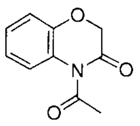
Remarkable Thiocarbonyl and Ring-Size Effects on the Amide Bond Twisting

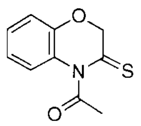
Shinji Yamada* and Kaori Matsuda
Department of Chemistry, Faculty of Science, Ochanomizu University, Bunkyo-ku, Tokyo 112-8610

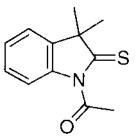
(Received May 7, 2001; CL-010415)

Remarkable thiocarbonyl and ring-size effects on the amide bond twisting were observed for *N*-acetylamides **1**–**3**. The amide linkage of **2** is perpendicularly twisted, whereas the oxygen analog **1** and five-membered analog **3** are virtually planar, which were revealed by ^{13}C NMR and IR spectroscopies, and X-ray analysis.

It has been well documented that amide linkages have planar geometry due to amide resonance.[1] This fundamental character of amide linkages is responsible for the conformation of various compounds containing an amide group. However, steric and electronic effects of the substituents around the amide bond change the conformational preference or cause deformation in the amide linkage.[2] Therefore, it will be important to explore the factors which affect the amide geometry because the geometry plays key roles in the bioactivity of various compounds and the process of biochemical reactions.[3] We have previously reported the structure and reactivity of sterically-hindered extremely twisted amides[2] having thiazolidine-2-thiones[4] and phthalimide[5] frameworks, where a bulky pivaloyl group was required to twist the amide bond using steric repulsion. In this communication, we report that replacing of a carbonyl group of *N*-acetylbenzoxazinone **1** by a thiocarbonyl group resulted in significant amide bond twisting; moreover, the ring-size of the framework structure is also critical for the geometry of the amide linkage.


1


2


3

The geometries of amides **1**[6] and **3**[7], and newly prepared **2** by the acetylation of 2*H*-1,4-benzoxazine-3(4*H*)-thione[8] were studied by ^{13}C NMR and IR spectroscopies, and X-ray analysis. *N*,*N*-Dimethylacetamide (**4**) was used as a standard for ^{13}C NMR ($\delta_{13_{C=O}}$ for **4** = 170.6) and IR ($\nu_{C=O}$ for **4** = 1634.6 cm^{-1}) spectroscopic analysis. Table 1 lists the $\delta_{13_{C=O}}$ and $\nu_{C=O}$ values for **1**–**3**, and the $\Delta\delta_{13_{C=O}}$ and $\Delta\nu_{C=O}$ values. Among the $\Delta\delta_{13_{C=O}}$, that of **2** was the highest. A similar tendency was observed for the $\Delta\nu_{C=O}$. Since it has been known that the $\Delta\delta^{13}_{C=O}$ and $\Delta\nu_{C=O}$ increase with increasing in the amide bond twisting,[2,9] these data suggest that the amide linkage of **2** is more twisted than those of **1** and **3**.

Table 1. $\delta_{13_{C=O}}$[a] (ppm) and $\nu_{C=O}$[b](cm^{-1}) values for **1–3** and the $\Delta\delta$[c] and $\Delta\nu$[d] values

Compd	$\delta^{13}_{C=O}$	$\Delta\delta_{C=O}$	$\nu_{C=O}$	$\Delta\nu_{C=O}$
1	171.1[e]	0.5	1729.2	94.6
2	175.3	4.7	1775.2	140.6
3	173.1	2.5	1717.1	82.5

[a] Measured at 100 MHz. In CDCl$_3$. [b] In CHCl$_3$. [c] $\Delta\delta_{C=O} = \delta_{C=O} - 170.6$, [d] $\Delta\nu_{C=O} = \nu_{C=O} - 1634.6$ cm^{-1}. [e] *N*-Acetyl carbonyl.

To elucidate the geometrical differences among **1**–**3**, X-ray analyses were carried out at 230 K.[10] Figure 1 shows their crystal structures and Figure 2 indicates the projection of their amide groups down the C(O)–N bonds. Though a single crystal of **1** contains two independent molecules in a unit cell, one of which is displayed in Figure 1 because of their sufficient similarity. Winkler–Dunitz parameters[11] for them are listed in Table 2. As expected, Figures 1 and 2 clearly show remarkable geometrical differences among them. Thus, the amide linkage of **2** is perpendicularly twisted (τ = 89.0°), whereas that of **1**, an oxygen analog of **2**, is virtually planar (τ = 10.4°). This means that replacing of the carbonyl to a thiocarbonyl plays a critical role in the amide geometry. Harrison and his coworkers have found that the thiocarbonyl affects the geometry of 1,6-diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril, the twist angle of which is 55.0°, while that of the oxygen analog is 21.6°.[12] Since an S atom has a much larger size than an O atom, the steric repulsion between the thiocarbonyl and the acetyl groups in **2** would be larger than that between the carbonyl and the acetyl groups in **1**. An electronic effect of the thiocarbonyl group would be another important factor. Thus, in an *N*-acylthioamide system, it has been known that the lone pair electrons of the nitrogen atom conjugate more efficiently with the thiocarbonyl than the carbonyl,[13] therefore, the adjacent N–C(O) double bond character in **2** is weakened compared to that in **1**; as a result, the thiocarbonyl would induce the amide bond twisting.

Table 2. Winkler–Duniz parameters for **1–3**[a]

Compd	τ / °	χ_C / °	χ_N / °
1	10.4	1.5	8.6
2	89.0	3.6	0.4
3	3.1	1.3	3.4

[a] The absolute values are indicated.[4]

Comparison of the crystal structures between **2** and **3** clarified a critical role of the ring-size of the framework structure on the amide geometry; amide **2** having a six-membered ring is extremely twisted as described above, while five-membered analog **3** is planar (τ = 3.1°) despite possessing a thiocarbonyl group. This ring-size effect would arise from the difference in the bond angles of C1–N1–C2 between **2** and **3**, the angles of which are 119.1° and 128.1°, respectively. Therefore, the thiocarbonyl group of **2** closely approaches the acetyl group compared to **3**, thus causing steric repulsion sufficient to effect significant amide bond twisting. The effect of crystal packing on the amide geometry will be negligible because no intermolecular interaction around the amide groups was observed in the crystal packing structures. This was supported by the fact that the calculated geometries by the RHF/3-21G* optimization of those amides closely resembles the observed geometries.[14]

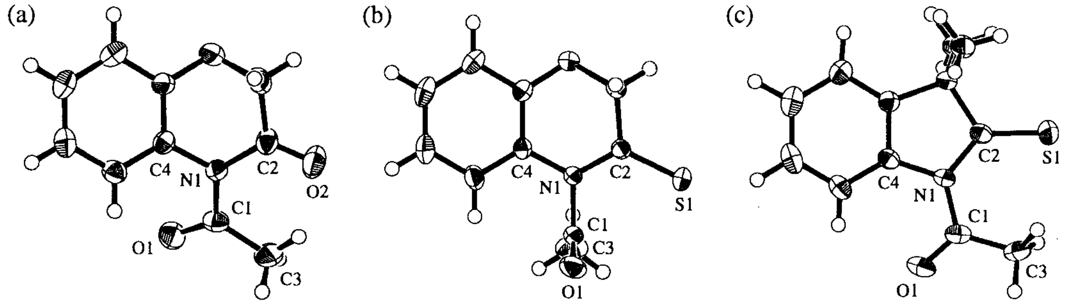


Figure 1. X-ray structures for **1** (a), **2** (b) and **3** (c) The thermal ellipsoids are set at the 50 % probability level, respectively. Selected bond lengths (Å), bond angles (°), and torsion angles (°): **1**: N1-C1 1.432(3), N1-C2 1.405(3), N1-C4 1.443(3), C1-N1-C2 123.2(2), C2-N1-C1-O1 164.5(2), C4-N1-C1-O1 -6.9(3). **2**: N1-C1 1.477(2), N1-C2 1.339(2), N1-C4 1.420(2), C1-N1-C2 119.06(13), C2-N1-C1-O1 90.6(2), C4-N1-C1-O1 -89.2(2). **3**: N1-C1 1.427(2), N1-C2 1.400(2), N1-C4 1.438(2), C1-N1-C2 128.1(2), C2-N1-C1-O1 -179.3(2), C4-N1-C1-O1 4.1(2).

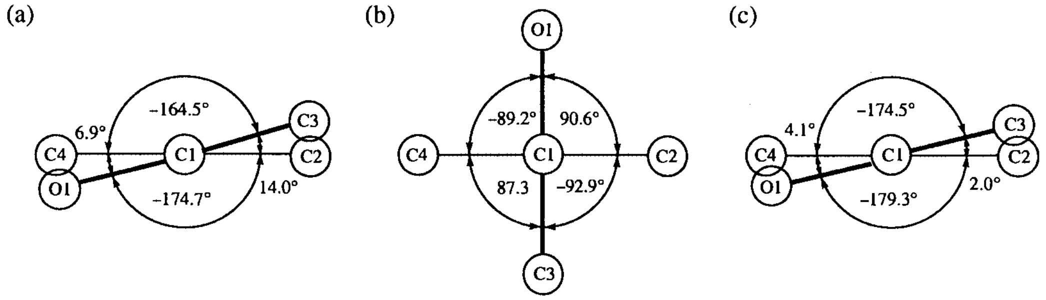


Figure 2. Projection of the amide groups of **1** (a), **2** (b) and **3** (c), down the C–N bond.

The structural differences are observed not only in the twist angles but also in the bond lengths. The C1–N1 distance of 1.475(2) Å in **2** is much longer than those in **1** and **3** [1.432(3) and 1.427(2) Å, respectively] and close to the C–N single bond length. In contrast, the C2–N1 distance of 1.338(2) Å in **2** is significantly shorter than those in **1** and **3** [1.405(3) and 1.400(2) Å, respectively]; moreover, the distance of C1–O1 in **2** is also shorter than those in **1** and **3**, and the C2–S1 distance of **2** is longer than that of **3** [1.649(2) and 1.622(2) Å, respectively]. These significant differences in the bond lengths are unambiguously ascribed to the amide bond twisting. Thus, the significant amide bond twisting inhibits the amide resonance, and instead, enhances the thioamide resonance, which resulted in the lengthening of the C1–N1 bond and shortening of the C2–N1 and C1–O1 bonds.

An additional characteristic feature of **2** is the very small χ_N value (Table 2). In general, amide bond twisting accompanies significant pyramidalization of the N atom; for example, 3,5,7-trimethyl-1-azaadamantan-2-one ($\tau = 90°$, $\chi_N = 60°$)[15] and *N*-pivaloyl-1,3-thiazolidine-2-thione ($\tau = 74.3°$, $\chi_N = 30°$).[5] This small χ_N in **2** may be ascribed to effective resonance of the nitrogen lone pair electrons with the aromatic ring as well as with the thiocarbonyl group. There are three types of distorted amides based on the distortion mode as previously defined by us[2]: twisted amide, nonplanar amide and twisted planar amide. According to the definition, amide **2** is a representative "twisted amide" because it has a planar nitrogen atom and a perpendicularly twisted amide linkage.

In conclusion, the structural studies of **1**–**3** elucidated that the significant amide bond twisting in **2** can be ascribed to both the steric and electronic effects of the thiocarbonyl group. The steric repulsion around the amide linkage of **2** would have an enough energy to inhibit the amide resonance weakened by the thioamide resonance.

References and Notes

1 M. B. Robin, F. A. Bovey, and H. Basch in "The Chemistry of Amides," ed. by J. Zabicky, Wiley-Interscience, London (1970), p 1.
2 S. Yamada in "The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science," ed. by A. Greenberg, C. M. Breneman, and J. F. Liebman, John Wiley & Sons, Inc., New York (2000), Chap. 8, p 215.
3 For examples see, a) L. T. Tan, R. T. Williamson, and W. H. Gerwick, *J. Org. Chem.*, **65**, 419 (2000). b) N. Xi, L. B. Alemany, and M. A. Ciufolini, *J. Am. Chem. Soc.*, **120**, 80 (1998). c) Y. Endo, M. Ohno, M. Hirano, A. Itai, and K. Shudo, *J. Am. Chem. Soc.*, **118**, 1841 (1996). d) M. K. Rosen, B. F. Standaert, A. Galat, M. Nakatsuka, and S. L. Schreiber, *Science*, **248**, 863 (1990).
4 S. Yamada, *Angew. Chem., Int. Ed. Engl.*, **32**, 1083 (1993).
5 S. Yamada, N. Nunami, and K. Hori, *Chem. Lett.*, **1998**, 451.
6 H. R. Bravo and B. E. Weiss-Lopez, *Bol. Soc. Chil. Quim.*, **44**, 443 (1999).
7 W. Adam, M. Ahrweiler, K. Paulini, H.-U. Reibig, and V. Voerckel, *Chem. Ber.*, **125**, 2719 (1992).
8 M. Mazaruddin and G. Thyagarajan, *Tetrahedron*, **25**, 517 (1969).
9 S. Yamada, *J. Org. Chem.*, **61**, 941 (1996).
10 Crystal data for **1**: $C_{10}H_9NO_3$, $M_r = 191.18$, monoclinic, space group $P2_1/n$, $a = 16.484(2)$, $b = 7.7481(8)$, $c = 16.455(3)$ Å, $\beta = 91.466(9)°$, $V = 1773.3(4)$ Å^3, $T = 230$ K, $Z = 8$, $D_c = 1.432$ g cm^{-3}, 5359 reflections measured ($2\theta < 135.9°$), 3209 unique data ($R_{int} = 0.0428$), 3168 data with $I > 2\sigma(I)$, 254 refined parameters, Final $R_1(F^2) = 0.0648$, $wR_2 = 0.2454$. Crystal data for **2** : $C_{10}H_9NO_2S$, $M_r = 207.24$, monoclinic, $P2_1/a$; $a = 8.0117(5)$, $b = 16.6759(13)$, $c = 7.4956(5)$ Å, $\beta = 107.074(5)°$, $V = 957.29(11)$ Å^3, $T = 230$ K, $Z = 4$, $D_c = 1.438$ g cm^{-3}, 2360 reflections measured ($2\theta < 135.9°$), 1714 unique data ($R_{int} = 0.0775$), 1706 data with $I > 2\sigma(I)$, 128 refined parameters, Final $R_1(F^2) = 0.0477$, $wR_2 = 0.1508$. Crystal data for **3** : $C_{12}H_{13}NOS$, $M_r = 219.29$, monoclinic, $P2_1/n$; $a = 9.2535(12)$, $b = 14.4384(11)$, $c = 8.7732(11)$ Å, $\beta = 109.976(10)°$, $V = 1101.6(2)$ Å^3, $T = 230$ K, $Z = 4$, $D_c = 1.322$ g cm^{-3}, 3416 reflections measured ($2\theta < 135.8°$), 2003 unique data ($R_{int} = 0.0439$), 2003 data with $I > 2\sigma(I)$, 137 refined parameters, Final $R_1(F^2) = 0.0389$, $wR_2 = 0.1558$.
11 For definitions of τ, see: F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, **59**, 169 (1971) and ref 4.
12 C. N. Cow, J. F. Britten, and P. H. M. Harrison, *Chem. Commun.*, **1998**, 1147.
13 Y. Nagao, T. Ikeda, T. Inoue, M. Yagi, M. Shiro, and E. Fujita, *J. Org. Chem.*, **50**, 4072 (1985).
14 The RHF/3-21G* calculations were performed by using PC Spartan pro. The twist angles are as follows: **1**: 21.6°; **2**: 69.3° **3**: 15.7°.
15 A. J. Kirby, I. V. Komarov, K. Kowski, and P. Rademacher, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 1313.