N-Acyl-Glutarimides: Resonance and Proton Affinities of Rotationally-Inverted Twisted Amides Relevant to N–C(O) Cross-Coupling

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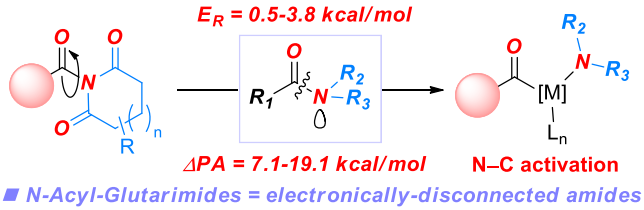
Supporting Information



ABSTRACT: Resonance energies and proton affinities of *N*-acyl-glutarimides, compared with related twisted acyclic amides of relevance to N–C(O) cross-coupling, are reported. The data demonstrate that amidic resonance in *N*-acyl-glutarimides practically disappears (E_R <2.8 kcal/mol), while, intriguingly, these amides favor O-protonation despite significant twist. In some cases, *N*-acyl-glutarimides undergo intramolecular N- to O-acyl migration, indicative of high capacity as acylating reagents. The understanding provided for the high reactivity of *N*-acyl-glutarimides should facilitate the development of a broadly general N–C(O) amide activation platform.

The selective N–C(O) activation of amide bonds represents a powerful transformation in organic synthesis (Figure 1A).[1,2] The ability to rationally modify amide linkages is of fundamental interest due to the ubiquity of amides in a broad range of pharmaceuticals, agrochemicals and functional materials,[3–5] as well as due to the key role of amides as versatile intermediates in chemical synthesis.[6] In this regard, oxidative addition is generally correlated with the extent of resonance stabilization of the amide bond,[7,8] wherein a number of amide precursors with varying amidic resonance have been developed over the past two years.[2,9–12]

Since the first examples in 2015,[13] *N*-acyl-glutarimides have emerged as by far the most reactive amide derivatives in catalytic cross-coupling reactions[2,9–12] owing to three critical and synergistic factors: (1) perpendicular twist of the amide bond in a rotationally-inverted scaffold (τ = 85.7°; χ_N = 5.6°);[14] (2) high stability of the amide acyl bond under various conditions due to the presence of N-glutarimide ring;[15] and (3) thermodynamically disfavored cleavage of the alternative N–C bond due to Nlp conjugation with the imide carbonyl groups.[16]

In the context of amide bond activation, our laboratory has recently applied *N*-acyl-glutarimides to accomplish a range of previously unknown reactions of amides by acyl- and decarbonylative pathways using Pd, Ni and Rh catalysis, including Suzuki-Miyaura,[13] Heck,[17] Negishi,[18] biaryl Suzuki,[19] C–H arylation,[20] cyanation[21] and phosphorylation[10b] (Figure 1B).

Elegant studies by Rueping et al. have established the utility of *N*-acyl-glutarimides in Ni-catalyzed decarbonylative amination,[22] reduction,[23] alkynylation,[24] cyanation,[25] silylation[26] and borylation[26] (Figure 1B). Furthermore, Han et al. recently reported a direct reductive approach to ketone formation using *N*-acyl-glutarimides as key precursors using Ni catalysis,[27] thus opening new vistas in reductive coupling by N–C activation (Figure 1B).[28] A recent elegant study by Hong et al. compared the effect of amide bond distortion in *N*-acyl-glutarimides on the decarbonylative amide reactivity in the first biaryl Suzuki-Miyaura cross-coupling of amides.[29]

It is prominent that while various amide precursors have been enlisted, in all reported examples, *N*-acyl-glutarimides showed decidedly the highest reactivity,[2,9–13,17–27] enabling the development of a range of powerful transformations by N–C(O) activation. Despite the important advances, energetic features that contribute to the high reactivity of *N*-acyl-glutarimides in site-selective N–C activation remain unknown.

Herein, we report resonance energies and proton affinities (protonation sites) in a series of *N*-acyl-glutarimides and compare them with related twisted acyclic amides of relevance to N–C(O) cross-coupling. The data demonstrate that amidic resonance in *N*-acyl-glutarimides practically disappears (E_R <2.8 kcal/mol),[3,8] while, intriguingly, these amides favor O-protonation despite significant twist.[30] We also show that in some cases these amides undergo intramolecular N- to O-acyl

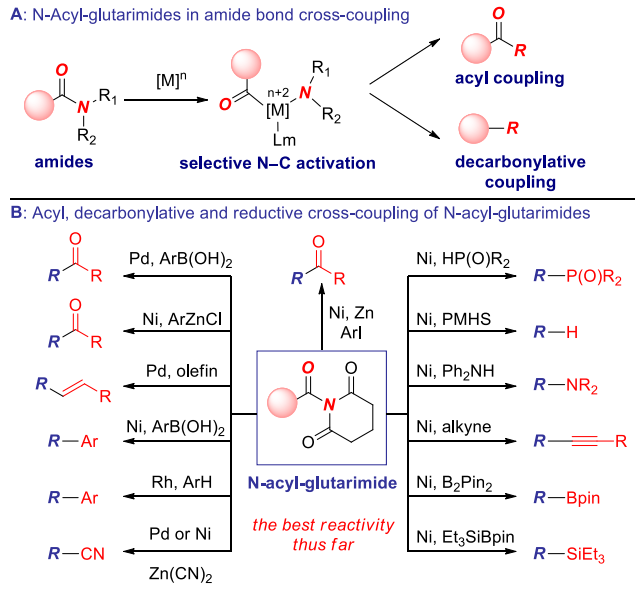


Figure 1. (a) Amide N–C bond activation. (b) *N*-Acyl-glutarimides in N–C bond cross-coupling.

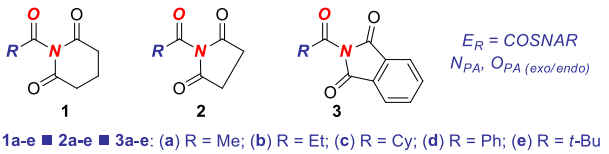


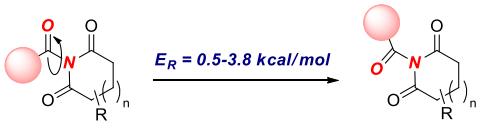
Figure 2. Structures of *N*-acyl-glutarimides and related amides employed in the present study.

migration,[31] indicative of high capacity as acylating reagents. We expect that the mechanistic details presented herein will facilitate the development of new and broadly general amide N–C(O) bond cross-coupling reactions.

Substrates selected for the study are shown in Figure 2. *N*-acyl-glutarimides with varying substitution at the alpha carbon were selected because these derivatives are known to undergo highly efficient cross-coupling by N–C insertion.[2] For comparison, *N*-acyl-succinimides and *N*-acyl-phthalimides were selected because although less reactive in amide N–C coupling, the capacity for selective oxidative insertion has been demonstrated in numerous examples.[2,9–12] The COSNAR method was used to calculate resonance energies of amides selected for the study.[30a] B3LYP/6-311++G(d,p) was selected to conduct optimization as a result of good reproducibility of geometries and energetics of amides[14c] and method practicality. Extensive studies have showed that this level is accurate in predicting properties and resonance energies of amides.[8d,14b] The method was further verified by obtaining good correlations between the calculated and X-ray structures in the series. N,N-dimethylacetamide (DMAc) is included for comparison.

Resonance energies of amides **1-3** are presented in Table 1. Total energies for all compounds calculated in the present study with zero-point energies and thermal corrections (amides, ketones, amines, hydrocarbons) are summarized in the SI (Table SI-1). In general, resonance energies reflect the extent of $n_N \rightarrow \pi^*_{C=O}$ delocalization. The $n_N \rightarrow \pi^*_{C=O}$ delocalization determines the electrophilic reactivity of amides, with the well-established approximation that planar amide bonds feature ca. 40% double bond character (e.g. DMAc, E_R = 18.3

Table 1. Resonance Energies for *N*-Acyl-Glutarimide N–C(O) Rotation Calculated using B3LYP/6-311++G(d,p)[a]



entry	amide	R	E_R [kcal/mol]	E_R (corr) [kcal/mol]
1	**1a**	Me	0.95	0.50
2	**1b**	Et	0.53	0.04
3	**1c**	Cy	1.15	0.74
4	**1d**	Ph	-1.40	-1.49
5	**1e**	*t*-Bu	2.81	2.43
6	**2a**	Me	0.78	0.45
7	**2b**	Et	3.43	2.92
8	**2c**	Cy	3.52	2.97
9	**2d**	Ph	-0.34	-0.64
10	**2e**	*t*-Bu	3.81	3.48
11	**3a**	Me	0.65	0.46
12	**3b**	Et	1.20	0.96
13	**3c**	Cy	1.15	0.91
14	**3d**	Ph	-1.56	-1.83
15	**3e**	*t*-Bu	2.78	2.60

[a]Uncorrected and corrected for zero-point energy and thermal corrections. Energies and bond lengths, see Supporting Information. Representative data on acyclic twisted amides: ref 14b. Representative data on bridged lactams: ref 30a–d. R = H (series 1, 2), R = Ph (series 3, phthalimide).

kcal/mol).[3] *Remarkably, the data in Table 1 indicate that in all amides **1-3** (N = glutarimide, succinimide, phthalimide), the resonance practically disappears (<1.0 kcal/mol) or is very low (<4.0 kcal/mol)* irrespective of the R substituent on the amide side of the molecule (**1**: -1.5-2.4 kcal/mol; **2**: -0.6-3.5 kcal/mol; **3**: -1.8-2.6 kcal/mol). The negative resonance energy for amides **1d-3d** (R = Ph) indicates that these amides are the most reactive in the series in terms of electronic delocalization, as observed experimentally.[2,9–12] The resonance energies strongly suggest that amides **1-3** should behave as highly reactive acylating reagents, whereby the amide carbonyl is electronically disconnected from the nitrogen atom. Note that correlations between resonance energies and bond lengths in acyclic amides typically give scattered results.[14b]

Resonance energies combined with the rotational profile studies, obtained by systematic rotation along the O–C–N–C dihedral angle in both directions (Figure 3),[14a] demonstrate that the high N–C cross-coupling reactivity of amides **1** (cf. **2-3**) observed experimentally has its origin in steric ground-state-destabilization. The twist (τ = 85.7°, **1d** vs. τ = 46.1°, **2d**)[14a] and electronic activation appear to be the major contributors to the electronic N_{lp} from C=O disconnection in **1-3**. Further studies of energetic parameters in acyclic amides will shed light into the relationship between the steric and electronic contribution on the amide bond reactivity.[14b]

Proton affinities (PA) and differences between N- and O-protonation affinities (ΔPA) in amides **1-3** are listed in Table 2. The site-selectivity of amide protonation (N- vs. O-) is a process of high theoretical and synthetic interest;[3,8.30,32] O-protonation increases the barrier to rotation, while N-protonation activates the N–C(O) bond by disrupting amidic resonance. On the basis of literature precedents, we initially hypothesized that synthetically valuable metal insertion into

the N–C(O) amide bond should correlate with the N–protonation aptitude.[13] In this scenario, a productive insertion

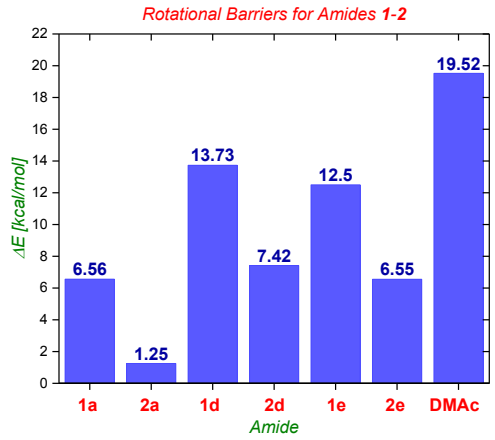


Figure 3. Rotational barriers of amides **1-2** and DMAc (kcal/mol). The barrier for **1-2** represents energy to twist the non-planar N–C(O) bond, cf. DMAc, rotation of the planar N–C(O) bond.

Table 2. Proton Affinities (PA) and Differences in Proton Affinities (ΔPA) for *N*-Acyl-Glutarimides Calculated using B3LYP/6-311++G(d,p)[a]

entry	amide	uncorrected			corrected		
		N_{PA}	O_{PA}	ΔPA	N_{PA}	O_{PA}	ΔPA
1	**1a**	190.1	203.9	-13.8	183.0	196.2	-13.1
2	**1b**	192.0	205.2	-13.2	185.0	197.6	-12.6
3	**1c**	199.0	209.9	-10.8	n/a[b]	n/a[b]	n/a[b]
4	**1d**	196.3	208.7	-12.4	189.1	201.0	-11.9
5	**1e**	194.9	202.0	-7.1	n/a[b]	n/a[b]	n/a[b]
6	**2a**	184.4	204.1	-19.6	177.6	196.2	-18.6
7	**2b**	186.8	206.1	-19.3	180.0	198.4	-18.4
8	**2c**	191.3	210.1	-18.8	n/a[b]	n/a[b]	n/a[b]
9	**2d**	191.8	209.6	-17.9	184.7	201.8	-17.1
10	**2e**	191.7	204.7	-13.0	n/a[b]	n/a[b]	n/a[b]
11	**3a**	195.3	211.6	-16.3	188.0	203.6	-15.6
12	**3b**	197.6	213.5	-15.9	190.3	205.6	-15.3
13	**3c**	201.2	217.2	-16.0	193.9	209.1	-15.2
14	**3d**	201.9	216.2	-14.3	194.4	208.2	-13.8
15	**3e**	202.8	212.5	-9.7	195.5	204.5	-9.0

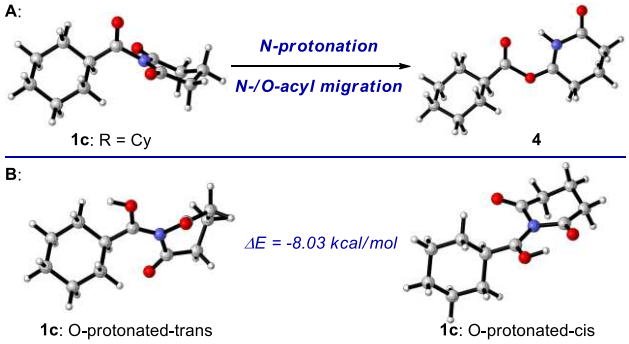
[a]Values (kcal/mol) are uncorrected and corrected for zero-point energy and thermal corrections. [b]N to O-acyl rearrangement. Fixed bond lengths using phthalimides. Representative data on bridged lactams: ref 30[a–d].

step would occur around the $(\tau+\chi_N)$ = 50-70° cross-over point as established by theoretical studies.[30d] Surprisingly, contrary to our expectations[13] (Table 2), we found that all amides **1-3** favor protonation at the oxygen atom (**1**: ΔPA = 7.1-13.8 kcal/mol; **2**: ΔPA = 13.0-19.6 kcal/mol; **3**: ΔPA = 9.7-16.3 kcal/mol). These values can be compared with 11.5 kcal/mol for O- vs. N-protonation in formamide.[30b]

Detailed examination of the protonation aptitude in the studied series of compounds reveals several intriguing points:

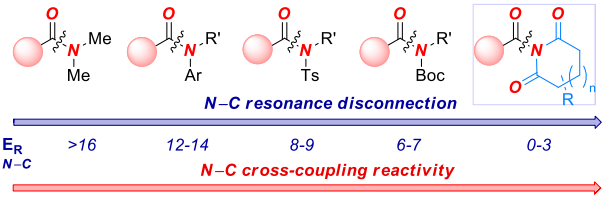
(1) Upon N-protonation, amides **1c** (R = Cy), **1e** (R = *t*-Bu), **2c** (R = Cy) and **2e** (R = *t*-Bu) undergo intramolecular N- to

Scheme 1. N-/O-Acyl Migration and O-Protonation in Representative Amide 1d[a]



[a]Energies, see SI. Images generated using CylView.

Scheme 2. Reactivity Scale of Amides Relevant to Metal-Catalyzed N–C Cross-Coupling[a]



[a]Scission of the N–X bond (X = Ts, Boc) is a major side reaction in amide N–C(O) coupling. Reactivity of anilides in N–C insertion is rare.[2,9b]

O-acyl migration, indicative of high capacity of these amides as acylating reagents (Scheme 1A).[31] For the model compound in this class, **1a**, a barrier of 0.70 kcal/mol has been found. The N-/O-rearrangement is not observed for other compounds in series **1-2** and **3** (N = phthalimide). The geometry of **1** and **2** that undergo the rearrangement was minimized using fixed bond lengths obtained for phthalimide derivatives. Selective acylation reactions by sterically-twisted amides have been reported by Yamada.[15] The present findings confirm that amides **1-2** should serve as highly reactive acylating reagents.

(2) The presence of an intramolecular hydrogen bond between the O-protonated form (exocyclic C=O bond) and one of the ring oxygens (Scheme 1B) significantly reinforces the O-protonation aptitude in all compounds examined (**1**: ΔPA = 16.5-23.5 kcal/mol; **2**: ΔPA = 21.0-28.8 kcal/mol; **3**: ΔPA = 18.1-25.1 kcal/mol) (Table SI-2). This finding strongly suggest that ΔPA in these twisted amides can be further fine-tuned by judicious choice of experimental conditions.[13,17–20]

(3) *Most importantly, O-protonation of the ring carbonyls is easily accessible for all ring systems studied* ($\Delta PA_{Oexo/Oendo}$, kcal/mol, **1**: Me = 0.4, Et = 0.1, Cy = 1.1, Ph = 1.2, *t*-Bu = –0.1; **2**: Me = 0.8, Et = 0.7, Cy = 1.9, Ph = 2.7, *t*-Bu = 0.7; **3**: Me = 2.9, Et = 2.8, Cy = 3.9, Ph = 4.4, *t*-Bu = 2.7). This suggests that amides **1-3** are unique in their N-/O-protonation aptitude in that they may undergo switchable O-/O- protonation activating the N–C(O) bond (*but not N-/O-protonation*),[30a] while its magnitude depends on the ring system, R-substituent, and the intramolecular hydrogen bond. The hydrogen bond is stabilized by the exocyclic carbonyl O-protonated form.

Collectively, these results provide a rationale for the N–C cross-coupling selectivity observed experimentally (Scheme

2).[2,9–13,17–27] These studies demonstrate that steric[30] (twist) and electronic[15] (presence of polar N-substituents) activation of amide bonds could lead to the design of more efficient acylating reagents by amide N–C bond cleavage.

In summary, *N*-acyl-glutarimides have emerged as the most reactive amide derivatives in transition-metal-catalyzed amide N–C bond activation. This study demonstrates that electronic properties of the amide bond in *N*-acyl-glutarimides are best represented as electronically-disconnected amide bonds. Notably, the amide bond resonance practically disappears (<1.0 kcal/mol) or is very low (<4.0 kcal/mol). Moreover, these amides vastly favor O-protonation despite significantly twisted structures. We have also demonstrated the viability of intramolecular O-/O-protonation switch, activating the acyl amide bond, and shown that some of these amides undergo intramolecular N- to O-acyl migration, indicative of high capacity as acylating reagents. We fully expect that the mechanistic details will facilitate the development of new and efficient methods for cross-coupling of amides. Future work will be directed at determination of bond activation steps and expanding the generality of coupling partners that can be utilized in this powerful cross-coupling manifold.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates and energies. Detailed description of computational methods used. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

Rutgers University and the NSF (CAREER CHE-1650766) are gratefully acknowledged for support. The 500 MHz spectrometer was supported by the NSF-MRI grant (CHE-1229030). We thank the Wroclaw Center for Networking and Supercomputing (Grant Number WCSS159).

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