Enhanced Solvolysis

DOI: 10.1002/anie.201108173

A New Twist on Amide Solvolysis

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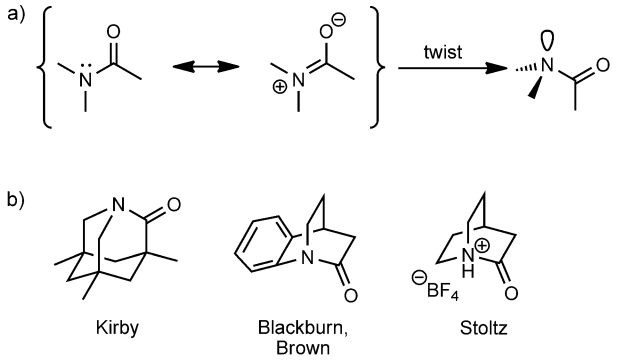
amides · hydrolysis · solvolysis

A fascinating feature of amide bond chemistry is the effect of conformation on reactivity. Every first-year organic chemistry student is taught that both the planar nature of most amide bonds and their stability arise from overlap between a lone pair of electrons on nitrogen with the carbonyl π orbital (Scheme 1a). It has been recognized since the 1930s that

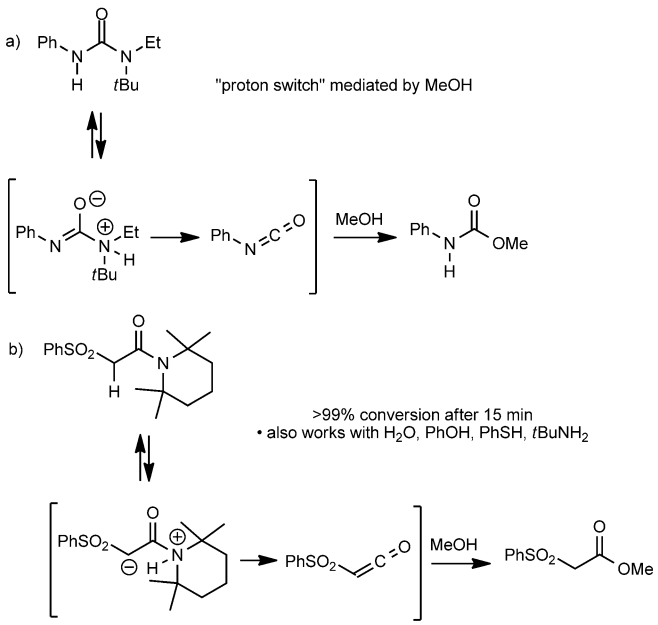


Scheme 1. a) The standard depiction of resonance in a normal, planar amide bond and the effect of twisting the amide bond. b) Iconic examples of twisted amides embedded in bridged frameworks.[2–4]

deviation from planarity—such as observed during *cis/trans* isomerization occurring in protein folding—should result in major changes in reactivity and other chemical properties of the amide bond. For example, rotation of the amide bond is coupled with formal rehybridization of the nitrogen atom to sp^3, with attendant pyramidalization and greatly increased basicity.[1]

The most common experimental approach to studying non-planar amides involves rigging a system such that the poor amide bond has no choice but to exist in a highly destabilized perpendicular arrangement. The most common way to do this is to embed the amide into a bicyclic ring system (Scheme 1b).[2–4] Such molecules have both enhanced reactivity and basicity relative to planar amides. For example, Kirby's "most twisted amide" hydrolyzes in less than a minute and has a pK_a of ca. 5.2 (still attenuated relative to a typical trialkyl amine because the carbonyl group is such a strong electron-withdrawing group).[2]

Now, Lloyd-Jones, Booker-Milburn, and co-workers have shown that one need not resort to such drastic measures to dramatically enhance the reactivity of amide bonds.[5] Their approach is based in part on the group's previously reported solvolysis of ureas, which they proposed to proceed through an initial "proton switch" step, mediated by solvent, that led to the high-energy intermediate shown (Scheme 2a).[6] This



Scheme 2. Hydrolysis of a) ureas[6] and b) amides[5] under neutral conditions.

material would, in turn, break down to afford an isocyanate that is easily trapped by solvent to afford product. The present version exports many of these features to the reaction of an amide bearing both a large group on nitrogen and an electron-withdrawing α substituent (Scheme 2b). Here the likeliest fate of the zwitterion is conversion to a ketene, although this point has yet to be rigorously proven.[5] In pure methanol, the reaction is over in 15 min; hydrolysis using 2 equiv of H_2O in THF allows for the quantitative conversion of the amide to the acid in about a day. The hydrolysis rates of standard amide conversions are famously hard to obtain because they are so slow; estimated half-lives in the literature range in the

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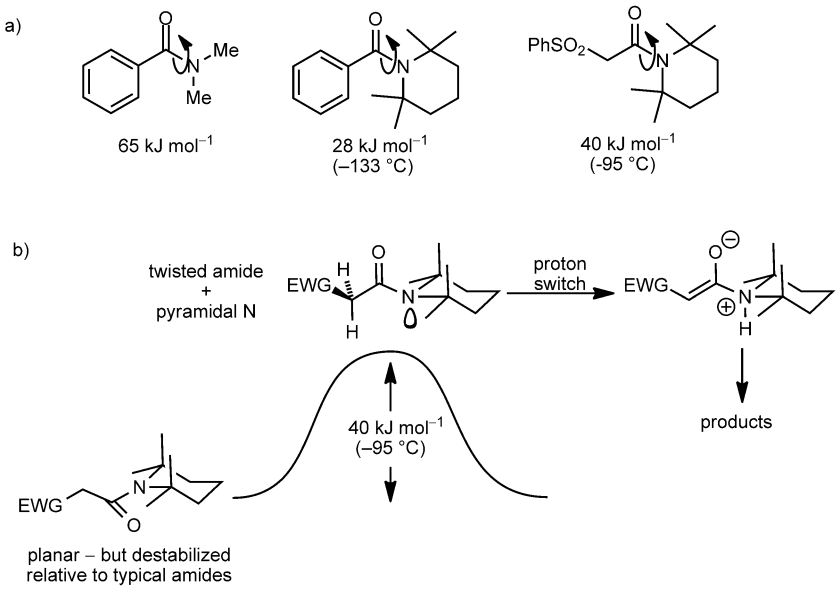

Scheme 3. a) Relative $\Delta G^{\neq}$ values for bond rotations over a series of related amides.[12,13] b) Proposed effect of amide bond rotation on the reactivity of amides utilized in the present study.

hundreds of years.[7] Any way one looks at it, this is a profound rate enhancement.

There are important differences between the apparently similar processes in Scheme 2. The protonation of standard amide bonds generally occurs at oxygen. While the facile protonation of the amide nitrogen has been regularly proposed and observed in bridged lactams (e.g., by crystallography;[4,8] a theoretical treatment has also appeared[9]), its occurrence in an acyclic system under such mild conditions is remarkable. The corresponding reaction of a urea is similarly unusual, but less so because of cross-conjugation of the carbonyl with the other nitrogen atom. The aniline nitrogen in the urea also helps to stabilize the reactive zwitterionic species, a role requiring an electron-withdrawing group on the amide carbon. Although the phenylsulfonyl group shown worked particularly well (and was used in the preparative-scale reaction shown), these researchers also demonstrated the utility of aryl groups as α-electron withdrawing moieties.

One of the most intriguing aspects of this work lies in the mechanistic details behind the proposed proton switch step. Consider this: although the amide in Scheme 2b has many of the same characteristics as bridged lactams (e.g., those in Scheme 1b), it is not a twisted amide in the usually understood sense of the term. Specifically, spectral and X-ray studies of the structure show the amide bond to be almost mundanely planar, with only small distortions arising from the bulky nature of the tetramethylpiperidine (TMP) amide group. The key conformational phenomenon leading to the enhanced reactivity of these compounds is therefore not ground-state distortion—which has been the central point of nearly all discussion involving twisted amide hydrolysis to date—but rather enhanced access to higher-energy intermediates. This stands in contrast to another acyclic amide containing a bulky substituent on the carbon side reported by Yamada, which exhibited a strong ground-state twist and for which was also reported high susceptibility toward hydrolysis.[1,10,11]

Scheme 3 gives the particulars. Previous researchers have recognized that adding steric bulk to the nitrogen side of an amide results in drastically enhanced amide bond rotation rates; for example, Clayden and co-workers studied the effect of such changes on lithiation processes.[12,13] These enhancements can be traced to the destabilization of the ground-state amide. In the present case, the increased access to the "twisted" form results in nitrogen pyramidalization and greater basicity that, along with the acidification of the α carbon, leads to the proton switch. It's all downhill from there: expulsion of neutral amine and addition of solvent complete the reaction sequence shown in Scheme 2b. This differs from the conventional wisdom of previous twisted amide behavior in two important, groundbreaking ways: 1) it is no longer necessary to constrain a molecule into twisted geometry to take advantage of unconventional amide properties so long as the non-planar form can be accessed readily enough and 2) the change in mechanism from standard amide bond hydrolysis routes to the amide→ketene version shown here.

Besides its theoretical impact, the work of the Lloyd-Jones/Booker-Milburn team may well have practical ramifications in areas that would benefit from easy hydrolysis. To name just a few examples, protease inhibitor design and peptide/protein ligation come to mind as exciting possibilities.

Received: November 21, 2011
Published online: February 22, 2012

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