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Twisted Amides: Synthesis and Structure of 1,6-Dipivaloyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril

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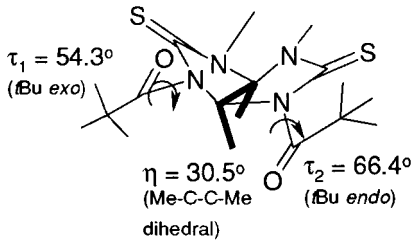
ABSTRACT



The 1,6-dipivaloyl derivative of 3,4,7,8-tetramethyl-2,5-dithioglycoluril (6) was prepared and the crystal structure determined by X-ray diffraction; 6 is a twisted amide in which severe ring strain and nonbonded interactions compel both pivaloyl groups to twist dramatically out of the ring plane. The amide oxygen atoms point in opposite directions with respect to the mean plane through the glycoluril core, and the bridgehead methyl groups are forced out of the symmetric *syn* geometry (η = 30.5°). The structure of 7, a rearrangement product generated during synthesis of 6, was also determined by single-crystal X-ray diffraction.

Resonance involving the nitrogen lone pair and the carbonyl π system provides a simple explanation for the preferred flat geometry, the slow interconversion of the two planar, *cis* and *trans* forms, and the low reactivity of most amides. However, several amides adopt nonplanar equilibrium geometries in the ground state.[1,2] These twisted structures exhibit long N−CO and short C═O bond lengths, enhanced reactivity, and a plethora of spectral characteristics which are not normally associated with amides.[1−6] Twisted amides are of intense theoretical interest in understanding amide structure and exploring ideas of resonance.[7] They have also attracted considerable attention due to practical applications, for example, as potent acylating agents[3−6] and as models of biologically relevant peptidic processes such as the action of proteases and catalysis of *cis*−*trans* peptide isomerization.[1−3]

One approach to enforcing this normally unfavorable geometry within an amide involves restraining the structure by covalent bonding.[1] Another group of twisted structures results from steric effects which are severe in the untwisted structure but which are relieved upon rotation around the N−C(═O) bond.[2,6]

We have reported the crystal structure of 1,6-diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril **1a**.[8] The plane through one of the two acetyl moieties ($H_3C-C{=}O$) is twisted by τ = 55.0° with respect to the C2−N1−C7 plane, where τ is the amide twist, as defined by Winkler and Dunitz[9] and modified by Yamada.[6] In contrast, the second acetamide entity

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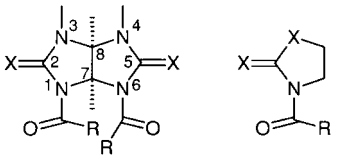
is an essentially flat amidic system. Recently, we have reported a similar but less dramatic effect in the analogue **1b** which was reproduced in the calculated ab initio optimized geometry.[10] Together, these results suggest that the twisting of these amides relieves an unfavorable closed-shell interaction between the two oxygen atoms of the acetyl groups.



1a X = S, R = Me **2a**
1b X = O, R = Me **2b**
6 X = S, R = *t*Bu **2c**

Compound **1a** was also compared to *N*-acetylthiazolidinethione **2a**,[3−6] which has $\tau = 20°$[6] and similar to oxygen analogue **2b**[5] is unreactive. However, the trimethylacetyl (pivaloyl) derivative **2c** exhibits a severe amidic twist ($\tau = 74.3°$)[6] and high reactivity as an acylating agent.[3−6] Further, spectral data, including, inter alia, a high-frequency C═O stretch in the IR and a high-field carbon-13 carbonyl chemical shift, support the notion that the crystal structure of **2c** is preserved in solution. Taken together, these observations suggest that the dipivaloyl glycoluril **6** might exhibit dramatic twisting in one or possibly both pivaloyl amide entities. Herein, we describe the preparation of **6** and related compounds and their structure determination by spectroscopic and single-crystal X-ray diffraction studies.

First, dithioglycoluril **3** was treated with potassium *tert*-butoxide and pivaloyl chloride, following a proven protocol for acetylation of **3**.[11] This resulted in not one but two monopivaloyl derivatives (subsequently shown to be **4** and **5**), as well as two distinct compounds containing two pivaloyl groups (which were later determined to be **6** and **7**). In contrast, when **3** was treated with pivaloyl chloride and Et_3N, a single dipivaloyl derivative (**6**) was obtained exclusively (96%).[12] Products **4**−**7** were purified and analyzed. Characteristic features of the NMR and IR spectra of each compound are summarized in Table 1.

Table 1. Selected Spectral Data for Compounds **4**−**7**[a]

parameter	4	5	6	7
ν_{max} (C═O)/cm^{-1}	1717	1632	1730, 1708	1705, 1639
NMR δ ((CH_3)$_3$C)	1.40	1.17	1.36, 1.36	1.36, 1.17
NMR δ (*C*═O)	187.5	191.0	185.4	190.9, 187.0
NMR δ (*C*═S)	181.3, 178.1	180.8	179.1	177.9
NMR δ (*C*═N)		167.4		168.4
NMR δ (N*C*N)	86.7, 83.3	88.0, 75.1	89.0, 86.8	86.6, 79.7
NMR δ (*C*C═O)	44.7	41.2	44.9	44.4, 41.2

[a] Solvent $CDCl_3$ at room temperature.

Compound **6** possessed two pivaloyl groups which were equivalent by NMR (at room temperature, see below), whereas **7** had two clearly different pivaloyl entities: one that resembled those in **6** and another with a distinct electronic environment. Product **4** exhibited some NMR chemical shifts and an IR C═O stretch similar to that in **6**, suggesting a similar connectivity for the acyl group, but the pivaloyl entity in **5** resembled the unique one in **7**. While the spectral data established that there were two distinct classes of pivaloyl group in **4**−**7**, it remained unclear which of **6** or **7** was the desired target and what the structure of the other product was. Possible explanations of the data at this juncture included the formation of products by both *N*- and *S*-acylation and atropisomerism of the twisted amides (giving separable structures in which the symmetric structure **6** had both pivaloyl carbonyl oxygen atoms pointed either toward the *endo* or the *exo* face of the glycoluril core, while the unsymmetric structure **7** had one pointed toward the *endo* and one to the *exo* face).

X-ray crystallographic analyses of **6** and **7** were thus undertaken to resolve these issues. The results show that **6** is the desired isomer (Figure 1). In **7**, one pivaloyl group is

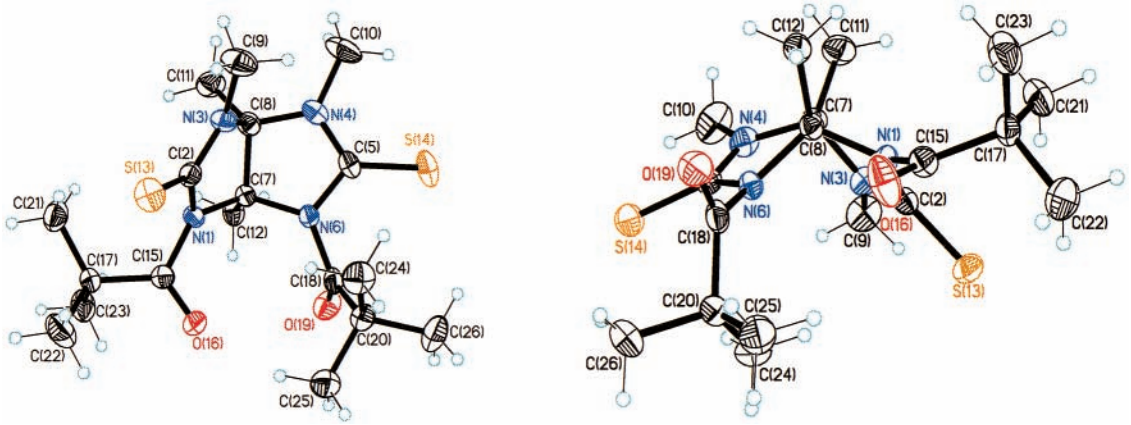


Figure 1. Two approximately orthogonal 50% thermal ellopsoid diagrams of the X-ray crystallographic geometry of glycoluril **6** ($C_{18}H_{30}N_4O_2S_2$, monoclinic, space group *C*2/*c* $a = 24.130(3)$, $b = 14.2521(17)$, $c = 15.4884(17)$ Å, $\beta = 126.367(2)°$, $T = 299(2)$ K, $Z = 8$, R1 = 0.0445 for reflections with $I > 2\sigma$).

attached to the nitrogen atom of a glycoluril-like ring; however, the other ring of the glycoluril core has rearranged to the isomeric iminothiazolidine (Figure 2). From the spec-

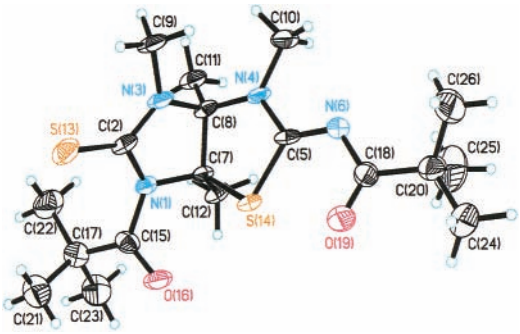
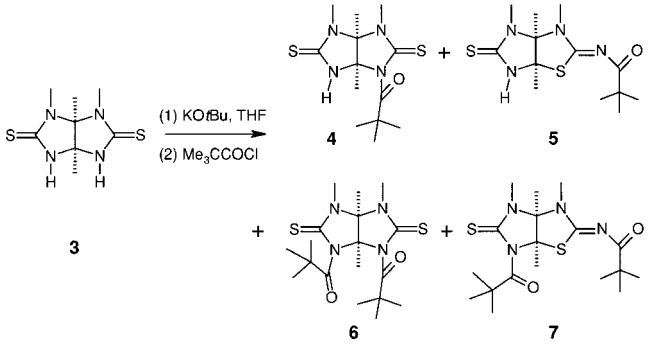


Figure 2. 50% thermal ellipsoid diagram of the X-ray crystallographic geometry of the rearrangement product **7** ($C_{18}H_{30}N_4O_2S_2$, monoclinic, space group $P2(1)/n$, $a = 11.8072(17)$, $b = 13.6435(17)$, $c = 27.751(4)$ Å, $\beta = 98.089(4)°$, $T = 299(2)$ K, $Z = 8$, R1 = 0.0919 for reflections with $I > 2\sigma$).

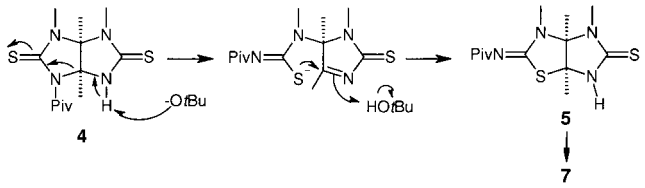
troscopic arguments (above), the monoacyl derivatives **4** and **5** can then be assigned the structures shown in Scheme 1.

Scheme 1



The absence of a rearranged product corresponding to **7** when **3** was acetylated under otherwise similar conditions (KO*tert*Bu), despite a careful search, suggests the following sequence of events. Both acetylation and pivaloylation of **3** proceed normally to give the monoacyl derivatives. Subsequent deprotonation of the monoacetyl compound is followed by a rapid second acetylation to give **1a**, but greater steric encumbrance both within the anion derived from **4** and in the reacting pivaloyl chloride slow the formation of **6** relative to that of **1a**. The longer-lived anion can undergo ring opening (Scheme 2) prior to reclosure at sulfur. Product **5**

Scheme 2



allows the *tert*-butyl group to be positioned remote from the glycoluril entity and thus probably represents an unencumbered, stable planar amide, whereas **4** is more sterically crowded and may be twisted. Indeed, the crystal structure of **7** shows that the pivaloyl group attached to the imidazolethione ring is twisted but that the one located on the iminothiazoline ring is close to planar, supporting this view (Table 2). Compound **5** is then converted to **7** by normal *N*-pivaloylation. Presumably when the weaker base Et_3N is used to prepare **6**, the anion of **4** is not involved in the

Table 2. Selected Geometric Parameters for Compounds **6**, **1a**, and **7**[a]

parameter	value for **6**	value for **1a**	value for **7**
N1−C2	1.389(3)	1.394(3)	1.415(6)
N1−C15	1.429(3)	1.397(3)	1.456(7)
N1−C7	1.468(3)	1.505(3)	1.456(6)
C2−S13	1.664(3)	1.650(2)	1.638(6)
C5−N6	1.380(3)	1.367(3)	1.284(7)
C5−S14	1.650(3)	1.660(2)	1.751(6)
N6−C18	1.467(4)	1.447(3)	1.384(9)
N6−C7	1.498(3)	1.461(3)	1.284(7)[b]
C15−O16	1.202(3)	1.211(3)	1.200(7)
C18−O19	1.201(3)	1.190(3)	1.217(7)
C5−N6−C18	119.8(2)	122.6(2)	120.0(7)
C2−N1−C15	125.4(2)	129.9(2)	121.7(5)
Q(A)	0.289	0.164	0.297
ϕ(A)	140.3	119.8	138.0
Q(B)	0.271	0.160	0.317
ϕ (B)	133.0	116.8	142.8
η	30.5(4)	21.2	31.5(7)
τ(A)	54.3(3)	55.0	59.6(5)
τ(B)	66.4(2)	2.6	−17.9(5)[c]
Pyram(N1)	1.9(4)	0.1(4)	14.2(8)
Pyram(N6)	5.4(4)	0.2(4)	

[a] Distances are in Å and angles in degrees. Values for **1a** taken from ref 8. Values for **7** are weighted averages over the two crystallographically independent geometries. These values are given by $x = (\sigma_2^2 x_1 + \sigma_1^2 x_2)/(\sigma_1^2 + \sigma_2^2)$ and $\sigma_x = \sqrt{1/[(1/\sigma_1^2)+(1/\sigma_2^2)]}$, where x and σ_x represent the geometrical parameter and its respective standard deviation and the subscripts 1 and 2 refer to the two different geometries.[15] Ring A bears the least twisted amide moiety (N1−C15−O16) while ring B refers to the ring with the most twisted amide moiety (N6−C18−O19) or the ring with S14 as a member in **7**. Puckering parameters, Q (Å) and ϕ (degrees) are defined according to Cremer and Pople[14a] and are computed using the RING program.[14b] The amide twist angles (τ) are the average of the two pseudo-*cis* C−N−C−O angles. The pyramidalization of the nitrogens is defined as 360 −Σ, where Σ is the sum of the valence angles of the nitrogen atom in question. Standard deviations of the pyramidalization are given by the square root of the sum of squares of the three standard deviations, those for τ by the equation above. [b] N6−C5 distance. [c] Taken as ∠(C5−N6−C18−C20) − 180.

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process. The structure of the iminothiazolidine ring in **7** resembles that in 3,7-diimino-2,6-dithia-4,8-diazabicyclo-[3.3.0]octane, the product of reaction of glyoxal with thiourea isolated by Long and co-workers.[13]

The X-ray crystallographic structure of **6** exhibits some remarkable features, which are summarized in Table 2. Both pivaloyl carbonyl groups are severely twisted relative to the planes of the ureido moieties to which they are attached (τ = 54.3° at N1 and 66.4° at N6), but the pivaloyl oxygen atoms are opposed, pointing to the concave, *endo* side of the glycoluril core at the N1 group but to the convex, *exo* face at N7. The *tert*-butyl moieties thus avoid interaction with each other as well as with the glycoluril bridgehead methyl groups and the thioureido sulfur atoms. The pivaloyl carbonyl oxygen atoms are also far apart in this conformation (O16···O19 3.15 Å), consistent with our view that the twisting effects in **1a** and **1b** are driven by an unfavorable closed-shell interaction between the two oxygen atoms. The pivaloyl groups probably still repel one another, as evidenced by the observation that the C5−N6−C18 and C2−N1−C15 angles are both smaller than those in **1a**. Twisting causes the N1−C15 (1.429 Å) and N6−C18 (1.467 Å) bonds to lengthen even more than in **1a**, consistent with a reduction in the extent of resonance of the N lone pair into the pivaloyl carbonyl groups as τ increases. Both C═O bond lengths are similar, and shorter than in **1a**, supporting this view.

The dihedral angle across the bridgehead, η (angle C11−C8−C7−C12),[10] is a remarkable 30.5°, larger than any glycoluril reported to our knowledge to date. In **1a**, this effect was proposed to be due to the different acetyl twists creating unequal electron density at N1 and N6, which translates into a differential anomeric-like effect at C7. In contrast, since both pivaloyl twists in **6** are similar, N1 and N6 should possess approximately equal electron density: this is seen in the N1−C7 and N6−C7 bond lengths which are more similar in value than in **1a**. Rather, the core glycoluril rings are dramatically puckered, with N1 pushed toward the convex face while N6 moves to the concave side. These effects, which are probably caused by the unfavorable closed-shell steric interactions around the pivaloyl entities, are seen in the significant pyramidalization at N6 (5.4° vs 1.9° at N1, <2° in **1a** and **1b**), as well as in the larger values of the Cramer−Pople puckering parameters Q and ϕ for **4** (as determined by the RING program)[14] than for **1a** (Table 2). The distortions of N1 and N6 then compel the C12 methyl group to turn away from the N1 and toward the N6 side of the molecule, while the C11 methyl group is balanced between N3 and N4, giving rise to the large dihedral η. It is also notable that **7** has a highly distorted bridgehead geometry and a remarkable pyramidalization at N1 (14°).

Finally, spectroscopic evidence suggests that the crystal structure of **6** is maintained in solution: **6** exhibits two C═O stretches in the solution-phase IR, both at high wavenumber, indicating that the two amides are distinct but that both are twisted. VT-NMR studies were also undertaken. The results show that the *tert*-butyl proton resonances in **6**, which appear to be equivalent at room temperature, separate into two signals upon cooling. At −94 °C in dichloromethane, the interconversion is slow. The same effect was observed for the *N*-methyl resonances. Coalescence was found to occur at −70.5 °C, giving a value for $\Delta G^{\ddagger}$ of 43.8 kJ/mol at 273 K. In contrast, when we examined diacetyl derivative **1a** at temperatures down to −90 °C, single *N*-methyl and acetyl proton resonances were still observed. Although further studies are needed to establish the nature of the process that interconverts the two sites in **6**, the data are consistent with and suggestive of a process in which the two pivaloyl groups are switched between *endo* and *exo* conformations similar to those observed in the crystal structure.

In summary, **6** is an extraordinarily strained structure in which nonbonded interactions enforce a geometry where both pivaloyl groups adopt highly twisted conformations. The reactivity of **6** toward nucleophiles is under study, and the preparation of other related structures is being actively pursued.

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Supporting Information Available: Experimental and spectral data for compounds **4**−**7**. Tables of crystallographic data and cif files for compounds **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **Representative experimental procedure; preparation of 6:** compound **3** (0.5 g, 2.17 mmol) was suspended in CH_2Cl_2 (20 mL), and Et_3N (0.91 mL, 6.52 mmol) was added. Pivaloyl chloride (0.80 mL, 6.52 mmol) was added, and the mixture was stirred at room temperature for 1 h. The solution was washed with 5% HCl (3 × 10 mL), and the organic layer was dried over Na_2SO_4. After concentration, the product was purifed by planar chromatography in CH_2Cl_2 to afford 827 mg (2.08 mmol, 96%) of **6**.

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