X-Ray crystal structure of 1,6-diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril, a highly twisted acetamide

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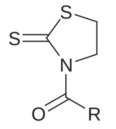
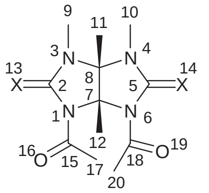
In the structure of 1,6-diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril, as determined by X-ray crystallography, one acetyl group lies essentially coplanar with the attached thioureido ring (τ = 2.6°), while the plane through the other acetyl group is highly twisted (τ = 55.0°) relative to the corresponding thiourea moiety to which it is appended.

Twisted amides, in which interaction between the nitrogen lone pair and the carbonyl π system is diminished or prevented, have attracted considerable interest, since they display unusually high reactivity towards nucleophiles, and have thus been proposed to act as models for the enzymic activation of peptide units.[1,2] In many cases, the amide bond is forced into a twisted conformation as a result of the covalent chemical bonding within the molecule,[2,3] while in others, the twist results either from enforced pyramidalization of nitrogen,[4] or else from steric effects.[1,5,6] In the latter regard, for example, Yamada[6] reported that 3-pivaloyl-1,3-thiazolidine-2-thione **1** has a twist angle τ = 74.3°, where τ is defined as $1/2\ (\omega_1 + \omega_2)$, and ω_1 and ω_2 are the O=C–N–C and C–C(O)–N–C′ dihedral angles, as defined by Winkler and Dunitz,[7] with the alteration suggested by Yamada.[6] The N–C(O) bond in **1** is long (1.448 Å) when compared to 3-acetyl-1,3-thiazolidine-2-thione **2**, (1.413 Å), which also possesses a much smaller twist angle (τ = 20.1°). Compound **1** is highly reactive towards nucleophiles, even at neutral pH.[1,6,8] In contrast, 3-pivaloyl-1,3-oxazolidine-2-one is unreactive;[1] the presence of the thione moiety thus contributes to the twisting of the amide bond in **1**.



1 R = Bu^t
2 R = Me



3 X = S
4 X = O

We have shown that glycoluril derivatives can act as templates to facilitate a rapid, intramolecular Claisen-like condensation reaction between acyl groups attached to N(1) and N(6).[9] We have proposed that this process is facilitated in part by the comparatively high electrophilicity of the acyl groups attached to the glycoluril moiety, as has been observed for tetraacetylglycoluril by Hase and Kuhling as well as by Tice and Ganem.[10] In view of the steric strain between the two *N*-acyl groups attached to the same side of a glycoluril system, and the close structural relationship between glycolurils and oxazolidinones,[9] we reasoned that this electrophilic character might result from twisting around the bond between the glycoluril and the attached acyl groups. To test this hypothesis, we examined the X-ray crystal structures of several acylglycolurils. Herein, the X-ray crystal structure of 1,6-diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril‡ **3** is described. The results show that steric crowding in this derivative enforces a highly twisted conformation in *one* of the two acetyl groups in **3**.

The preparation of diacetyl dithioglycoluril **3** has been reported previously.[11] Crystals of **3** were obtained by slow evaporation of a solution in CH_2Cl_2.§ ORTEP drawings of two orthogonal views of the molecule are given in Fig. 1, along with selected bond lengths. In this structure, one acetyl group is held close to coplanar with the thioureido ring of the glycoluril (τ = 2.6°), while the other is twisted significantly out of the ureido ring plane, with τ = 55.0°. This out of plane twist is accompanied by a significant lengthening of the N–C(O) bond, from 1.397(3) Å for the coplanar acetyl group [N(1)–C(15)] to 1.447(3) Å for the twisted amide [N(6)–C(18)]. Careful examination of the crystal packing in **3** showed no close non-bonded interactions around the twisted acetyl group.¶ Although the protons of both acetyl groups appeared at the same chemical shift by NMR analysis, at least down to −60 °C, IR spectroscopy of **3** confirmed the presence of one twisted amide bond in solution. Thus, the spectrum‖ exhibits two distinct C=O stretching absorptions, at 1738 and 1680 cm^{-1}. In contrast, monoacetyl dithioglycoluril[11] exhibits a single stretch at 1681

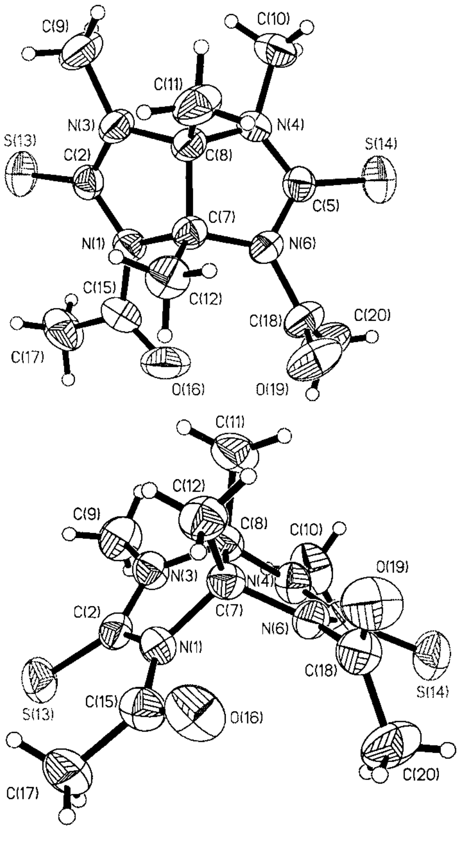


Fig. 1 Two approximately orthogonal ORTEP diagrams of the X-ray crystallographic structure of glycoluril **3**. Selected bond lengths (Å) and angles (°): N(1)–C(2): 1.394(3), N(1)–C(15) 1.397(3), N(1)–C(7) 1.505(3), C(2)–S(13) 1.650(2), C(5)–N(6) 1.367(3), C(5)–S(14) 1.660(2), N(6)–C(18) 1.447(3), N(6)–C(7) 1.461(3), C(15)–O(16) 1.211(3), C(18)–O(19) 1.190(3), C(5)–N(6)–C(18) 122.6(2), C(2)–N(1)–C(15) 129.9(2).

cm^{-1}. This shift to higher frequency with increasing τ is analogous to that reported by Yamada.[6] Thus, the twisted and untwisted acetyl groups apparently interconvert on a time scale between that of NMR and IR analysis.

The observed twist angle is unique to the best of our knowledge for any acetamide: **3** is much more twisted than **2**, and approaches the value for the far more hindered pivaloyl derivative **1**, without requiring the presence of the *tert*-butyl group for steric interaction. The presence of sulfur plays an important role in this effect, since the oxygen analog **4** has τ = 1.5 and 21.6° for the untwisted and twisted acetyl groups respectively, but otherwise resembles **3** in geometry.[12] The twist in glycolurils **3** and **4** is probably the result of unfavourable electrostatic interactions between the two acyl oxygen atoms, which would be forced into close proximity if both acetyl groups were to remain coplanar with their respective attached ureido rings. The larger twist in **3** could result from further steric interactions between the acyl methyl group and the thione (*cf.* **2**); however, the lack of twisting of one acetyl group in **3** suggests that this effect is not major. Rather, we prefer to explain the twist as being due to electron density on nitrogen being pushed into the thione in **3** to a greater extent than into the corresponding carbonyl group in **4**.[14] This effect results in less overlap of the nitrogen lone pairs with the carbonyl groups of the twisted acetyl moieties. The unfavourable interaction of the two acyl oxygen atoms can thus more readily be mitigated in **3** by twisting one acetyl group into the observed twisted conformation. The distances between the two acyl oxygen atoms are 3.03 Å in **3** and 2.84 Å in **4**. One amide resonance interaction in **3** is thus almost fully maintained, while that in the twisted acetyl group is severely compromised. This explanation is consistent with greater electron density on N(6) than on N(1) which results in an increased bond length for N(1)–C(2) compared to N(6)–C(5). Also, shortening of the N(6)–C(7) and concomitant lengthening of the C(7)–N(1) bonds, as well as the tilt of the C(12) methyl group towards the N(1) side of the molecule, and other distances and angles on the acyl-substituted side of **3** are fully in agreement with our interpretation.

Whether activation of the acyl carbon of **3** as a result of this twist enhances the intramolecular Claisen-like condensation of diacylglycolurils is under investigation. It is interesting to speculate that similar unfavourable interactions between a substrate amide carbonyl oxygen atom and another negatively polarized oxygen functionality in a protease could provide a mechanism for twisting of the substrate amide bond prior to nucleophilic attack by water.

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Notes and References

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‡ For nomenclature and numbering system for **3**, see ref. 11.

§ *Crystal data* for **3**: $C_{12}H_{18}N_4O_2S_2$, M = 314.42, T = 300 K, monoclinic, space group $P2_1/n$ (no. 14), a = 10.1648(1), b = 14.4512(3), c = 10.2116(2) Å, β = 99.881(1)°, V = 1477.77(4) Å^3, Z = 4, D_x = 1.413 Mg m^{-3}, graphite monochromated Mo-Kα rotating anode radiation, λ = 0.71073 Å, μ = 3.67 cm^{-1}, crystal size 0.3 × 0.2 × 0.1 mm, 12 100 reflections (3035 unique) with $\theta > 26.5°$ measured using a Siemens SMART CCD area detector; R_{int} = 0.040 after SADABS absorption correction ($T_{\text{min,max}}$ = 0.684, 0.940); full-matrix least-squares refinement on F^2 using SHELXTL software, $wR2$ = 0.123 for all data, $R1$ = 0.047 for 2150 reflections with $I > 2\sigma$, 254 parameters, S = 1.071, non-hydrogen atoms anisotropic, hydrogens isotropic; residual $\Delta\rho_{\text{min,max}} = -0.195$, 0.226 e Å^{-3}. CCDC 182/840.

¶ There appears to be only one other reported crystal structure for an acylglycoluril, that of 1,4-dinitro-3,6-diacetylglycoluril (ref. 13), which is described as having only a small twist angle. In this case, similar arguments were made in relation to the crystal packing not influencing the twist of the acyl groups.

∥ The FT-IR spectrum of **3** was recorded in $CHCl_3$, on a Bio-Rad SPC 3200 spectrophotometer.

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