Structures of the Most Twisted Thioamide and Selenoamide: Effect of Higher Chalcogens of Twisted Amides on N–C(X) Resonance

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Abstract: *Amide bond replacement with planar isosteric chalcogen analogues has an important implication for the properties of the N–C(X) linkage in structural chemistry, biochemistry and organic synthesis. Herein, we report the first higher chalcogen derivatives of non-planar twisted amides. The synthesis of twisted thioamide in a versatile system has been accomplished by direct thionation without cleavage of the σ N–C bond. The synthesis of twisted selenoamide has been accomplished by selenation with Woollins' reagent. The structures of higher chalcogen analogues of non-planar amides were unambiguously confirmed by x-ray crystallography. Reactivity studies were conducted to determine the effect of isologous N–C(O) to N–C(X) replacement on the properties of the amide linkage. Computational studies were employed to evaluate structural and energetic parameters of amide bond alteration in higher chalcogen amides. The study provides the first experimental evidence on the effect of chalcogen isologues on the structural and electronic properties of the non-planar amide N–C(X) linkage.*

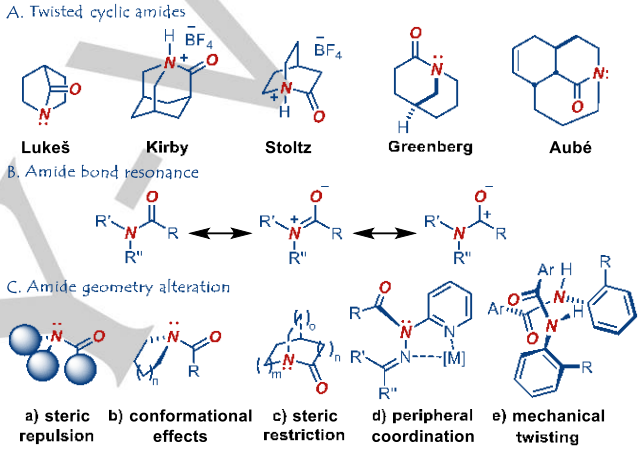


Figure 1. (A) Previously reported examples of highly distorted amides in cyclic frameworks. (B) Amide bond resonance. (C) Methods of alteration of amide bond geometry.

The amide bond is the key structural motif in chemistry and biology.[1–3] As elucidated by Pauling in 1930s, typical amides are planar as a consequence of $n_N \rightarrow \pi^*_{C=O}$ resonance rendering the N–C(O) bond approximately 40% double bond in character.[4] Non-planar amides featuring distortion around the amide linkage have attracted major attention from the standpoints of structure, reactivity and intrinsic presence in various facets of chemistry[5] ranging from enhanced hydrolysis[6] and amino-ketone like properties[7] through unique σ bond reactivity[8] and role in cis-trans isomerization of peptide bonds[9] to ground-state-destabilization of amides in biological systems.[10] The most common way to restrict the amide bond in a non-planar conformation is to embed the amide linkage in a rigid bicyclic ring system with the nitrogen atom placed at a ring fusion (Figure 1).[5] Since the first proposal by Lukeš in 1938,[11] these bridged twisted amides have been a staple for our understanding of the properties of non-planar amide bonds with landmark examples reported by Kirby,[12] Stoltz,[13] Greenberg[14] and Aubé[15] (Figure 1A). In these systems, the ring torsion permits to freeze the otherwise unstable conformation of the amide bond with a control of N–C bond rotation (τ, twist) and nitrogen pyramidalization (χN), which in turn affect nitrogen lone pair to C=O delocalization and amidic resonance (Figure 1B).[16] The effect of geometric alteration of amide bond has been the subject of intense studies from theoretical perspectives.[17]

Recently, there has been a major surge of research in other methods of alteration of amidic resonance through steric repulsion,[18] conformational changes,[19] peripheral coordination[20] and mechanical twisting[21] (Figure 1C) as each of these mechanisms offers a unique approach to achieving non-planarity of amide bonds of broad interest in chemistry and biology for accessing non-planar amide bonds.[22]

However, in contrast to studies on amide bond deformation, non-planar higher chalcogen analogues of twisted amide bonds are unknown.[23,24] Higher chalcogen analogues of planar amides, such as thioamides[25] and selenoamides,[26] are among the most important 'single-atom' amide bond bioisosteres[27] wherein the replacement of the oxygen atom by sulfur or selenium offers a mimic to modify polarization of the amide bond,[28] increase enzymatic stability of peptides[29] and induce conformational changes, including through photoisomerization.[30] The privileged role of sulfur[31] and selenium[32] in medicinal chemistry and materials science has led to considerable interest in compounds containing higher chalcogen analogues of amides.

Herein, we report the first higher chalcogen derivatives of twisted amides. The study provides the first insight into the effect of important chalcogen isologues on the structural and electronic properties of non-planar amide N–C(X) linkage, with key insights into the structure, reactivity and electronic properties.

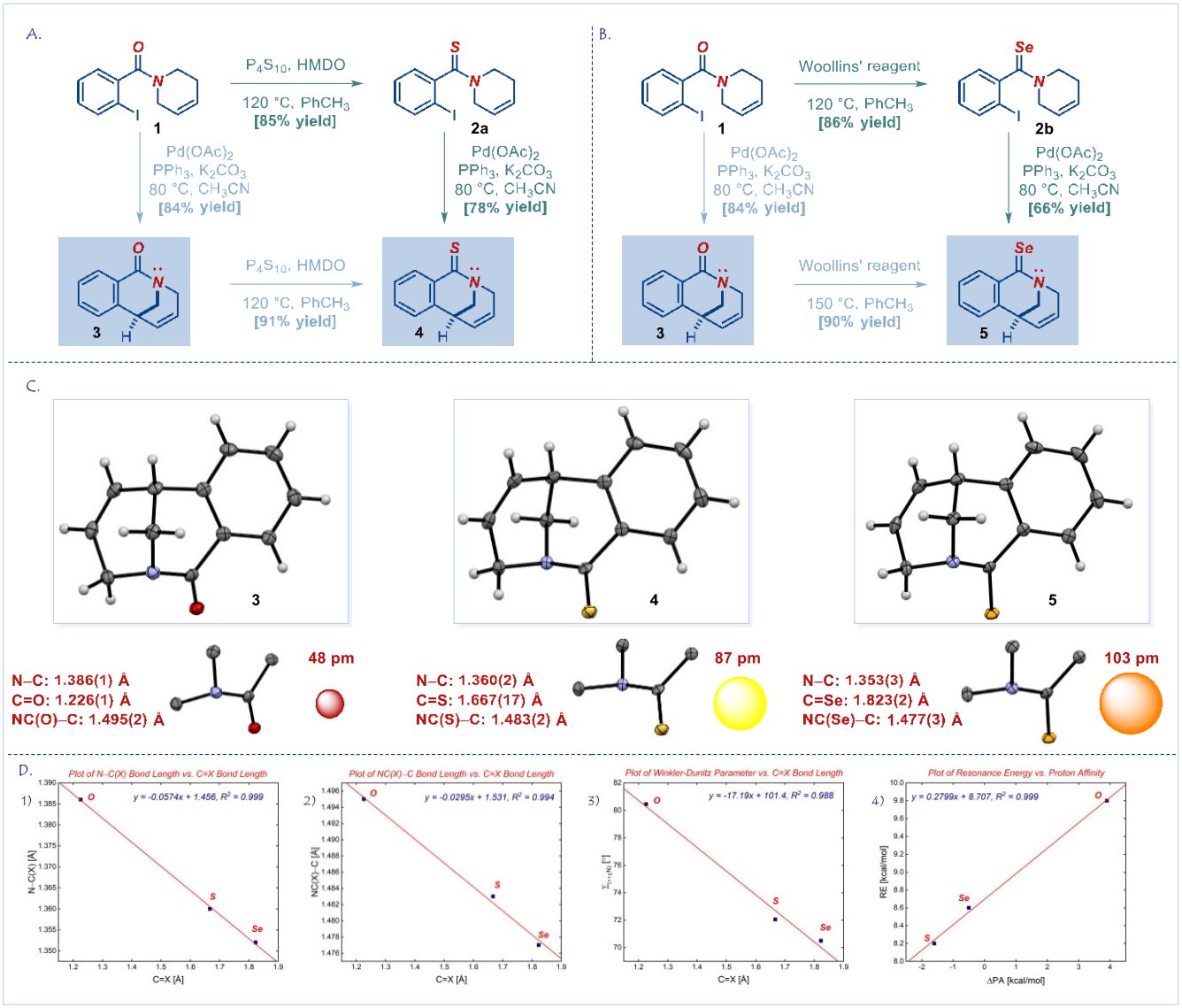


Figure 2. (A) Synthesis of twisted thioamide. (B) Synthesis of twisted selenoamide. (C) Crystal structures of amides **3–5**. Selected bond lengths of amide N–C(X) bond (Å). Note that the spheres represent atomic radius of oxygen, sulfur and selenium scaled to the size of the red sphere. (D) (1) N–C(X) bond length to C=X bond length. (2) NC(X)–C bond length to C=X bond length. (3) $\Sigma_{(\tau+\chi N)}$ to C=X bond length. (4) Resonance energy to ΔPA. X-ray data: CCDC 2168010, CCDC 2168011.

Based on our experience in non-planar amide bonds,[7,18,33] we selected bridged 1-azabicyclo[3.3.1]nonan-2-one system studied by Greenberg[14] as a model scaffold to investigate the synthesis of twisted higher chalcogen amides. This system features significantly distorted amide bond (τ = 30.8°; χN = 49.7°; $\Sigma(\tau+\chi_N)$ = 80.5° in the parent amide, Winkler-Dunitz parameters).[16] Electronically, N-/O- protonation is at the cross-over point, where N- and O-protonated forms are almost equal in energy,[14] while the x-ray structure of the parent amide[34] and reactivity of the amide linkage in 1-azabicyclo[3.3.1]nonan-2-one system are well-established, including N–C(O) reactivity,[34] σ N–C scission,[34,35] remote C=C cleavage[36] and polymerization,[37] permitting facile comparison of structure and reactivity.

The synthesis of twisted thioamide **4** was accomplished by intramolecular Heck cyclization of thioamide **2a** (Figure 2A). Furthermore, direct thionation of twisted amide **3** in the presence of P_4S_{10} provided an alternative method of accessing **4**. Lawesson's reagent can be used, however, it resulted in lower yields. The product was found to be air- and moisture-stable to work-up and chromatographic purification conditions.[38] The structure of **4** was unambiguously confirmed by x-ray crystallography (Figure 2C). The structure of **4** shows that the thioamide bond features significant non-planarity. The observed bond lengths in **4** are N–C(S) length of 1.360 Å, and C=S bond length of 1.667 Å. The Winkler-Dunitz parameters in **4** indicate χ_N of 48.3° and t of 23.8°, with the additive parameter $\Sigma(\tau+\chi_N)$ of 72.1°. The availability of the x-ray structure of the parent twisted amide **3**[34] (Figure 2C) permits to elucidate the structural changes of isologous N→C=O to N→C=S exchange. The thioamide bond distortion in **4** can be compared with the amide bond parameters of χ_N = 49.7°, τ = 30.8°, N–C(O) = 1.386 Å; C=O of 1.226 Å. Thus, amide to thioamide replacement significantly increases the C=X bond length (by 0.441 Å), while the N–C(X) bond is shortened (by 0.026 Å), which altogether translates to a small decrease in twist and pyramidalization (by 7.0° and 1.4°).

The successful synthesis of twisted thioamide **4**, prompted our attempts to extend the higher chalcogen exchange to selenium

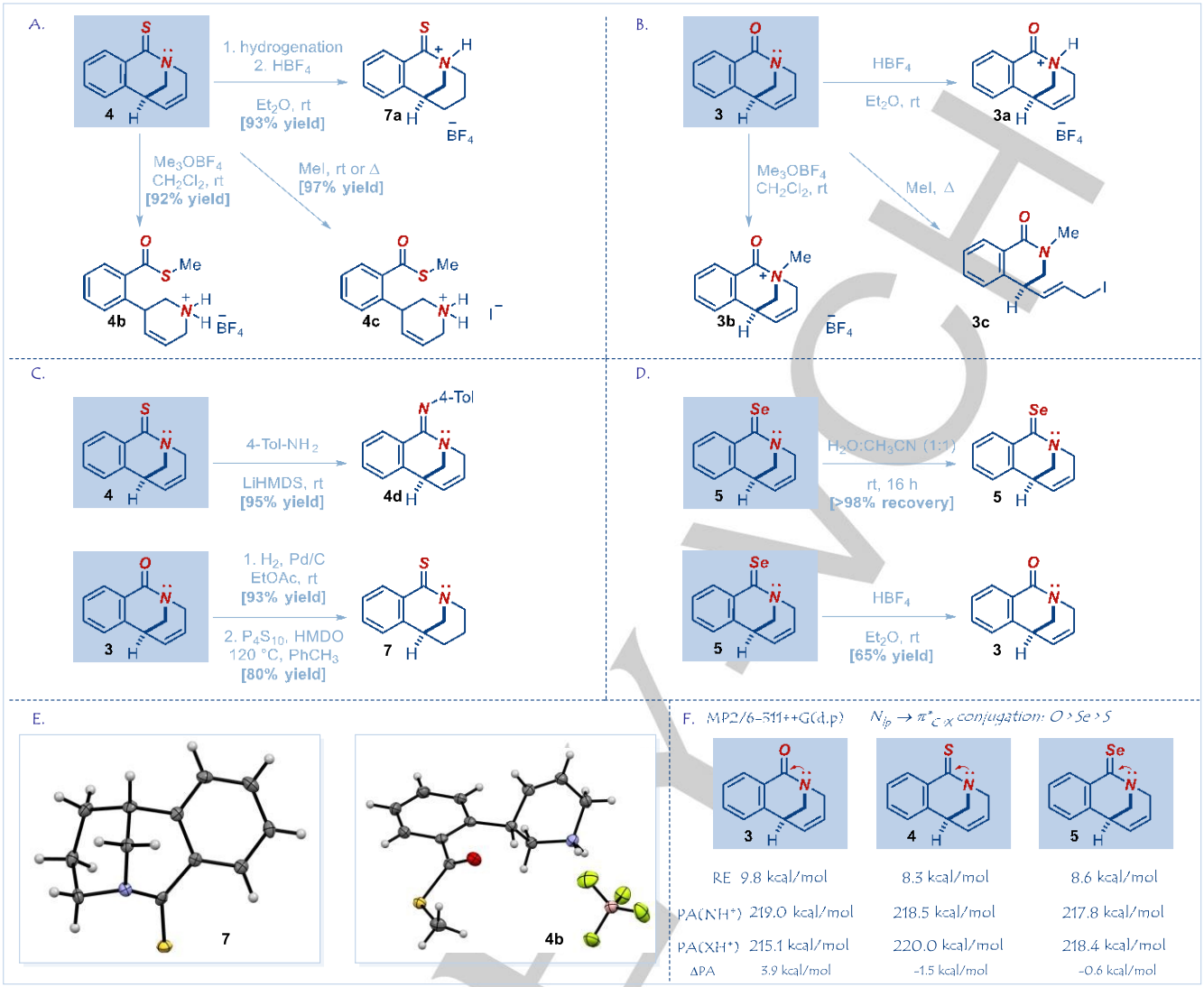


Figure 3. (A) Reactivity of twisted thioamide. (B) Reactivity of twisted amide. (C) Reactivity of twisted thioamide with preservation of the bicyclic ring. (D) Reactivity of twisted selenoamide. (E) Crystal structures of **7** and **4b**. CCDC: 2168012; CCDC: 2168689. (F) Resonance energies and proton affinities of amides **3–5** calculated at MP2/6-311++G(d,p) level.

(Figure 2B). Although attempts to prepare twisted selenoamide **5** using LiAlSeH were unsuccessful due to difficulty in forming bridged iminium,[39] we determined that the use of Woollins' reagent[40] gave the twisted selenoamide **5** by Heck cyclization of selenolactam **2b** or direct selenation of twisted amide **3**. The product **5** was found to be air- and moisture-stable under work-up and purification conditions. The structure of **5** was unambiguously determined by x-ray crystallography (Figure 2C). Crystallographic analysis revealed that selenoamide **5** is characterized by the N–C(Se) bond length of 1.353 Å and C=Se bond length of 1.823 Å. The Winkler-Dunitz distortion of **5** shows χ_N of 46.8° and τ of 23.7°, with the additive parameter $\Sigma(\tau+\chi_N)$ of 70.5°. These values can be compared with the parent twisted amide **3**, indicating a remarkable increase of the C=X bond length (by 0.597 Å). In contrast, the N–C(X) bond is shortened (by 0.034 Å). The overall effect is a modest flattening of the amide bond, with twist and pyramidalization decrease by 7.1° and 2.9°. See, Table 1 for additional discussion.

Further insight into the effect of isologous N–C(O) exchange is gained from correlating structural and energetic parameters (Figure 2D). The correlations can be summarized as follows:

(1) There is an excellent inverse correlation between the N–C(X) bond length and the C=X bond length (R^2 = 0.99), indicating a shortening of the N–C(X) bond length for higher chalcogen amides.

(2) There is an excellent inverse correlation between the NC(X)–C bond length and the C=X bond length (R^2 = 0.99), corresponding to shortening of the C–C bond (1.495 to 1.477 Å) in higher chalcogen amides.

(3) Most interestingly, a plot of the additive Winkler-Dunitz parameter $\Sigma(\tau+\chi_N)$ vs. the C=X bond length gives an excellent inverse linear correlation in the series (R^2 = 0.99).

(4) Finally, there is an excellent linear correlation between resonance energy and ΔPA in **3–5** (R^2 = 0.99) (*vide infra*, Figure 3F).

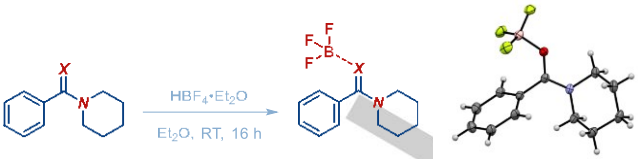
Altogether, the observed structural changes indicate a significant structural and electronic alteration of the amide bond by isologous exchange with higher chalcogen atoms. From the structural standpoint, the N–C(X) shortening corresponds to reinforced Nlp to C=X conjugation and C–C shortening is indicative of enhanced Ar to C=X conjugation, while these

changes occur with a concomitant major elongation of the C=X bond. For comparison of other structural parameters with unstrained parent systems, see SI, page S50.

To gain further insight into the characteristics of twisted chalcogen analogues of amides, we next investigated the reactivity of twisted thioamide **4** (Figure 3A). We found that **4** after hydrogenation of the double bond undergoes *N*-protonation to give unstable **7a** with preservation of the bridged structure. See SI for expanded discussion of the protonation/methylation sites, page S28. Furthermore, methylation with Meerwein's reagent, Me_3OBF_4, or MeI afforded the open form thioester amines **4b–4c** by *S*-methylation/hydrolysis; the oxygen atom comes from hydrolysis. The structure of **4b** was unambiguously confirmed by x-ray crystallography (Figure 3E). This reactivity stands in sharp contrast to the isologous twisted amide **3**, which has been shown to undergo N-protonation,[34] N-methylation[34] and s N–C scission[35] under identical reaction conditions (Figure 3B). Furthermore, we established that the twisted thioamide **4** undergoes reactions with the preservation of the bridged structure to give an unusual bridged amidine (**4d**) and saturated twisted thioamide **7** (Figure 3C). In the latter case, cleavage of the s N–C bond[34] has not been observed. The structure of **7** was confirmed by x-ray crystallography (N–C(S) = 1.365 Å; C=S = 1.661 Å; χ_N = 47.4°; τ = 27.6°; $\Sigma(\tau+\chi_N)$ = 75.0°) (Figure 3E). Note that the bridged thioamide **4** is also stable under aqueous conditions, resulting in quantitative recovery after incubation at 23 °C or 100 °C for 16 h.[8] We were further curious to examine the reactivity of the bridged selenoamide **5** (Figure 3D). This analogue was found to be stable to aqueous conditions, allowing for quantitative recovery after incubation in H_2O:CH_3CN (1:1) at 23 °C for 16 h. Interestingly, this selenoamide was found to be unstable under acidic conditions, resulting in hydrolysis to the twisted bridged amide **3**. This reaction proceeds via *Se*-protonation in analogy to the bridged *S*-thioamide salt **4a**. Full reactivity comparison with planar analogues of twisted thio and selenoamide has been performed (see SI, page 51).[42] Interestingly, we observed the formation of BF_3-adducts from planar analogues of **3** and **4** (Figure 4). The amide-BF_3 adduct **8a** was characterized by x-ray crystallography (CCDC 2181240) with the bond lengths of N–C: 1.305 Å, C=O, 1.294 Å and C–C(O), 1.488 Å, indicating a significant increase of $n_N \rightarrow \pi^*_{C=X}$ conjugation. The comparison of the spectroscopic and structural parameters of twisted vs. non-twisted C=X derivatives provides additional insight into the structures. It should be noted that the values should be normalized for a valuable comparison with the differential change of twisted vs. non-twisted as a key descriptor (Table 1). In the case of twisted amide, thioamide and selenoamide, the change of 2.6%, 2.0%, 2.4% (N–C), 1.3%, 0.8%, 0.4% (C=X) and 0.6%, 0.7%, 0.9% (C–C(X)), respectively suggest that the trends between twisted and planar thio and selenoamides are a consequence of being twisted. Collectively, these studies demonstrate unique reactivity of higher chalcogen analogues of twisted amides.

Computations at the MP2/6-311++G(d,p) level were employed to provide insights into the energetic parameters of the isologous amide exchange (Figure 3F). Resonance energies of **3–5** were calculated using the COSNAR method pioneered by Greenberg (eq 1).[14]

$$-RE = E_{T(amide)} - [E_{T(amine)} + E_{T(ketone)} - E_{T(hydrocarbon)}] \quad \text{(eq 1)}$$



8: X = O
9: X = S

8a: X = O, 88% yield
9a: X = S, 80% yield

8a

Figure 4. Formation of BF_3-adducts from planar analogues of **3** and **4**.

Table 1. Comparison of spectroscopic and structural properties of twisted and non-twisted derivatives.[a]

Entry	Amide	C=X	Amide IR $\nu_{C=X}$ [cm^{-1}]	Amide NMR C=X ^{13}C [ppm]
1	**3 (twisted amide)**	C=O	1667	177.0
2	**4 (twisted thioamide)**	C=S	1588	209.3
3	**5 (twisted selenoamide)**	C=Se	1568	214.3
4	**8 (planar amide)**	C=O	1522	170.2
5	**9 (planar thioamide)**	C=S	1488	199.3
6	**10 (planar selenoamide)**	C=Se	1400	203.4
7	**5 (twisted selenoamide)**	C=Se	-	1022.2[b]
8	**10 (planar selenoamide)**	C=Se	-	681.0[b]

Entry	Amide	C=X	N–C [Å]	C=X [Å]	(X)C–C [Å]
9[c]	**3 (twisted amide)**	C=O	1.386 (102.59)	1.226 (98.71)	1.495 (99.40)
10[c]	**4 (twisted thioamide)**	C=S	1.360 (102.03)	1.667 (99.23)	1.483 (99.26)
11[c]	**5 (twisted selenoamide)**	C=Se	1.352 (102.35)	1.823 (99.56)	1.477 (99.13)
12	**Ph-C(O)-NMe_2 (planar amide)**	C=O	1.351	1.242	1.504
13	**Ph-C(S)-NMe_2 (planar thioamide)**	C=S	1.333	1.680	1.494
14	**Ph-C(Se)-NMe_2 (planar selenoamide)**	C=Se	1.321	1.831	1.490

[a]See SI for additional discussion. [b]^{77}Se NMR (95 MHz). [c]Normalized values (twisted vs. non-twisted as percentages, (twisted/non-twisted)*100) are shown in parentheses.

Resonance energy in twisted thioamide **4** is lower than in twisted amide **3** (RE = 8.3 kcal/mol vs. 9.8 kcal/mol), while resonance energy of the twisted selenoamide **5** is 8.6 kcal/mol. These values can be compared with the corresponding dimethylacetamide, dimethylthioamide and dimethylselenoamide (RE = 16.5 kcal/mol, 15.0 kcal/mol and 16.4 kcal/mol)[41] calculated at the same level. Furthermore, proton affinity (ΔPA = PA(NH^+) – PA(XH^+)) indicates that protonation of the amide nitrogen in **3** is favored by 3.9 kcal/mol, while the twisted thioamide **4** is closer to the cross-over point with the *S*-protonated form energetically favored (ΔPA = -1.5 kcal/mol). The twisted selenoamide **5** is characterized by ΔPA of -0.6 kcal/mol. Thus, the computations show a significant decrease of $n_N \rightarrow \pi^*_{C=X}$ resonance in higher chalcogens analogues of twisted amides and indicate that N-/X-protonation is at the cross-over point in these amides. In general, N–C bond shortening and higher reactivity of the X atom implies stronger resonance contribution from the nitrogen atom within the same series of amide derivatives.[43,44]

In conclusion, we reported the first higher chalcogen derivatives of twisted amides within a robust bridged 1-azabicyclo[3.3.1]nonan-2-one framework. Characterization by x-ray crystallography determined structural changes of isologous N–C(O) to N–C(X) replacement. The study provides the first

experimental evidence on the effect of higher chalcogen isologues on the stability, structural and electronic properties of the twisted amide N–C(X) linkage. The ability to study higher chalcogens of twisted amides may significantly expand the scope of application of non-planar amide linkages in broad areas of chemistry that exploit amide bonds.

Acknowledgements

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Keywords: amides • conformational analysis • Winkler-Dunitz parameters • bond lengths • structure elucidation

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[42] Reactivity comparison of Ph-C(X)-N(C_5H_{10}) showed the following: 1) HBF_4: X = O: amide-BF_3 complex; X = S: thioamide-BF_3 complex; X = Se: hydrolysis. 2) Me_3OBF_4: X = O, no reaction; X = S: thioiminium; X = Se: hydrolysis. 3) MeI: X = O, no reaction; X = S: thioiminium; X = Se: selenoiminium (see SI, page S51, for details).
[43] Note that electronic changes of the N–C(X) bond in twisted higher chalcogen amides **3–5** are also evident from the ^{13}C NMR and IR spectra. See Supporting Information, Table S9.
[44] Note that C=X bending angle (ξ)[13b] in **3–5** showed negative values of –0.05°, –0.73°, –0.59°, **3**, **4** and **5**, respectively, indicating C=X bending towards the aromatic ring. This effect is consistent with stabilizing n_X to σ_{C-C} and destabilizing n_X to σ^*_{C-N} interactions in the series.
[45] Crystallographic data have been deposited with the Cambridge Crystallographic Data Center. **4**: CCDC 2168010; **5**: CCDC 2168011; **7**: CCDC 2168012; **4b**: CCDC 2168689; **8a**: CCDC 2181240.

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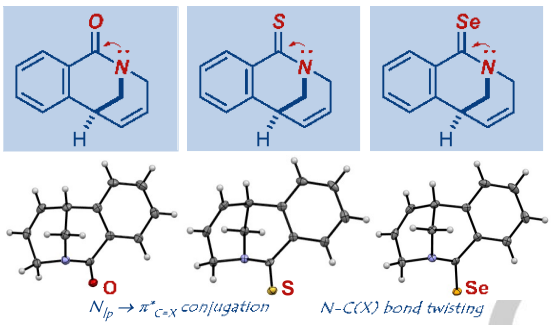

We report the first higher chalcogen derivatives of non-planar twisted amides. The study provides the first experimental evidence on the effect of chalcogen isologues on the structural and electronic properties of the non-planar amide N–C(X) linkage with implications in broad areas of chemistry that utilize amide bonds through the modification of $n_N \rightarrow \pi^*_{C=O}$ resonance and amide bond geometry.

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