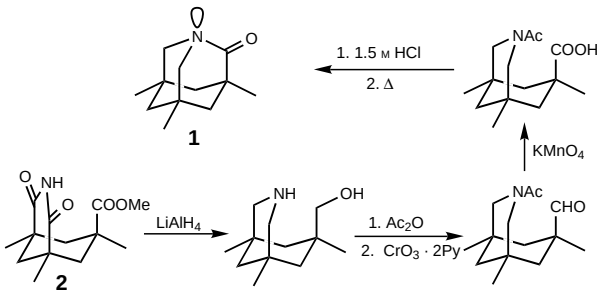
The Most Twisted Amide: Structure and Reactions**

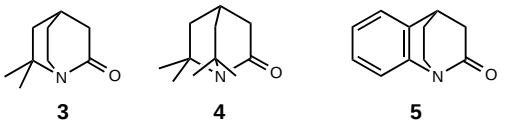
Anthony J. Kirby,* Igor V. Komarov, Peter D. Wothers, and Neil Feeder

We report the preparation, the crystal structure, and some remarkable chemistry of 1-aza-2-adamantanone (**1**). This is the extreme case of a twisted amide, in which overlap of the lone pair on the nitrogen atom with the π system of the carbonyl group is prevented by the rigid geometry of the tricyclic compound. It is prepared from the ester imide **2**[1] of the Kemp triacid by the simple route shown in Scheme 1.



Scheme 1. Synthesis of the twisted amide **1**. Py = pyridine.

The known examples of highly twisted amides (**3**–**5**)[2] are based on the tricyclo[2.2.2]octane skeleton. No detailed structural information is available for these compounds: Only



5 has even been crystallized, and there is evidence that all three polymerize on standing. In contrast, **1** is thermally very stable (m.p. 142–144 °C; it is conveniently purified by sublimation), and gives crystals suitable for structure determination.[3] This shows that the carbonyl group is accurately planar (the three bond angles at the C=O carbon atom add up to 359.9°), and the "amide" nitrogen atom pyramidal (the sum of three bond angles at N is 325.7°; Figure 1).[4] The N–C and C=O bond lengths are 1.475(11) and 1.196(5) Å: substantially longer and shorter, respectively, than expected (1.352, 1.233 Å)[5] for the amide group of an unconstrained tertiary δ-lactam. The twist angle[6] $\tau = 90.5°$ indicates that the nitrogen lone pair lies almost in the nodal plane (a molecular mirror plane) of the π system of the carbonyl group. The most

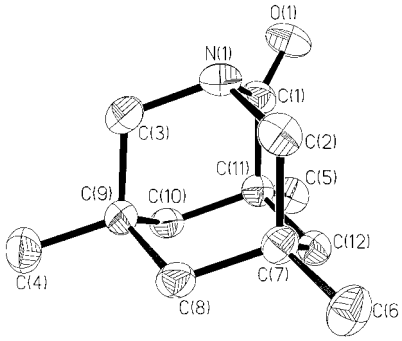
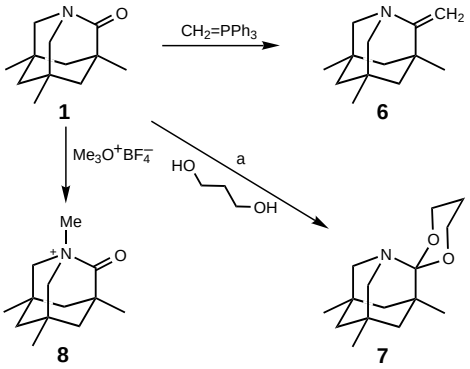


Figure 1. Molecular structure of **1** (ORTEP drawing; ellipsoids are drawn at the 30% probability level).[3] Hydrogen atoms are omitted for clarity.

twisted simple[7] amides for which crystal structures have been reported are two isomeric homologues of **5** that have twist angles of about 40°.[8]

In organic media **1** behaves spectroscopically and chemically as a ketone. The C=O group absorbs at 1732 cm^{-1} in the IR (both in solution in $CDCl_3$ and in a KBr disc), and its ^{13}C NMR chemical shift (in $CDCl_3$) is $\delta = 200$. It reacts with phosphorus ylids under the standard conditions of the Wittig reaction, for example, to form the twisted enamine **6** (Scheme 2), and even forms an "acetal" (**7**) when heated



Scheme 2. Characteristic reactions of the twisted amide **1**. a) p-Toluenesulfonic acid (cat.), benzene, reflux.

with a diol under acid catalysis. Compounds **1**, **6**, and **7** can be methylated at the nitrogen atom by methyl iodide;[7] however, the cation **8** obtained from **1** is an active alkylating and acylating agent, and Meerwein's reagent is needed to give a stable product in this case.

Perhaps most remarkable is the behavior of **1** in water. Pracejus measured an apparent pK_a of 5.3 for the twisted amide **3**.[2] His method (extrapolating the measured pH of a 50% neutralized solution to zero time) fails in the case of **1**, because it is rapidly hydrolyzed when dissolved in water containing a half equivalent of HCl (no signals for **1** were observed in a ^1H NMR spectrum taken in D_2O after 45 s). When the solution is titrated with base, two dissociations are observed with apparent pK_a values of 4.57 and 10.56 (at 25 °C). We take these to be the ionizations of the ring-opened amino acid: The solution shows ^{13}C NMR shifts (in D_2O containing 1% acetonitrile as standard) of $\delta = 188.1$ and 187.8 at pH 7.45 and 12.5, respectively, which are assigned to the

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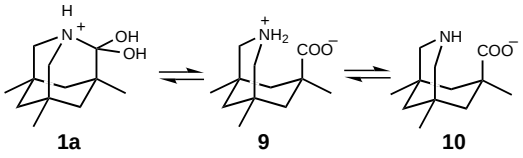
carboxylate carbon atoms of zwitterion **9** and anion **10** [Eq. (1)]. However, at pH 3.30 there is no absorption in this



1a **9** **10** (1)

region, but a new peak at $\delta = 106.3$. This signal can be assigned with some confidence to the orthoamide carbon atom of the hydrate **1a**[11] of the conjugate acid of the twisted amide **1**: The very similarly substituted carbon atom of N-methylated **7** (which has been fully characterized) absorbs at $\delta = 111$ in $CDCl_3$.

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[1] K. S. Jeong, K. Paris, P. Ballester, J. Rebek, Jr., *Angew. Chem.* **1990**, *102*, 550 – 551; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 555-556. We are grateful to Prof. Rebek, Jr. for detailed experimental instructions for the preparation of **2**.

[2] Compound **3**: H. Pracejus, *Chem. Ber.* **1959**, *92*, 988 – 993; Compound **4**: E. I. Levkoeva, E. S. Nikitskaya, L. N. Yakhontov, *Khim. Geterotsikl. Soedin*. **1971**, *3*, 378 – 384; Compound **5**: G. M. Blackburn, C. J.Skaife, I. T.Kay, *J. Chem. Res. Miniprint* **1980**, 3650 – 3669; V. Somayaji, R. S. Brown, *J. Org. Chem.* **1986**, *51*, 2676 – 2686.

[3] Crystal data for **1**: $C_{12}H_{19}NO$, $M_r = 193.28$, crystal dimensions $0.40 \times 0.20 \times 0.10$ mm, monoclinic, space group $P2_1/c$ (no. 14) $a = 8.962(8)$, $b = 6.298(16)$, $c = 19.399(7)$ Å $\beta = 97.38(5)^\circ$, $V = 1085.4(29)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.183$ Mg m^{-3}, $\mu = 0.074$ mm^{-1}, $2\theta_{max} = 49.98^\circ$, $Mo_{K\alpha}$, $\lambda = 0.71069$ Å, data collected by the $\omega/2\theta$ method, $T = 150(2)$ K. Of 2040 measured reflections, 1909 were independent ($R_{int} = 0.0268$). Data reduction was performed within the TEXSAN program. The crystal structure was solved by direct methods with SIR92 and refined by full-matrix least squares on F^2 with SHELXL-93; final residuals (1909 included reflections, 137 parameters): $R1[I > 2\sigma(I)] = 0.0557$, $wR2 = 0.1232$, $S = 1.143$, ($w = 1/[\sigma^2(F_o^2) + (0.0526P)^2 + 0.3815P]$ where $P = (F_o^2 + 2F_c^2)/3$). Hydrogen atoms were fixed geometrically, riding on the relevant heavy atom, and refined with isotropic temperature factors; largest peak and hole in the final difference map: 0.165 and -0.201 e Å^{-3}, respectively. The C=O group is disordered over two sites: The bond lengths quoted for C=O and C–N represent the weighted mean values from the two disordered fragments. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-100711. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[4] The figure of 325.7° is very similar to those observed for acyclic tertiary amines, and identical to that measured for the sum of the three bond angles at the N atoms of diazabicyclooctane: S. Sorriso in *The Chemistry of Functional Groups, Supplement F, Part 1* (Ed.: S. Patai), Wiley-Interscience, Chichester, **1982**, p. 1.

[5] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1 – S19. The effect of the adjacent nitrogen appears to be to shorten the C=O bond in **1** with respect to that in a simple ketone: The mean value for cyclohexanones is 1.211(9) Å.

[6] The angle of twist (not a simple torsion angle) was defined by F. K.Winkler, J. D.Dunitz, *J. Mol. Biol.* **1971**, *59*, 169.

[7] We consider as simple amides compounds with only one N–C=O bond. The rotational barrier is significantly reduced if a second C=O (or C=S) group is attached to the same nitrogen atom.

[8] Relevant known structures: A. Greenberg, C. A. Venanzi, *J. Am. Chem. Soc.* **1993**, *115*, 6951-6957.

[9] The MeN^+ derivative of **7** is of special interest in the context of the reverse anomeric effect[10] and was the primary objective of this work. Our structural and conformational studies on this compound will be reported shortly.

[10] C. L. Perrin, *Tetrahedron*, **1995** *51*, 11901 – 11935.

[11] Protonated hydrates such as **1a**, high-energy intermediates in the acid-catalyzed hydrolysis of normal amides, are formed with particular ease from twisted amides[12] and derive further stabilization from the adamantane framework in our system.

[12] N. H. Werstiuk, R. S. Brown, Q. Wang, *Can. J. Chem.* **1996**, *74*, 524 – 532.

Amidoglycosylation of Polymer-Bound Glycals: A Complete Solid-Phase Synthesis of the Oligosaccharide Domain of the Lewis^b Blood Group Determinant**

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Blood group determinants are a class of cell surface glycoconjugates that are involved in a variety of functions such as cell – cell adhesion, control of cell growth and differentiation, and immune response.[1] Docking of viral and bacterial pathogens is also often initiated through binding of cell surface carbohydrates.[2] In this regard the Lewis^b blood group antigen (Le^b) is of particular interest, as it has been identified as a mediator for the binding of *Helicobacter pylori* to human gastric epithelium.[3] Clinical studies have identified *H. pylori* as a causative agent in gastric and duadenal ulcers.[4] Antimicrobial treatments are currently the means of combatting infection.[5] Since bacterial attachment is a prerequisite to infection,[6] small-molecule lookalikes of the Le^b antennary structure may serve as therapeutic alternatives to broad-spectrum antibiotics.

Although many carbohydrate antigens of the A, B, H, and Lewis families has been synthesized in solution phase, synthetic access has often been laborious and time-consuming.[6] A particularly desirable goal would be the development of generally applicable methods for the rapid assembly of oligosaccharides with a long-term view toward automation. Our laboratory has been investigating an approach in which glycals are key building blocks for the synthesis of oligosaccharides and glycoconjugates.[7] This approach has also proven to be amenable to the synthesis of complex structures on solid supports.[7]

Our solution-phase synthesis of glycosides of 2-deoxy-2-acetylamidoglucose (GlcNac) and -galactose (GalNAc) takes

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