Preference of *cis*-Thioamide Structure in *N*-Thioacyl-*N*-Methylanilines

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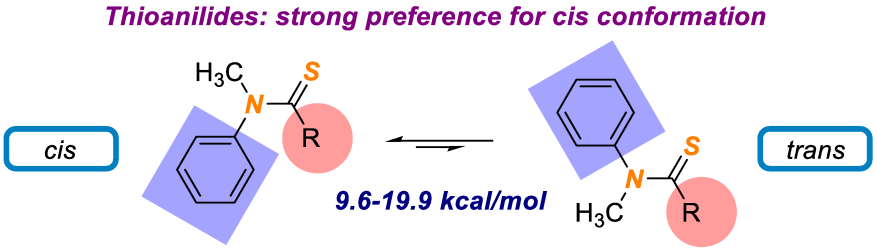
Supporting Information



ABSTRACT: The thioamide group represents a highly attractive isostere of the amide bond. We report a combined structural and computational study on *cis*-thioamide conformation of N-thioacyl-N-methylanilines. Amide to thioamide replacement in a class of anilides that are highly valuable as conformational locks results in a higher preference for *cis* conformation in a unique compacted template intrinsic to the thioamide structure. The study strongly supports the use of N-methyl-thioanilides as *cis*-conformational locks in various facets of chemistry.

In their classic study, Itai demonstrated the *cis*-preference of the amide bond in N-methylbenzanilides (Figure 1A).[1] Although acyclic amides strongly prefer trans conformation around the N–C(O) bond,[2,3] as exemplified by closely related benzanilides, their N-methylated counterparts undergo the conformational switch arising from avoidance of unfavorable steric interactions,[4,5] while retaining substantial double bond character of the amide bond through $n_N \rightarrow \pi^*_{C=O}$ conjugation.[6,7] This unexpected finding opened the door for the implementation of *trans* to *cis* conformational switch to control substituent geometry around the amide bond in a variety of fields utilizing amides, including medicinal chemistry, biochemistry, molecular recognition, conformation relays, synthetic switches and organic synthesis.[8–11]

Recently, significant attention has been given to thioamides as attractive amide bond isosteres.[12] The oxygen to sulfur replacement is particularly attractive considering (1) the privileged role of sulfur-based functional groups in pharmaceuticals, wherein more than 25% of APIs contain sulfur as the key component;[13] and (2) the unique electronic properties inherent to thioamides vs. amides, including long van der Waals radius of sulfur vs. oxygen (1.85 Å vs. 1.40 Å), elongated C=X bonds (1.64 Å vs. 1.19 Å, HC=XNH$_2$) and significantly lower polarization of the C=X bond (electronegativity, S: 2.58 vs. O: 3.44).[14] A prominent feature of thioamides is their role in increasing the stabilization of proteins owing to strong $n \rightarrow \pi^*$ interactions[15] and a plethora of thioamide-containing natural

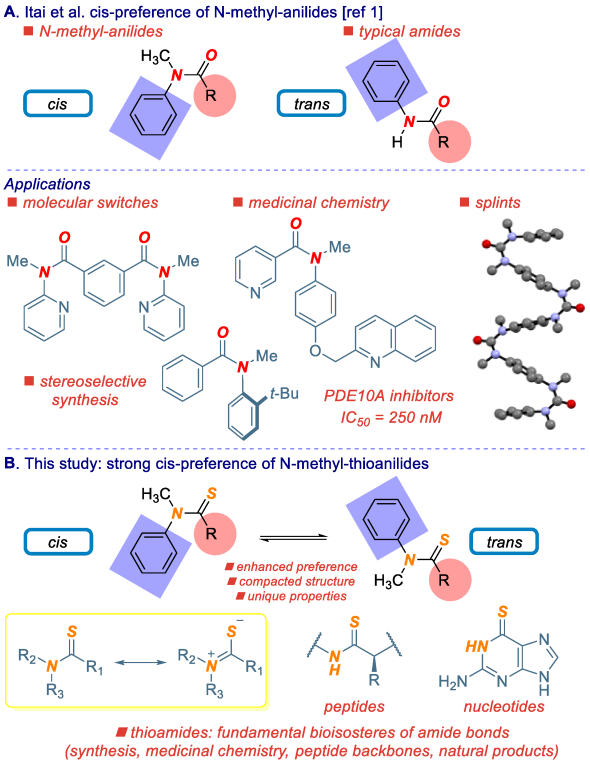


Figure 1. (a) Classical study on *cis*-preference of anilides, selected applications. (b) This work: Conformational preference of thioanilides.

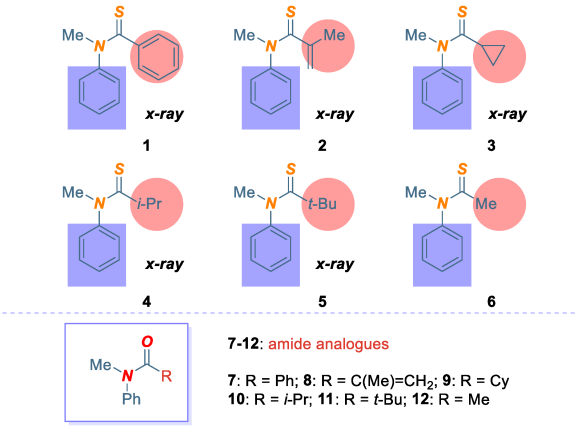


Figure 2. Structures of thioamides used in the present study.

products.[16] Elegant studies on macrocyclic amide to thioamide replacement have attracted considerable interest over the last years.[17,18]

As part of our program on amide bonds,[19,20] herein, we report a combined structural and computational study on *cis*-thioamide conformation of N-thioacyl-N-methylanilines. Most importantly, we demonstrate that amide to thioamide replacement results in a higher preference for *cis* conformation in a unique compacted template intrinsic to the thioamide structure. The present study strongly supports the use of N-methylthioanilides as highly valuable *cis*-conformational locks[8–11] in various facets of chemistry.

Guided by the study by Itai and our own studies in amide bond chemistry, we selected six thioamides shown in Figure 2 (**1-6**). These thioamides are readily synthesized from the corresponding amides using Lawesson's reagent (see SI, Supporting Information). The selected compounds mirror the amide counterparts used by Itai (Figure 2, **7-12**).

We commenced by obtaining X-ray structures of N-methylthioanilides (Figure 3). All thioamides **1-5** feature *cis* conformation in the crystal. Selected structural parameters relevant to the thioamide geometry are presented in Table 1 and SI. Compound **6** is a liquid and is not suitable for crystallographic analysis (*vide infra*). There are several instructive structural correlations between thioamides **1-5** and their amide counterparts **7-11** obtained from crystallographic studies, including (1) a significant decrease of the N–C(X) bond length (avg. 1.337 Å, X = S; avg. 1.352 Å, X = O); (2) a significant increase of the C=X bond length (avg. 1.660 Å, X = S; avg. 1.228 Å, X = O); (3) an increase in C–C(Ph) bond length (avg. 1.443 Å, X = S; avg. 1.439 Å, X = O); and (4) an excellent linear correlation between the C–C(S) and C–C(O) bond lengths (R^2 = 0.92, see SI for correlation plots).[21]

Next, we performed computational studies to gain insight into the structures of thioamides **1-6** and compare them with their oxygen counterparts **7-12**. As shown by our previous studies,[19] computed data provide vastly improved correlations vs. solid state structures, and this approach is particularly effective when considering multiple series of compounds using x-ray structures for geometry optimization. Geometry optimization was performed at the B3LYP/6-311++G(d,p) level. Extensive studies have shown that this level is accurate in predicting structural and energetic properties of amides.[19]

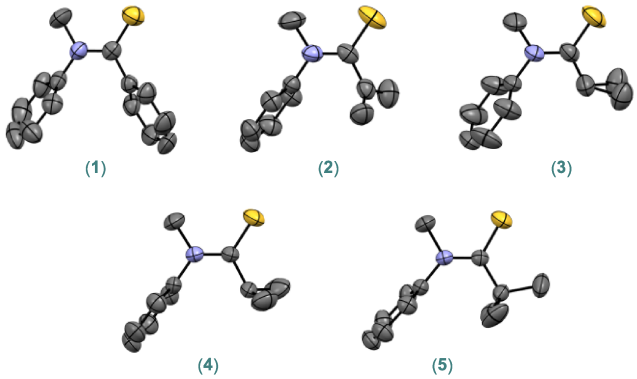


Figure 3. Crystal structures of **1-5**. See SI for expanded structures. 50% ellipsoids. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center. CCDC 2039785 (**1**); CCDC 2039803 (**2**); CCDC 2039815 (**3**); CCDC 2039816 (**4**); CCDC 2039817 (**5**).

Table 1. Selected Crystallographic Structural Parameters of Thioamides 1–5[a]

no.	thioamide (R)	N–C [Å]	C=S [Å]	C–C(S) [Å]	N–Ph [Å]	N–Me [Å]
1	Ph	1.342	1.658	1.485	1.440	1.463
2	$C(CH_3)=CH_2$	1.333	1.655	1.490	1.447	1.466
3	Cy	1.332	1.664	1.481	1.441	1.467
4	*i*-Pr	1.338	1.659	1.519	1.442	1.469
5	*t*-Bu	1.341	1.662	1.546	1.444	1.476

[a]This study. X-ray structures, see SI for details.

Computations closely parallel the experimental properties of the amide to thioamide bond substitution, and allow to include non-crystalline compounds **6** and **12** in the correlation (Figure 4 and SI). Thus, amide to thioamide replacement is accompanied by a reinforced n_N to $\pi^*_{C=X}$ conjugation as evidenced by a shortening of the N–C(X) bond. This effect is accompanied by C=X bond elongation as well as C–C(X) bond shortening and $C–C_{(Ph)}$ bond elongation, consistent with a weakened $n_N \rightarrow$ Ar conjugation. Overall, these effects lead to a compacted *cis* amide bond geometry in the thioanilide template.

Next, resonance energies of the thioamide bond in **1-6** were calculated using the COSNAR method.[22] Resonance energy in **1-6** ranges between 9.6-19.9 kcal/mol and is higher than in the corresponding oxygen counterparts **7-12** (9.8-15.4 kcal/mol) (Figure 5A and SI). Remarkably, there is an excellent inverse linear correlation between a plot of log(ΔRE) of the sulfur and oxygen analogues and the steric Charton (ν) value (Figure 5B, R^2 = 0.91). Overall, the energetic parameters in **1-6** vs. **7-12** indicate a reinforced bond resonance upon O to S replacement. The resonance manifests as a function of the R substituent converging at the sterically-demanding substitution. This unexpected effect likely arises from the increased van der Waals radius of sulfur vs. oxygen atoms minimizing steric interactions.

To gain further insight into the effect of O to S replacement, we obtained a detailed rotational profile of the parent thioamide **1** by systematic rotation along the X–C–N–C dihedral angle (Figure 5C). The rotation was performed in both directions using the X-ray structure of **1** as the starting geometry. Figure 5C shows rotational profile of **1** (X = S) in comparison with **7** (X = O). Rotational profile in **1** confirms significantly higher

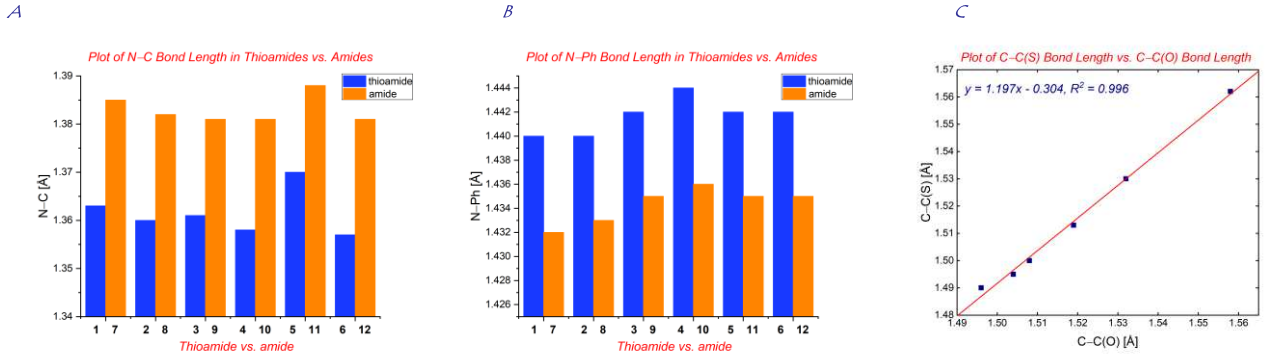


Figure 4. (a) Plot of N–C bond length [Å] in thioamides **1-6** vs. amides **7-12**. (b) Plot of N–Ph bond length [Å] in thioamides **1-6** vs. amides **7-12**. (c) Correlation of C–C(S) bond length [Å] to C–C(O) bond length [Å] for thioamides **1-6** vs. amides **7-12** (B3LYP/6-311++G(d,p)). See SI for additional details.

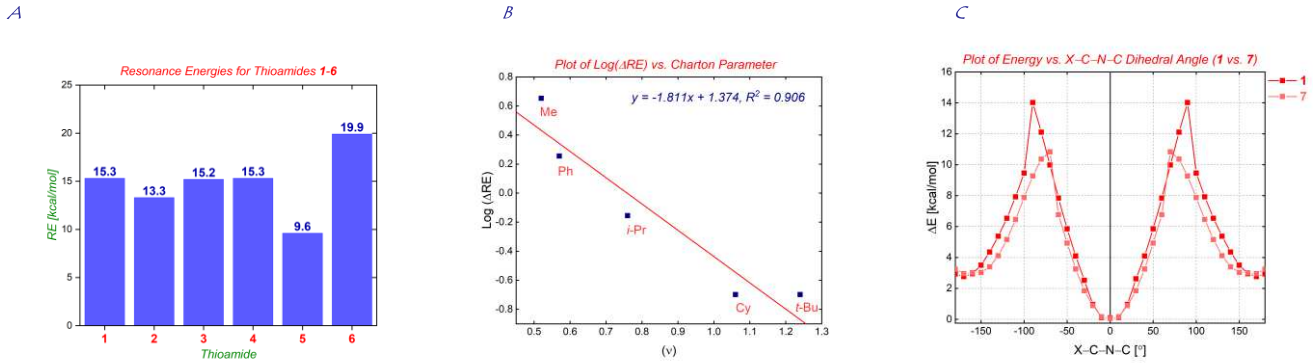
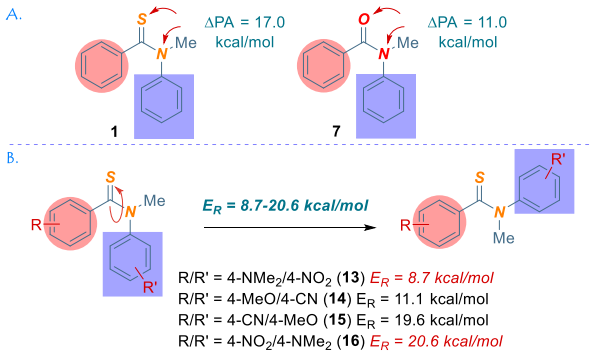


Figure 5. (a) Resonance energies for thioamides **1-6** (kcal/mol). (b) Plot of log(ΔRE) vs. Charton parameter in thioamides **1-6** vs. amides **7-12**. Note that (ν) value for $C(CH_3)=CH_2$ is not available. (c) Correlation of ΔE [kcal/mol] to X–C–C–C [°] in **1** and **7** (B3LYP/6-311++G(d,p)). See SI for additional details.

barrier to rotation than in the oxygen counterpart with a planar thioamide bond conformation (the energy minimum at ca. 0° S–C–N–C angle; the energy maximum at ca. 90° S–C–N–C angle). The rotational barrier was determined to be 14.02 kcal/mol (90° S–C–N–C angle), and 10.84 kcal/mol (70° O–C–N–C angle). It is worth noting that as suggested by the resonance energies thioamide **6** shows one conformer in the NMR spectrum. This effect is driven by minimization of steric interactions between the R substituent and the sulfur atom. Both steric and electronic effects of the substituents play a key role in adopting the *cis* conformation.

Several additional studies were conducted (Scheme 1 and see SI). (1) To further confirm the intrinsic preference of N-methyl-thioanilides to exist in the *cis* conformation, the relative stabilities of *trans* isomers for both sulfur and oxygen analogues were determined at the B3LYP/6-311++G(d,p) level, showing that *cis* isomers are more stable in all cases (S: avg. 3.1 kcal/mol; O: avg. 2.7 kcal/mol, see SI). (2) Difference in proton affinities (ΔPA) in representative thioamide **1** indicates that these thioanilides strongly favor protonation at sulfur[19] (ΔPA = 17.0 kcal/mol, S_{PA} vs. N_{PA}), which can be compared with the oxygen analogue **7** (ΔPA = 11.0 kcal/mol, O_{PA} vs. N_{PA}),[19e] and is in agreement with the findings on the enhanced $n_N \rightarrow \pi^*_{C=X}$ conjugation in thioamides (Scheme 1A). (3) To push the prospects of resonance alteration, RE of derivatives **13-16** varying by a single substituent on each aromatic ring were determined (Scheme 1B) (**13**: R = 4-NMe_2/R' = 4-NO_2; **14**: R = 4-MeO/R' = 4-CN; **15**: R = 4-CN/R' = 4-MeO; 16: R = 4-NO_2/R' = 4-NMe_2). The RE in **13-16** of 8.7, 11.1 19.6, 20.6 kcal/mol spans the range of 11.9 kcal/mol, which supersedes the effects observed in the oxygen counterparts of 9.5 kcal/mol determined earlier.[19e] Overall, these studies strongly support significantly enhanced conformational buttressing effects upon O to S substitution.

Scheme 1. Protonation Aptitude and Resonance Energies



In summary, amide bond architecture represents one of the most vital motifs in organic chemistry and biology. Although typical acyclic amides exist in the *trans* conformation, N-methyl-anilides undergo conformation switch to the *cis* geometry, an effect that has been engaged as a conformational anchor in many systems across chemical disciplines.[8–11] The present study demonstrates and quantifies that the amide to thioamide replacement in these systems results in a higher

preference for *cis* conformation in a unique compacted template intrinsic to the thioamide structure. The effect of sterics, substitution, resonance effects, barriers to rotation and proton affinities have been discussed and quantified. The attractive properties of thioamides, including photoisomerization, should facilitate the widespread use of N-methyl-thioanilides as *cis*-conformational locks in various facets of chemistry. Future studies will focus on further determination of conformational preferences of amides and thioamides by spectroscopic and computational methods.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. Cartesian coordinates and energies. Detailed description of computational methods used. CIF files for **1-5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

J.Z. thanks the CSC (No. 201808610096). Support was provided by the Foundation for Young Scholars of SUST (No. BJ12-26). M.S. thanks Rutgers University and the NSF (CHE-1650766). We thank the Wroclaw Center for Networking and Supercomputing (grant no. WCSS159, R.S.).

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