in a series of non-planar amides.[11,12]

Selected structural parameters relevant to amide bond distortion of amides **1-7** are listed in Table 1. For clarity, structural parameters of amides **8-15** are shown in Table 2. The data in Table 1 clearly demonstrate than in the series **1-3**, Tröger's base twisted amide **3** contains by far the most twisted amide bond (additive Winkler-Dunitz parameter, 70.1°, 87.5°, 97.5°, respectively). To our knowledge, amide **3** represents one of the most twisted bridged lactams isolated to date in its unprotonated form. Furthermore, Tröger's base twisted amide **4** embedded in a more flexible [3.3.2] scaffold features a larger distortion than more constrained 1-azabicyclo[3.3.1]nonan-2-one **1** (78.0° vs. 70.1°). Comparison of amide bond distortion of **3-4** with Tröger's base twisted amide analogues lacking aromatic rings (**5-6**) (69.5°, 60.6°) demonstrates that the high distortion of **3-4** results from rigidifying effect of aromatic rings on the amide bond. The effect is mirrored in distortion of amide **2**. The increase is substantial, and corresponds to Δ of 17.5° (25% increase) for amide **2**, as well as Δ of 28.0° (40% increase) for amide **3** and Δ of 17.4° (29% increase) for amide **4**. In contrast, twisted urea **7** contains fully twisted amide bond (additive Winkler-Dunitz parameter, 143.1°). As such, this amide would not be expected to be stable under the experimental conditions employed for the synthesis of Tröger's base twisted amides; however, this compound would represent an interesting twisted urea model for future experimental studies. Optimized geometries of ring systems **1-7** together with Newman projections along the N–C(O) axis are presented in Figure 3.

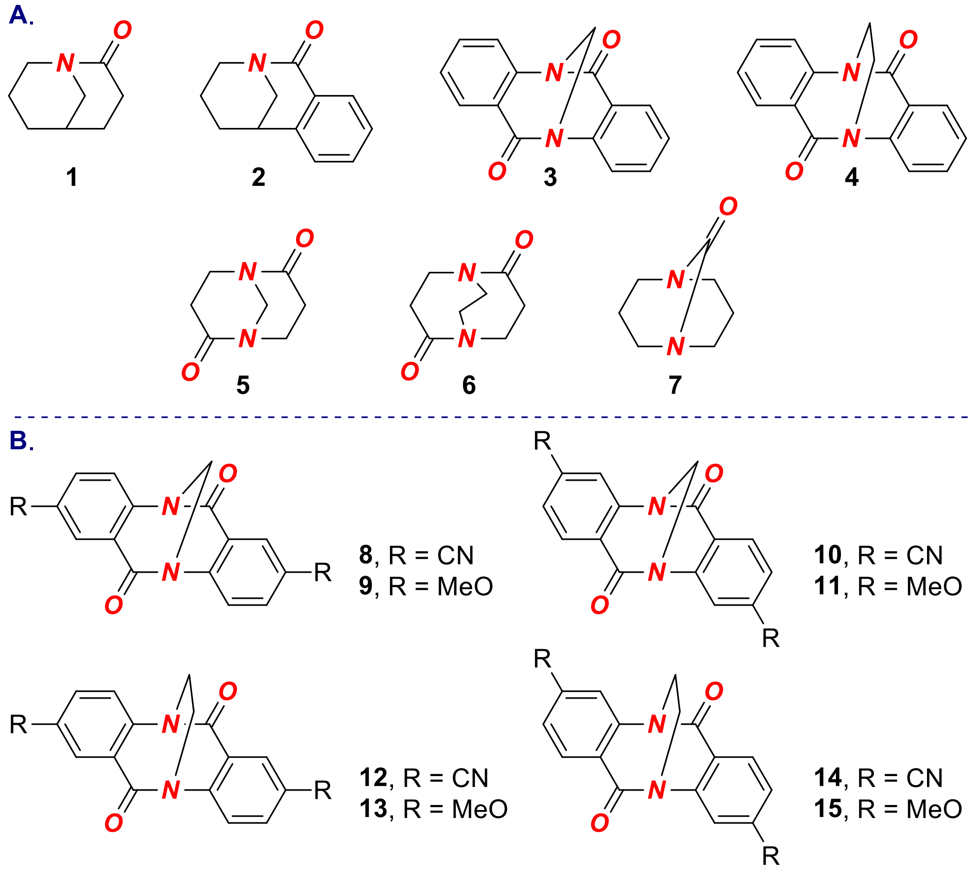


**Figure 2.** Structures of model twisted lactams calculated in the current study.

**Table 1. Selected Geometric Parameters of Amides 1-7**[a]

| entry | amide | N–C(O) [Å] | C=O [Å] | $\tau$ [deg] | $\chi_N$ [deg] | $\tau+\chi_N$ [deg] |
|---|---|---|---|---|---|---|
| 1 | **1** | 1.395 | 1.219 | 20.91 | 49.18 | 70.09 |
| 2 | **2** | 1.405 | 1.218 | 36.56 | 50.93 | 87.49 |
| 3 | **3** | 1.438 | 1.209 | 41.92 | 55.54 | 97.46 |
| 4 | **4** | 1.415 | 1.212 | 37.16 | 40.84 | 78.00 |
| 5 | **5** | 1.407 | 1.213 | 15.89 | 53.62 | 69.51 |
| 6 | **6** | 1.402 | 1.215 | 24.14 | 36.44 | 60.58 |
| 7 | **7** | 1.447 | 1.196 | 90.00 | 53.05 | 143.05 |

[a] This study. Computed using B3LYP/6-311++G(d,p) level. Representative data on acyclic twisted amides: ref. 12a,b. Representative data on bridged lactams: ref. 11b,18a,b.

**Table 2. Selected Geometric Parameters of Amides 8-15**[a]

| entry | amide | N–C(O) [Å] | C=O [Å] | $\tau$ [deg] | $\chi_N$ [deg] | $\tau+\chi_N$ [deg] |
|---|---|---|---|---|---|---|
| 1 | **8** | 1.439 | 1.206 | 42.48 | 54.97 | 97.45 |
| 2 | **9** | 1.436 | 1.210 | 41.81 | 56.05 | 97.86 |
| 3 | **10** | 1.436 | 1.206 | 41.19 | 55.31 | 96.50 |
| 4 | **11** | 1.442 | 1.210 | 42.87 | 55.75 | 98.62 |
| 5 | **12** | 1.414 | 1.210 | 36.52 | 40.71 | 77.23 |
| 6 | **13** | 1.413 | 1.213 | 37.95 | 40.56 | 78.51 |
| 7 | **14** | 1.413 | 1.210 | 36.38 | 40.81 | 77.19 |
| 8 | **15** | 1.420 | 1.213 | 39.64 | 40.57 | 80.21 |

[a] This study. Computed using B3LYP/6-311++G(d,p) level. Representative data on acyclic twisted amides: ref. 12a,b. Representative data on bridged lactams: ref. 11b,18a,b.

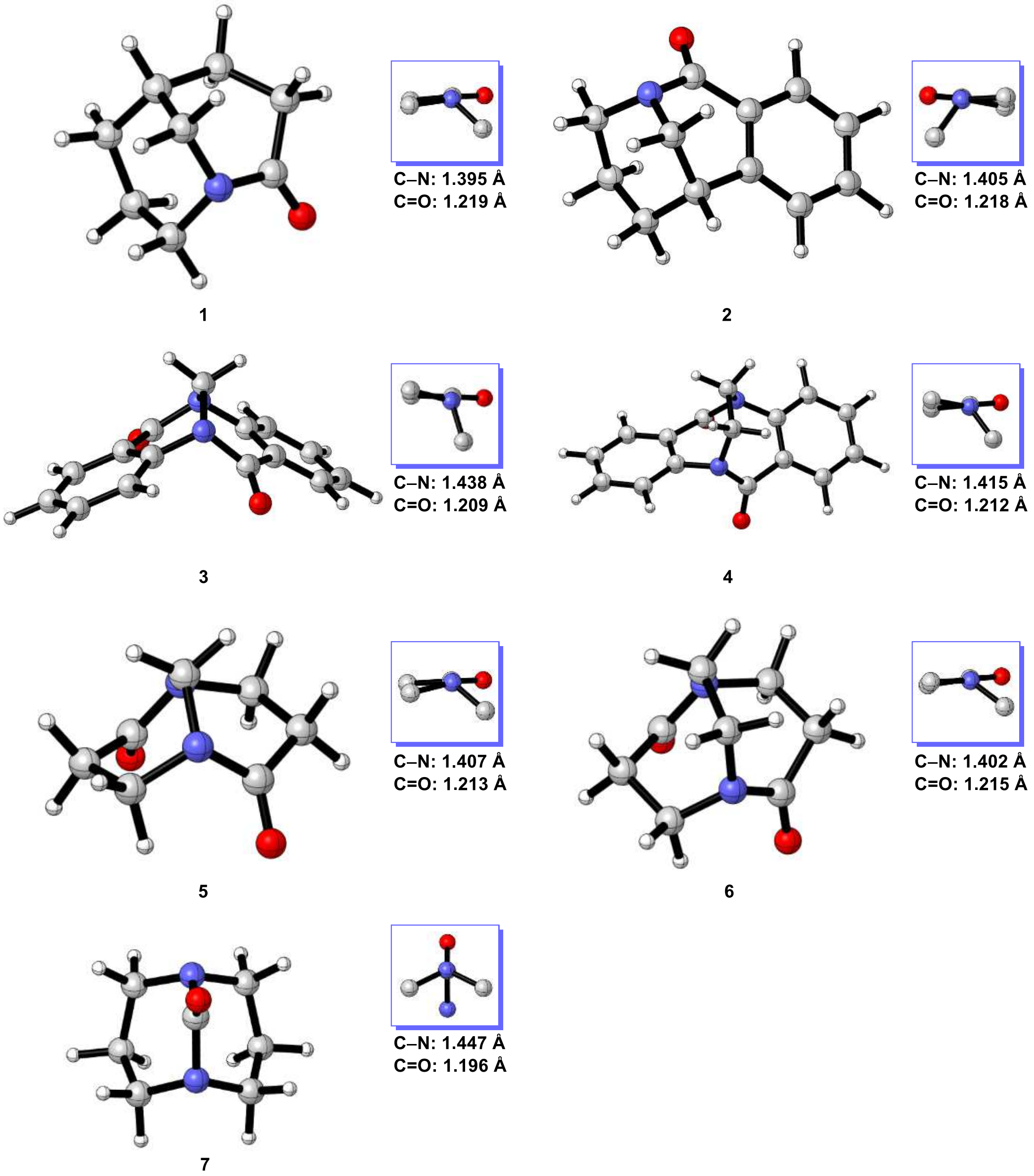


**Figure 3.** Optimized geometries of bridged lactams **1-7** (B3LYP/6-311++G(d,p)). Insets show Newman projections along N–C(O) bonds. Bond lengths are given in Å. For optimized geometries of bridged lactams **8-15** (B3LYP/6-311++G(d,p)) see SI.

The study further validates the use of additive Winkler-Dunitz parameter ($\Sigma\tau+\chi_N$)[17,12] to predict distortion of non-planar amides. Several features should be noted: (1) There is an excellent positive linear correlation between the sum of twist angles and nitrogen pyramidalization ($\Sigma\tau+\chi_N$) and the length of the N–C(O) bond for lactams embedded in the same scaffold (**3-6**, $R^2 = 0.98$) (Chart 1), while the plots of twist angle vs. N–C(O) bond length ($R^2 = 0.66$) or nitrogen pyramidalization vs. N–C(O) bond length ($R^2$ = 0.39) give scattered results. (2) Likewise, a plot of the sum of twist angles and nitrogen pyramidalization ($\Sigma\tau+\chi_N$) versus the length of C=O bond gives excellent negative linear correlation (**3-6**, $R^2$ = 0.99) (Chart 2), while the use of either twist ($R^2$ = 0.57) or nitrogen pyramidalization alone ($R^2$ = 0.51) gives inaccurate results. (3) The observed correlations clearly indicate that twisting of the amide bond from planarity in Tröger's base twisted amides leads to disruption of the $n_N \rightarrow \pi^*_{C=O}$ conjugation, which is reflected in a significant N–C(O) bond lengthening, while the C=O bond shortens. While one should be cautious in addressing a correlation based on four data points, (1) the data clearly show that there is a relationship between the additive Winkler-Dunitz parameter and energetic and structural properties of the amide bond in the studied scaffold, (2) the relationship is more accurate as compared to either twist or pyramidalization alone.

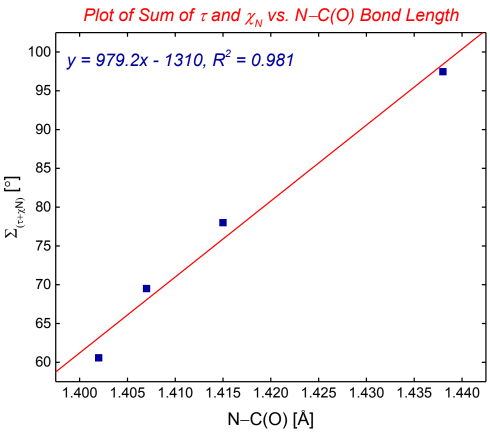


**Chart 1.** Correlation of the sum of twist and pyramidalization at nitrogen angles ($\Sigma\tau+\chi_N$, additive Winkler-Dunitz distortion parameter) to N–C(O) bond length for amides **3-6** (B3LYP/6-311++G(d,p) data).

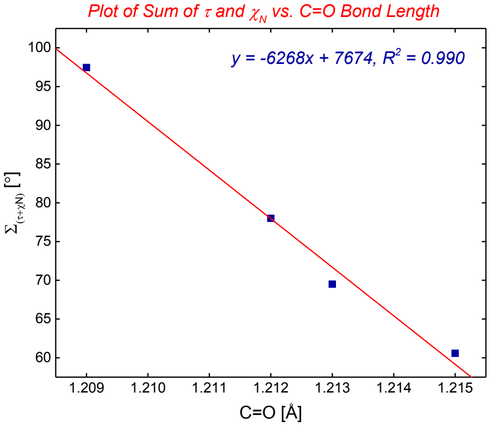


**Chart 2.** Correlation of the sum of twist and pyramidalization at nitrogen angles ($\Sigma\tau+\chi_N$, additive Winkler-Dunitz distortion parameter) to C=O bond length for amides **3-6** (B3LYP/6-311++G(d,p) data).

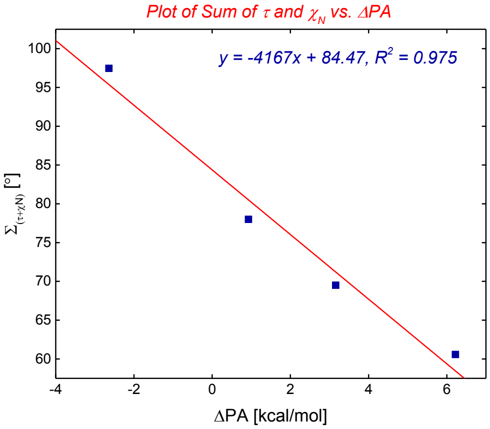


**Chart 3.** Correlation of the sum of twist and pyramidalization at nitrogen angles ($\Sigma\tau+\chi_N$, additive Winkler-Dunitz distortion parameter) to ΔPA for amides **3-6** (B3LYP/6-311++G(d,p) data).

*Since the additive Winkler-Dunitz parameter gives a much more accurate depiction of the structural features of the non-planar amide bond, it is critical that studies addressing properties of distorted amides report the sum of twist angles and nitrogen pyramidalization ($\Sigma\tau+\chi_N$) rather than focus on either twist or pyramidalization alone.*

Furthermore, our findings further confirm that the additive Winkler-Dunitz parameter is the guideline of choice for predicting the protonation aptitude of non-planar amides.[17] A plot of the sum of twist angle and nitrogen pyramidalization versus N-/O-protonation affinity difference for amides in the same series gives an excellent linear correlation (**3-6**, ΔPA, $R^2 = 0.98$) (Chart 3). This can be compared with a plot of twist angle vs. ΔPA ($R^2 = 0.61$) or nitrogen pyramidalization vs. ΔPA ($R^2 = 0.44$) in the same series. Note that in Tröger's base twisted amides the O- to N- cross-over point is located close to the ($\Sigma\tau+\chi_N$) value of 80°, which can be compared with approximately 50-60° cross-over point for one-carbon bridged twisted lactams (*vide infra*).[17] Future studies will shed considerable light into the relationship between amide bond distortion and structure as well as protonation aptitude of various classes of non-planar amides.[3b,11,12]

Structural parameters of amides **8-15** are listed in Table 2. As anticipated from the positioning of substituents on the aromatic rings, the amide bonds in **8-15** feature similar distortion to **3-4** (*vide infra*, *N.B.* N-/O-protonation aptitude).

Key information is gained from proton affinities (PA) and differences between N- and O-protonation affinities (ΔPA). The values for amides **1-7** are listed in Table 3; see also Chart 3. Extensive attention is focused on the site-selectivity of amide protonation.[23] N-Protonation of the amide bond is a process of high interest in biology and medicinal chemistry as a potential mechanism of amide bond proteolysis and cis-trans-isomerization,[4,5] while in organic chemistry N-protonation has been widely utilized to activate the N–C(O) bond by disrupting amidic resonance.[6] Previous theoretical studies established that the N-/O-protonation switch occurs around the ($\tau+\chi_N$) = 50-60° geometry in one-carbon bridged twisted lactams.[17,18] As such, Tröger's base twisted amide **3** would be expected to vastly favor N-protonation. However, this is not the case. Examination of the data in Table 3, clearly indicates that the best model for N-protonation is the benzofused 1-azabicyclo[3.3.1]nonan-2-one derivative **2** (ΔPA = -6.1 kcal/mol). While amide **3** still favors N-protonation (ΔPA = -2.4 kcal/mol), this is close to being equinergetic with respect to N-/O-protonation. Moreover, the more twisted **4** (ΔPA = 1.2 kcal/mol) is now in the same range as amide **1** (ΔPA = 1.1 kcal/mol). Evaluation of proton affinities at the nitrogen and oxygen atoms in **3-4** together with PA and ΔPA in Tröger's base analogous of **5** and **6** lacking the benzene rings (**5**:

ΔPA = 3.1 kcal/mol, **6**: ΔPA = 6.3 kcal/mol) reveals that Tröger's base twisted amides are not ideal models for N-protonation as a result of Nlp conjugation onto the aromatic rings.

As expected on the basis of amide bond distortion, twisted urea **7** vastly favors N-protonation (ΔPA = -20.7 kcal/mol), which would substantially decease stability of this and analogous compounds under standard handling conditions.

Equally revealing is comparison of proton affinities and differences between N- and O-protonation affinities in ring-substituted Tröger's base twisted amides **8-15** (Table 4).

**Table 3. Proton Affinities (PA) and Differences in Proton Affinities (ΔPA) for Amides 1-7 Calculated using B3LYP/6-311++G(d,p)**[a]

| entry | amide | uncorrected | | | corrected | | |
|---|---|---|---|---|---|---|---|
| | | $N_{PA}$ | $O_{PA}$ | ΔPA | $N_{PA}$ | $O_{PA}$ | ΔPA |
| 1 | **1** | 224.2 | 225.1 | 1.0 | 215.5 | 216.6 | 1.1 |
| 2 | **2** | 233.6 | 227.0 | -6.6 | 224.6 | 218.5 | -6.1 |
| 3 | **3** | 220.4 | 217.7 | -2.6 | 212.1 | 209.7 | -2.4 |
| 4 | **4** | 222.7 | 223.6 | 0.9 | 214.0 | 215.3 | 1.2 |
| 5 | **5** | 210.7 | 213.8 | 3.2 | 202.6 | 205.7 | 3.1 |
| 6 | **6** | 213.7 | 220.0 | 6.2 | 205.2 | 211.5 | 6.3 |
| 7 | **7** | 234.9 | 213.4 | -21.5 | 225.7 | 205.0 | -20.7 |

[a] Values (kcal/mol) are uncorrected and corrected for zero-point energy and thermal corrections. Representative data on bridged lactams: ref. 11b,18a,b.

**Table 4. Proton Affinities (PA) and Differences in Proton Affinities (ΔPA) for Amides 8-15 Calculated using B3LYP/6-311++G(d,p)**[a]

| entry | amide | uncorrected | | | corrected | | |
|---|---|---|---|---|---|---|---|
| | | $N_{PA}$ | $O_{PA}$ | ΔPA | $N_{PA}$ | $O_{PA}$ | ΔPA |
| 1 | **8** | 204.4 | 202.2 | -2.2 | 196.3 | 194.3 | -2.0 |
| 2 | **9** | 224.8 | 221.5 | -3.3 | 216.5 | 213.5 | -3.1 |
| 3 | **10** | 205.5 | 203.4 | -2.1 | 197.4 | 195.6 | -1.9 |
| 4 | **11** | 228.6 | 227.2 | -1.4 | 220.2 | 219.0 | -1.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 | **12** | 207.3 | 208.9 | 1.7 | 198.9 | 200.8 | 2.0 |
| 6 | **13** | 226.5 | 226.8 | 0.2 | 217.9 | 218.6 | 0.7 |
| 7 | **14** | 207.6 | 209.1 | 1.5 | 199.2 | 201.0 | 1.8 |
| 8 | **15** | 228.6 | 229.7 | 1.0 | 219.9 | 221.3 | 1.4 |

[a] Values (kcal/mol) are uncorrected and corrected for zero-point energy and thermal corrections. Representative data on bridged lactams: ref. 11b,18a,b.

Here, the most beneficial in terms of favoring N-protonation is substitution with the methoxy group at 2,8-positions (**9**: ΔPA = -3.1 kcal/mol, **13**: ΔPA = 0.7 kcal/mol), however, the gain from disfavoring Nlp to Ar conjugation is counterbalanced by an increased O-protonation affinity. In contrast, the unnatural 3,9-substitution[15] leads to a net decrease of ΔPA for amides **10-11** (**10**: ΔPA = -1.9 kcal/mol, **11**: ΔPA = -1.2 kcal/mol) as a result of decrease and increase of N- and O-protonation affinities by electron-withdrawing and donating substituents, respectively. As expected, this trend is mirrored in the [3.2.2] series.

It is interesting to note that excellent linear correlations were observed between ΔPA and Hammett $\sigma^*$ values for Tröger's base twisted amides substituted para to the nitrogen atom for both [3.3.1] ($Y = 0.823X - 2.674$, $R^2 = 0.997$) and [3.3.2] series ($Y = 0.991X + 0.986$, $R^2 = 0.995$) (not shown). This indicates that the N-/O-protonation aptitude in this series is governed by both amide bond distortion and electronic effects of the aromatic ring. In contrast, only poor correlations were observed with Tröger's base twisted amides substituted para to the carbonyl group.

## 3. Conclusions

In conclusion, this paper provides extensive insights into the structures and energetics of Tröger's base twisted amides. As discussed above, these scaffolds provide some of the most twisted non-planar amide bonds isolated to date in bicyclic lactams. A key feature of the investigated system is the finding that Tröger's base twisted amides are significantly more twisted than related 1-azabicyclo[3.3.1]nonan-2-one derivatives, which is rendered possible by a rigidifying effect of the aromatic rings. In contrast, while Tröger's base twisted amides still favor protonation at the nitrogen atom, these compounds are less efficient in probing N-protonation aptitude of non-planar amides than related 1-azabicyclo[3.3.1]nonan-2-one derivatives as a consequence on N-conjugation with the aromatic ring. Furthermore, our study demonstrated a significant effect of ring-substitution on proton affinities of the amide bond in Tröger's base twisted amides. Equally important is the validation of the additive Winkler-Dunitz distortion parameter as the vastly preferred descriptor of the properties of non-planar amide bonds. The results of this study provide the understanding for future design of non-planar bridged lactams to directly access N-protonated amide bonds. Future studies will address a statistical analysis of the structural and energetic description of the non-planar amide bond in an expanded range of analogues as well as the synthesis and evaluation of the experimental properties of Tröger base twisted amides.

More broadly, our ongoing studies are focused on further investigations of non-planar amides. Specifically, our results suggest that peripheral modification can be used as powerful tool in re-evaluating structural and energetic properties of twisted amides.

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**Supporting Information.** Cartesian coordinates and energies. Detailed description of computational methods used. This material is available free of charge via the Internet at http://pubs.acs.org.

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