Amide Solvolysis

DOI: 10.1002/anie.201107117

Switching Pathways: Room-Temperature Neutral Solvolysis and Substitution of Amides**

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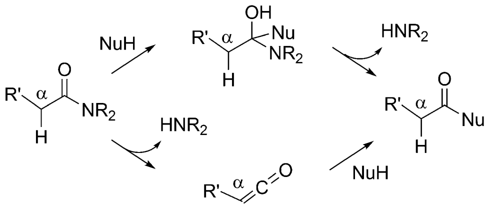
With aqueous half-lives in the range of $>10^2$ years at pH 7 and 25 °C,[1,2] preparative amide hydrolysis usually requires heating under strongly acidic or basic conditions. The notable exceptions to this are lactams in which the amide moiety is strained.[3,4] This phenomenon was explored as early as 1938,[5] and over the last three decades a number of highly strained lactams have been studied.[4,6] A feature common to all of these reactive lactams is the "ketonic" C=O bond, arising from resonance decoupling through N−CO torsion. Detailed mechanistic studies by Brown and co-workers[6d–g] have confirmed that resonance decoupling induces huge increases in solvolysis rates involving direct nucleophlic attack at the carbonyl carbon (upper pathway, Scheme 1). Torsion of the amide bond has also been implicated in polypeptide lyase.[7]

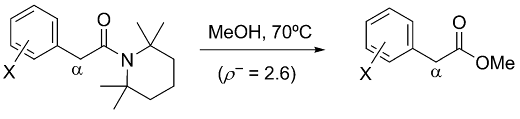


Scheme 1. Addition–elimination (upper) and elimination–addition (lower) pathways for amide substitution by a protic nucleophile (NuH).

Herein, we report on a new paradigm for inducing exceptionally high solvolytic reactivity in simple acyclic amides. Key to this reactivity is the facilitation of an elimination–addition mechanism, (lower pathway, Scheme 1) by a combination of steric hindrance at the nitrogen (NR_2) and an electron-withdrawing substituent (R′) at the α-carbon. The high reactivity arising from this new pathway may have a range of applications, including protection and functionalization in synthesis, and the controlled release of amines and reactive carbonyls in specific environments.

We recently reported isocyanate generation from trisubstituted ureas through a "proton switch" from N−H to N and amine elimination.[8] Transposing this process to function with simple amides under neutral conditions, presents a number of challenges, including the facilitation of an α-CH to NR_2 proton switch and the liberation of a ketene.[9] We began by exploring whether substantial *N*-centred steric hindrance in phenylacetamides would be sufficient to induce their unprecedented neutral methanolysis. Although the *N*,*N*-dimethyl-, diisopropyl- and *tert*-butylisopropyl amides were inert, slow generation ($t_{1/2} = 13$ days) of methyl phenylacetate was detected with the very hindered 2,2,6,6-tetramethylpiperidine (TMP)[10] substrate (Table 1, entry 1). Recognizing that the α-CH to NR_2 proton switch may not be synchronous with HNR_2 elimination, we probed the impact of electron-withdrawing

Table 1: Neutral methanolysis of substituted TMP aryl acetamides.



Entry	X	t[a]	Conversion[a]	$t_{1/2}$[b]
1	H	48 h	10%	13 days
2	*p*-NO_2	20 min	>99%	3.5 min[c]
3	*p*-NO_2	1.5 h	>99%	14 min[d]
4	*p*-CN	1.5 h	>99%	14 min[e]
5	*m*-NO_2	2 h	>99%	18 min[f]
6	3,5-$(CF_3)_2$	1 h	>99%	22 min[g]
7	*p*-$MeSO_2$	1 h	>99%	1 h[h]
8	*o*-NO_2	19 h	>99%	2.7 h[i]
9	*p*-CF_3	24 h	82%	9.7 h[j]
10	*m*-CF_3	48 h	87%	16 h
11	*p*-Br	48 h	88%	16 h
12	*o*-CF_3	48 h	85%	17 h
13	*m*-Br	48 h	84%	18 h
14	2-naphthyl	48 h	22%	5.6 days
15	*m*-MeO	48 h	12%	11 days
16	*p*-MeO	48 h	7%	19 days

[a] Determined by ^1H NMR analysis. [b] When the conversion is larger as 99%, $t_{1/2}$ is based on single time-point first-order solvolytic decays. [c] 86%/10 min. [d] Reaction at 18 °C. [e] 95%/1 h. [f] 77%/1 h. [g] 46%/20 min. [h] 21%/20 min. [i] 78%/9 h. [j] 82%/24 h.

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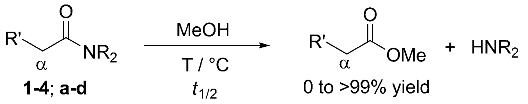
[**] We thank AstraZeneca and the EPSRC for the joint organic studentship initiative (M.H.) and the EPSRC for a grant to K.I.B.-M. and C.E.H (grant number EP/G036764/1). G.C.L.-J. is holder of a Royal Society Wolfson Research Merit Award.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107117.

substituents on the aromatic ring. The effect was remarkable with solvolysis of the *p*-nitrobenzyl substrate complete in minutes (entry 2), even proceeding efficiently at 18 °C (entry 3). Linear free-energy analysis against Hammett σ^- values confirmed that a resonance-stabilized partial negative charge accumulates at the α-C during the solvolysis ($\rho^- = 2.6$).

To probe whether activation was specific to α-aryl amides, a range of acetamides bearing electron-withdrawing substituents (R′) at the α-position (Table 2) were then tested for methanolytic reactivity. The diisopropyl amides **1a–d** were stable, undergoing only trace conversion at reflux for 48 h. On moving to the more hindered amides **2** and **3**, a significant increase in reactivity was observed, most notable in the cases of the phenylsulfonyl **3a** and cyano **3b** substituted examples. However, once again it was the TMP derivatives **4a–d** that showed exceptional reactivity, and with the phenyl sulfonyl derivative **4a** quantitative ester formation (> 99% isolated yield) occurred in minutes at room temperature.

Table 2: The effect of α-substituent (R′) and steric hindrance (R_2) on the methanolytic half-life of acetamides.



1 $NR_2 = N(iPr)_2$ **a** $R' = SO_2Ph$
2 $NR_2 = N(Et)tBu$ **b** $R' = CN$
3 $NR_2 = N(iPr)tBu$ **c** $R' = P(O)(OEt)_2$
4 $NR_2 = TMP$ **d** $R' = CO_2tBu$

NR_2 (T [°C])	$t_{1/2}$ [min][a] **a**	$t_{1/2}$ [min][a] **b**	$t_{1/2}$ [min][a] **c**	$t_{1/2}$ [min][a] **d**
1 (70 °C)	1.0×10^5[b]	1.9×10^5[c]	0.6×10^5	1.9×10^5[c]
2 (50 °C)	1.7×10^4[d]	2.7×10^4	2.1×10^4	0.5×10^4
3 (50 °C)	0.5×10^2[e]	0.7×10^2	4.0×10^2	3.8×10^2
4 (18 °C)	2.2[f,g]	8	23	3.4×10^2

[a] Based on conversion (^{1}H NMR) or isolated yield through first-order solvolytic decay. [b] α-CH/D $t_{1/2} = 2$ h at 21 °C. [c] ≤ 1% conversion/48 h. [d] α-CH/D $t_{1/2} = 51$ min at 21 °C. [e] α-CH/D $t_{1/2} = 9$ s at 21 °C. [f] α-CH/D $t_{1/2} = 3$ min at −10 °C. [g] $t_{1/2} = 48$ min at 3 °C.

Analysis of the kinetics[11] of methanolysis of the α-sulfone acetamide series **1a–4a** in CD_3OD revealed that H/D exchange of the protic solvent with the α-carbon proceeded 10^2–10^3 times faster than methanolysis. A key observation is that through the series (**1a–4a**) the two processes are linked, thus as the activation barrier to α-CH/D exchange decreases, so does the barrier for methanolysis.[12] In other words, the bulkier the substituents at N, the faster the reversible proton switch occurs. This might be envisaged as arising from an increasing level of amide distortion, and thus "ketonic" character, as the steric bulk increases. However, none of the amides studied showed any significant difference in their IR stretching frequency (around 1640 cm^{-1}) or ^{13}C NMR chemical shift (159.8–164.5 ppm) to that expected for classic planar amides. This conclusion was reinforced by an X-ray crystallographic study (see the Supporting Information) in which it is evident that the amide moieties in **1a, 2a**, and **3a** have a typical planar structure, and that even **4a** only has a small deviation from planarity. Thus even in these most hindered examples, the ground-state structures "measure" as normal amides and their exceptional reactivity does not arise from the dominant "ketonic" character[6] found in strained lactams.

Variable temperature NMR data provided an important clue in the analysis of the trend in proton switch/methanolysis rates. In the less reactive compounds, for example the *N,N*-diisopropyl amides **1**, the signals are analogous to those observed in all typical amides, where there is a high energetic barrier to *cis–trans* interconversion of *N*-substituents, because of the resonance decoupling that arises during N–CO rotation. However, for the other amides in the series, the barriers to N–CO rotation decrease substantially as the nitrogen center becomes more crowded, until at the stage of the highly reactive TMP amides **4**, the barrier is much less than half that found in a regular amide[13] The reduced energetic cost of N–CO torsion presumably arises because steric decompression can partially compensate for the resonance decoupling that results. In other words, unlike lactams where resonance decoupling is enforced, these new systems are able to twist about the N–CO bond more freely than normal amides, and thus generate a transiently decoupled system.

A mechanism that incorporates all of these observations is outlined in Figure 1. In cases where R is unhindered, the planar amide is conventional and inert because of the conformational rigidity afforded by the classical bonding picture. As the R groups are increased in steric bulk, a flatter energy surface for N–CO torsion (K_R) allows a greater extent of transient nitrogen pyramidalization. The concomitant increase in *N*-basicity in this minor population then accelerates nucleophile-mediated proton switch[12] (K_{PS}) to reversibly generate a zwitterion, Figure 1. Build-up of negative charge at the α-carbon is accommodated by the electron-withdrawing group (X, Table 1, $\rho^- = 2.6$ and R′, Table 2) and elimination (k_{elim})[11] of the neutral hindered amine, accelerated by steric decompression, then generates a transient ketene.[14]

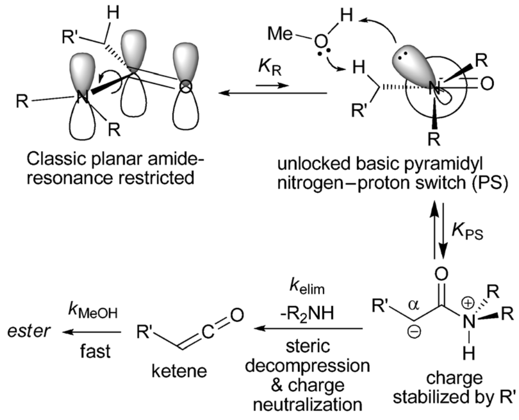
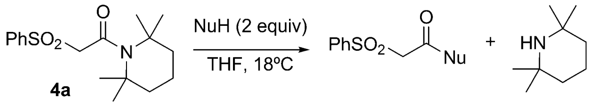


Figure 1. Model for the roles of steric hindrance (NR_2) and electron-withdrawing α-substituent (R′) in neutral methanolysis through elimination.

Table 3: Preparative substitution of TMP amide **4a** at room temperature under neutral conditions.



Entry	NuH	Conversion[a]	*t* [h]	Yield[b]
1	H_2O	> 99%	24	94%
2	MeOH	> 99%	6	95%
3	*t*BuOH	> 99%	24	89%
4	PhOH	> 99%	6	93%
5	PhSH	> 99%	2	97%
6	*t*BuNH$_2$	> 99%	4	97%

[a] Determined by ^{1}H NMR analysis. [b] Yield of analytically pure material isolated after evaporation and column chromatography.

With a mechanistic model in hand, we explored the synthetic utility of this new pathway by moving away from simple solvolytic processes to preparative reactions (Table 3). Upon employing just two equivalents of protic nucleophile, reactions with water, amines, alcohols, and thiols all proceeded efficiently at room temperature in THF. Entry 1 shows, for the first time, that neutral room-temperature hydrolysis can occur with acyclic amides that are not conformationally constrained in the sense of lactams.

Further inspection reveals processes that run contrary to the usual guidelines applied for prediction of classic acyl substitution. For example, PhSH ($pK_a = 6.6$) would not be predicted to displace an amine group ($pK_a > 30$) from an amide in a classical substitution; indeed aryl thioesters are used as acylating agents for amines[15] yet the reaction of **4a** is rapid and essentially quantitative. Entry 6 is an example of a neutral, room-temperature, non-catalyzed reaction that may have application in the important area of transamidation.[16]

In conclusion, we have shown the exceptional reactivity of a new class of amides towards nucleophilic substitution, proceeding at rates previously only observed with twisted lactams. Although these readily prepared[17] amides display reactivity akin to an acyl chloride, they are bench-stable and can be purified by silica-gel chromatography using an aprotic eluent. No acid, base or transition-metal catalysts are required for their nucleophilic substitution. Current evidence suggests their rapid substitution proceeds through an elimination–addition mechanism[9,14] (Scheme 1 and Figure 1); rather than the conventional nucleophilic addition to generate a tetrahedral intermediate, as occurs with regular amides and strained lactams. This new class of amides does not display the "ketonic" carbonyl bond that is characteristic of twisted lactams, but instead gains high reactivity towards protic nucleophiles through a combination of 1) reduced barriers to rotation around the N−CO bond, 2) the ability to accommodate a partial negative charge at the α-carbon, and 3) low nucleophilicity of the very hindered amines that are eliminated. These systems offer significant new opportunities for application and our further studies in these areas will be reported in due course.

Received: October 7, 2011

Keywords: amides · solvolysis · steric hindrance · substituent effects · substitution

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[11] Solvolyses of **2a**–**4a** in CL$_3$OL (L = H or D) to 65–95% conversion, yielded first (pseudo)order decays in substrate and α-CL, indicative that amine elimination is irreversible and that the rate unaffected by the basicity of the medium. Over a period of > 18 h at 50 °C, an equimolar mixture of **2a** and *i*Pr$_2$NH in CD$_3$OD generated **1a** in a yield ≤ 1%.

[12] Analogues of **1**–**4a**, in which the α-C was MeS-CH$_2$-, Cl$_2$CH- and F$_2$CH, were not reactive (a conversion ≤ 1% in 48 h at 70 °C in CD$_3$OD). In all cases, there was no detectable α-CH/D exchange. In α-methylated analogues of **1a**–**4a**, only α-Me **3a** (14%; 90 h, 70 °C) and α-Me **4a** (23%, 72 h, 70 °C) showed methanolytic activity. Heating α-Me **3a** and α-Me **4a** in CD$_3$OD

(50°C, 4 h) resulted in $\leq 1\%$ α-CH/D exchange; a key factor thus appears to be whether α-CH projection appropriate for K_{PS} is attainable.

[13] The barrier for RCO-TMP rotation (R = Ph, Me) is 28 kJ mol^{-1} at −150°C in CHF_2Cl (L. Lunazzi, D. Macciantelli, D. Tassi, A. Dondoni, *J. Chem. Soc. Perkin Trans. 2* **1980**, 717). Low barriers are also implicit in the NMR data reported for Ar-CO-TMP species (RT, $CDCl_3$).[10] Brown has reported on *N*-benozoyl aziridines with low barriers to N−CO rotation, because of attenuated amide resonance, that show increased solvolytic reactivity—but through the conventional addition mechanism.[6e]

[14] A free ketene may not be liberated as attempts thus far to trap such species have been unsuccessful; an alternative pathway would be α-C-mediated nucleophile delivery to the carbonyl carbon in the zwitterion.

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