Electrophilicity Scale of Activated Amides: ^{17}O NMR and ^{15}N NMR Chemical Shifts of Acyclic Twisted Amides in N–C(O) Cross-Coupling

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Abstract: *The structure and properties of amides are of tremendous interest in organic synthesis and biochemistry. Traditional amides are planar and the carbonyl group non-electrophilic due to $n_N \rightarrow \pi^*_{C=O}$ conjugation. In this study, we report electrophilicity scale by exploiting ^{17}O NMR and ^{15}N NMR chemical shifts of acyclic twisted and destabilized acyclic amides that have recently received major attention as precursors in N–C(O) cross-coupling by selective oxidative addition as well as precursors in electrophilic activation of N–C(O) bonds. Most crucially, we demonstrate that acyclic twisted amides feature electrophilicity of the carbonyl group that ranges between that of acid anhydrides and acid chlorides. Furthermore, a wide range of electrophilic amides is possible with gradually varying carbonyl electrophilicity by steric and electronic tuning of amide bond properties. Overall, the study quantifies for the first time that steric and electronic destabilization of the amide bond in common acyclic amides renders the amide bond as electrophilic as acid anhydrides and chlorides. These findings should have major implications on the fundamental properties of amide bonds.*

The amide bond represents one of the most fundamental and predominant functional groups in organic synthesis and biochemistry.[1,2] Typical amide bonds are planar and exploit amidic $n_N \rightarrow \pi^*_{C=O}$ conjugation (resonance in planar amides of 15-20 kcal/mol) (Figure 1) to achieve coplanarity of the six atoms comprising the amide bond and characteristic high resistance toward nucleophilic addition and hydrolysis.[3] The introduction of steric strain has been established to significantly alter chemical properties of amide bonds, as exemplified by the classic syntheses of twisted bridged lactams.[4,5] In particular, the most twisted bridged lactams have become models for cis-trans rotamer interconversion and instantaneous amide bond hydrolysis.[5a–d] Furthermore, the study of activated amides in biological molecules is an active area of research.[6,7]

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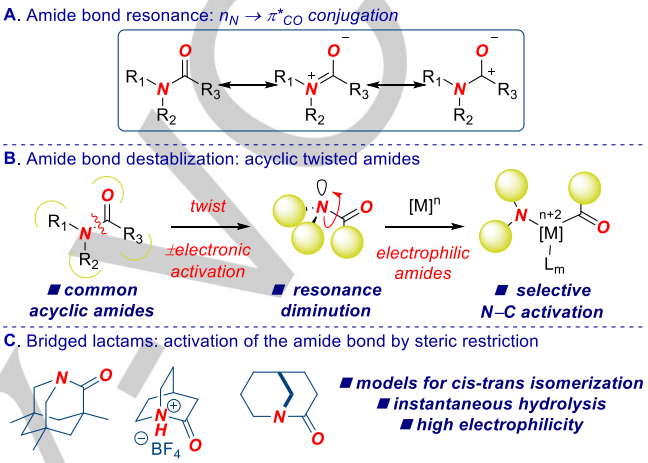

Figure 1. Amide bond resonance in the context of this work.

In the seminal study, Yamada used ^{17}O NMR chemical shifts to follow the carbonyl electrophilicity changes in a series of twisted *N*-acyl-1,3-thazolidine-2-thiones.[8] Dahn demonstrated that ^{17}O NMR chemical shifts provide a precise measure of the electron demand of the carbonyl group.[9] More recently, we showed the changes of amide bond electrophilicity by ^{17}O NMR chemical shifts in C-sterically-hindered amides.[10] It was found that C-steric hindrance affects the carbonyl electrophilicity, however, in all cases examined the amides were found less electrophilic than acyl fluorides.[10]

On the other hand, recent years have witnessed tremendous progress in the development of acyclic twisted and destabilized amides.[11] In particular, the development of ground-state-destabilization of common acyclic amides has enabled the launching of amide bond cross-coupling platform, wherein transition-metals insert selectivity into the N–C(O) amide bond.[12] In this dual reactivity manifold, common acyclic amides serve as acyl-metal or aryl-metal (after decarbonylation) chemically orthogonal equivalents to the more traditional halides and pseudohalides and examples in biomolecule synthesis have already started to appear.[13] Furthermore, the recent advances in transition-metal-free electrophilic activation of amide N–C(O) bonds have provided new avenues for employing amides as acyl precursors in organic synthesis.[14] Moreover, the recently discovered σ N–C scission reactions capitalize on diminishing amidic resonance in common acyclic twisted amides.[15]

However, despite the fundamental importance of acyclic twisted amides in various areas of chemistry and biochemistry, electrophilicity scale of these important amides has not been reported. The lack of electrophilic scale prevents the rational development of synthetic technologies, and more broadly affects the perception of the acyclic amide bond as the most stable

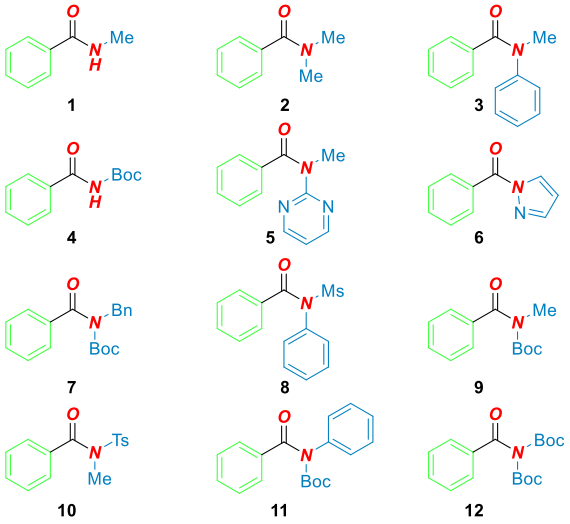

Figure 2. Structures of amides employed in the current study.

carboxylic acid derivative as outlined in all undergraduate organic chemistry textbooks.[1,2,16]

Herein, we report electrophilicity scale of acyclic twisted and destabilized acyclic amides by using ^{17}O NMR and ^{15}N NMR chemical shifts. Most importantly, this study quantifies that (1) acyclic twisted amides feature *electrophilicity of the carbonyl group that ranges between that of acid anhydrides and acid chlorides*, and (2) a wide range of electrophilic amides are available, and with gradually varying carbonyl electrophilicity, by steric and electronic tuning of amide bond properties.

The study provides the first experimental evidence of the gradual change of the carbonyl electrophilicity of activated acyclic amides. Since this class of amides is widely used across all chemical disciplines in both academia and industry, and considering both historical and topical importance of the amide bond in chemistry and biology,[1–6] the study provides the first insight into how electrophilic these amides are in reality, which is contrary to the common knowledge, and establishes a blueprint for the future studies of amide bond reactivity. The study is focused on ^{17}O NMR and ^{15}N NMR determination of acyclic twisted and electronically-activated amides. These are fundamental properties of carbonyl groups.[8,9] It is also worth noting that carbonyl electrophilicity enhances the reactivity to transition-metal oxidative addition of the N–C amide bond.[11]

Recently, we became interested in using ^{17}O NMR and ^{15}N NMR spectroscopy as a broadly useful analytical tool in evaluating electronic properties of amides.[17,18] In this context, ^{17}O NMR chemical shifts provide one of the most precise measures of π-electron density of amides in solution, while, importantly, ^{17}O NMR can be routinely measured at natural abundance, and the shifts are not affected by electronics of substituents.[9]

Following our expertise in amide cross-coupling,[11,12,14] we hypothesized that acyclic twisted amides would show electronic properties with vastly diminished electrophilicity of the carbonyl group. Amides selected for the study are shown in Figure 2. In general, amides were selected based on their twist and destabilization[11] as well as activity in cross-coupling and electrophilic activation reactions.[12,14] Amides (**1-2**) are control

Table 1 ^{17}O NMR Chemical Shifts for Amides **1-12**[a]

entry	amide	amide	δ(^{17}O)
1	*N,N*-Me/H	(**1**)	308.1
2	*N,N*-Me/Me	(**2**)	340.8
3	*N,N*-Ph/Me	(**3**)	356.2
4	*N,N*-Boc/H	(**4**)	386.5
5[b]	*N,N*-pym/Me	(**5**)	398.3
6	*N*-pyrazole	(**6**)	411.1
7	*N,N*-Bn/Boc	(**7**)	419.3
8	*N,N*-Ph/Ms	(**8**)	420.2
9	*N,N*-Me/Boc	(**9**)	425.2
10	*N,N*-Me/Ts	(**10**)	426.6
11	*N,N*-Ph/Boc	(**11**)	437.8
12	*N,N*-Boc/Boc	(**12**)	462.0

[a]Recorded at 54.1 MHz in CD_3CN. Chemical shifts are referenced to external H_2O. [b]4-Tol.

Table 2 ^{15}N NMR Chemical Shifts for Amides **1-12**[a]

entry	amide	amide	δ (^{15}N)
1	*N,N*-Me/H	(**1**)	98.2
2	*N,N*-Me/Me	(**2**)	101.2
3	*N,N*-Ph/Me	(**3**)	124.6
4	*N,N*-Boc/H	(**4**)	134.5
5[b]	*N,N*-pym/Me	(**5**)	134.4
6	*N*-pyrazole	(**6**)	238.7
7	*N,N*-Bn/Boc	(**7**)	150.3
8	*N,N*-Ph/Ms	(**8**)	176.1
9	*N,N*-Me/Boc	(**9**)	136.0
10	*N,N*-Me/Ts	(**10**)	153.3
11	*N,N*-Ph/Boc	(**11**)	157.2
12	*N,N*-Boc/Boc	(**12**)	165.3

[a]Recorded at 40.4 MHz in $CDCl_3$. Chemical shifts refer to the NH_3(l) scale. [b]4-Tol.

amides for 2° and 3° amides. *N*-methyl- *N*-phenylbenzamide (**3**) is an electronically-activated amide with Nlp delocalization onto the π aromatic ring (RE, resonance energy = 13.5 kcal/mol) that is effectively cross-coupled using Ni.[12b] Additional amides include *N*-mono-Boc electronically-activated amide (**4**), *N*-MAPA amide (**5**) (N-methylamino-pyrimidyl, RE = 6.7 kcal/mol) and N-pyrazolyl amide (**6**) (RE = 7.8 kcal/mol) that readily participate in Pd and Ni catalyzed cross-coupling and are activated by the conjugation onto the aromatic ring.[12a] Furthermore, *N*-carbamate and *N*-sulfonamide activation, such as *N*-Boc, *N*-Ms, and *N*-Ts leads to electronically-activated, twisted acyclic amides as is represented by *N,N*-Boc/Bn (**7**), *N,N*-Ms/Ph (**8**), *N,N*-Boc/Me (**9**), *N,N*-Ts/Me (**10**) and *N,N*-Boc/Ph (**11**) amides.[11] It is important to note that these amides are readily synthesized from either carboxylic acid derivatives or the corresponding 2° amides, thus representing an effective way to activate common amide bonds. Finally, *N,N*-Boc_2 amide (**12**) represents one of the most twisted acyclic amides (Winkler-Dunitz parameters, τ = 76.1°) and is prepared in a single *N*-di-*tert*-butoxycarbonylation step from 1°

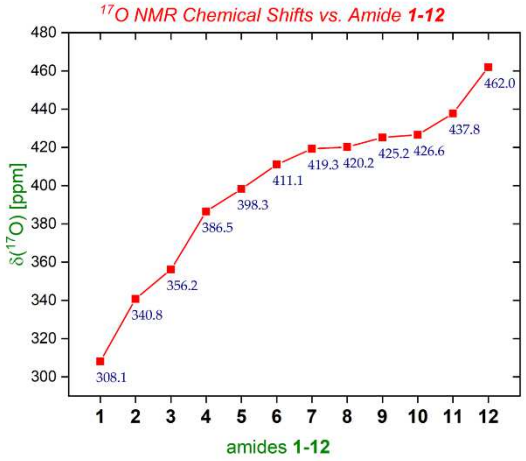

Chart 1 Plot of ^{17}O NMR chemical shifts vs. amides **1-12**.

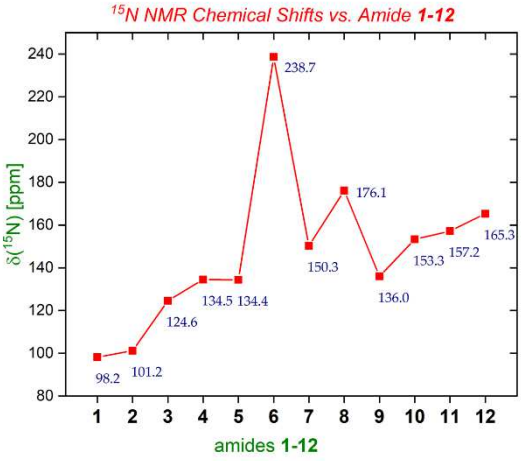

Chart 2 Plot of ^{15}N NMR chemical shifts vs. amides **1-12**.

benzamide.[11] In all cases, benzamide derivates were selected due to their key role in N–C(O) cross-coupling reactions.

^{17}O NMR spectra were recorded at 54.1 MHz in CD_3CN solutions at 297 K and referenced against external H_2O. The ^{15}N NMR chemical shifts were typically determined via ^{1}H-^{15}N HMBC spectra. Additional details are provided in the SI.[19,20]

^{17}O NMR chemical shifts of amides **1-12** are shown in Table 1. Chart 1 presents a graphical representation of ^{17}O NMR shifts vs. amide. Most importantly, the data provide a scale of changing carbonyl electrophilicity in amides **1-12**. Compared with *N*-Me and *N*,*N*-Me_2 amides (**1-2**), there is substantial effect resulting from electronic delocalization onto the *N*-aromatic ring (**3**). The chemical shift of 356.2 ppm in **3** is comparable with the available data for PhCOF (352.6 ppm).[9] *Thus, the data show that N-anilides should be considered as carbonyl electrophilic equivalents of acyl fluorides.* Furthermore, ^{17}O NMR chemical shifts of other electronically-activated amides **4-6** are in the range of acid anhydrides (386.5-411.1 ppm), the available data for PhCOOCOPh (386.4 ppm).[9] However, note that amide **4** (*N*,*N*-Boc/H) contains acidic NH, which affects its reactivity in the cross-coupling reactions. The effect of twisting on carbonyl electrophilicity in *N*-carbamate and *N*-sulfonamide derivatives **7-11** is even more pronounced with the *N*,*N*-Ph/Boc derivative being the most electrophilic in the series (419.3-437.8 ppm). Most remarkably, the *N*,*N*-Boc_2 twisted amide **12** is characterized by the ^{17}O NMR shift of 462.0 ppm, which is *significantly more electrophilic that acid anhydrides and close to the range of acid chlorides* (the available data for PhCOCl, 483.6 ppm).[9] Overall, the data in Table 1 quantify that (1) acyclic twisted amides feature vastly increased electrophilicity over classical *N*,*N*-di-alkyl-amides, (2) the electrophilicity of acyclic twisted amides in between acid anhydrides and acid chlorides, (3) steric and electronic tuning permits access to various amides with gradually varying electrophilicity. A graphical representation of the carbonyl electrophilicity scale of activated twisted amides in presented in Figure 4.

We were further intrigued to measure ^{15}N NMR chemical shifts of amides **1-12**. While the use of ^{15}N NMR chemical shifts is less straightforward than ^{17}O NMR chemical shifts, ^{15}N NMR shifts provide a good estimate of charge density at the nitrogen

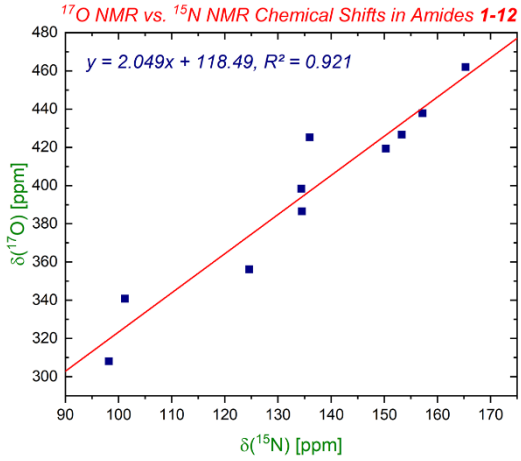

Chart 3 Plot of ^{17}O NMR vs. ^{15}N NMR chemical shifts in **1-12**. Outlier: **8**, $\delta(^{15}N)$ = 176.1 ppm; **6**, $\delta(^{15}N)$ = 238.7 ppm is not included.

atom in amide bonds.[20] ^{15}N NMR chemical shifts of amides **1-12** are shown in Table 2. Chart 2 presents a graphical representation of ^{15}N NMR shifts vs. amide. Remarkably, we found an excellent linear correlation between ^{17}O NMR chemical shifts and ^{15}N NMR chemical shifts in the studies acyclic twisted amides (R^2 = 0.92, outlier analysis: *N*,*N*-Ph/Ms, **8**) (Chart 3). Interestingly, the most twisted amides **10-12** are characterized by the ^{15}N NMR shifts of 153.3-165.3 ppm, which is in the range nitrogen of pyrroles (158 ppm, C_4H_4NH) and isonitriles (162 ppm, MeNC) rather than typical *N*,*N*-di-alkyl amides (104 ppm, DMAC cf. Table 2, entry 2).[18b] Taken together, the data indicate that (1) the charge density at the nitrogen atom in twisted acyclic amides follows the inductive effect destabilizing N-substituent, (2) ^{15}N NMR can be used as a predictive tool of the carbonyl electrophilicity in this class of compounds. However, it should be noted that amide **8** (R = Ms) is an outlier, while aromatic *N*-acyl-pyrazole derivative **6** is not considered in this analysis due to aromatic nitrogen (238.7 ppm). Note that pyrazole contains electronegative nitrogen atom connected to the amide bond, which further affects its ^{15}N NMR shifts (cf. pyrrole, Table 3).

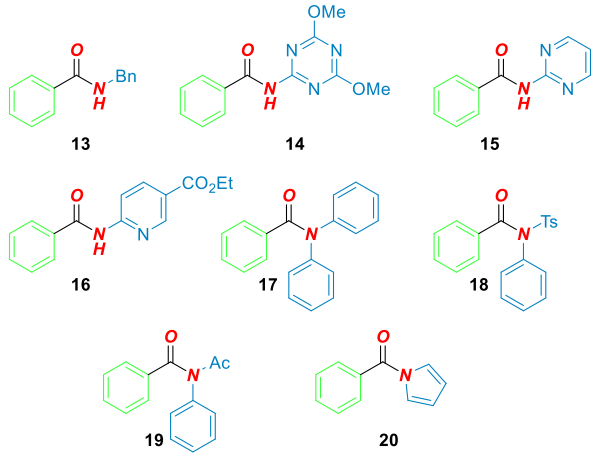

Figure 3. Structures of additional amides in the current study.

Table 3 ^{15}N NMR Chemical Shifts for Amides **13-20**[a]

entry	amide	amide	δ(^{15}N)
1	*N,N*-Bn/H	(**13**)	112.9
2	*N,N*-triazine/H	(**14**)	137.7
3	*N,N*-pym/H	(**15**)	138.1
4	*N,N*-4-CO_2Et-2-py/H	(**16**)	138.5
5	*N,N*-Ph/Ph	(**17**)	147.4
6	*N,N*-Ph/Ts	(**18**)	178.5
7	*N,N*-Ph/Ac	(**19**)	180.7
8	*N*-pyrrole	(**20**)	195.5

[a]Recorded at 40.4 MHz in $CDCl_3$. Chemical shifts refer to the NH_3(l) scale. See Figure 3 for structures.

More broadly, ^{15}N NMR shifts are useful in cases when ^{17}O NMR recording is problematic due to low solubility. To gain additional insight into the electronic properties of acyclic twisted and activated amides in solution, we have recorded ^{15}N NMR chemical shifts of additional amides **13-20** (see Figure 3).

These amides include a triazine derivative (**14**), an ester-containing *N*-pyridine derivative (**15**) that was used in esterification reactions, *N,N*-di-phenyl-benzamide (**17**), a sulfonamide derivative *N,N*-Ts/Ph (**18**) and mono-twisted *N,N*-Ac/Ph amide (**19**) (Table 3).[11–14] The ^{15}N NMR data indicate a gradual removal of the charge density from nitrogen atom, culminating in acyclic twisted amides *N,N*-Ts/Ph (**18**) and *N,N*-Ac/Ph (**19**) (178.5-180.7 ppm), pointing at the high electrophilicity of the amide bond in these amides.[21]

Furthermore, several reference amides have been recorded (see Table SI-1). (1) The simplest benzamide, Ph–C(O)NH_2 is characterized by the ^{17}O NMR shift of 286.7 ppm (CD_3OD, RT) and the ^{15}N NMR shift of 95.5 ppm. (2) Cyclic activated amides such as *N*-benzoyl-glutarimide and *N*-benzoyl-succinimide are among the most reactive amides to date and characterized by the ^{15}N NMR shift of 204.6 ppm and 206.3 ppm, respectively. (3) Cyclic *N*-benzoyl-azetidine is characterized by the ^{17}O NMR shift of 313.9 ppm and ^{15}N NMR shift of 110.0 ppm. (4) Reference compounds, Ph–C(O)F, Ph–C(O)Cl and (Ph–CO)$_2$O are characterized by the ^{17}O NMR shifts of 350.8 ppm, 481.6 ppm and 385.1 ppm, respectively (CD_3CN). Overall, these values provide further support for the electrophilicity scale of electronically-activated acyclic twisted amides. Studies on electrophilicity of other classes of amides are ongoing.

An interesting argument pertaining to amide bond destabilization involves the degree of torsion (Winkler-Dunitz τ parameter)[1,3] and inductive effect of the *N*-substituent with respect to the amide bond electrophilicity. In general, steric distortion has been used as a measure of amide bond destabilization in bridged lactams.[4,5] However, destabilization of acyclic twisted amides predominantly relies on inductive electronic effect rather than steric distortion.[11,12] As such, the twisting mechanism follows the inductive effect to minimize steric interactions, which has been amply demonstrated in several classes of acyclic twisted amides.[11,12] While full distortion of simple *N,N*-di-alkyl-amides would be of significant theoretical interest, at present these amides are limited to few examples of sterically-hindered *N*-*t*-Bu-amides. As such, ^{17}O NMR provide a precise measurement of the carbonyl π-electron density of amides that are unavailable by other methods.

Similarly, one could postulate that resonance energy (RE) could be a good predictor of the carbonyl electrophilicity of the amide bond. A summary of representative RE data of selected amides used in the current study is presented in Table SI-2. There is no correlation between RE and carbonyl electrophilicity in acyclic twisted amides. In general, electronically-activated amides feature dramatically decreased amidic resonance, ranging from 0 to ca. 13.5 kcal/mol (see Table SI-2). The resonance energy as typically calculated by the COSNAR approach and rotational barriers provide specific data on the N–C(O) bond stabilization,[3d,4] which should be regarded complementary to the carbonyl π-electron density.

In summary, we have developed the electrophilicity scale of acyclic twisted and activated amides using ^{17}O NMR and ^{15}N NMR chemical shifts. The strategy of activating common acyclic amides by twist and electronic ground-state-destabilization[22] has gained major attention as an enabling feature of N–C(O) cross-coupling and electrophilic N–C(O) activation reactions. This study clearly quantifies that acyclic twisted amides feature

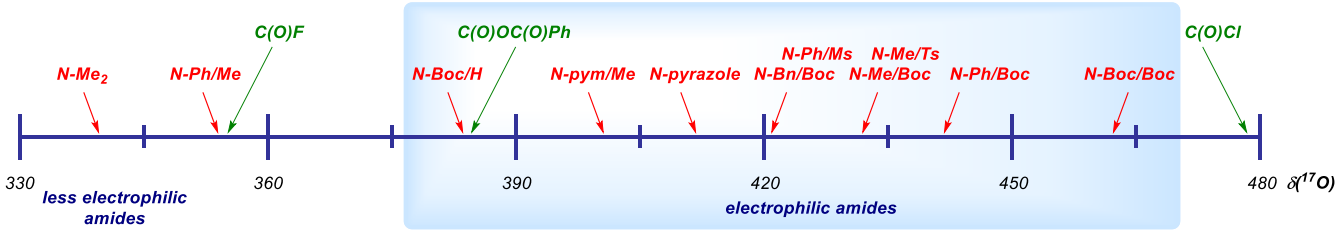

Figure 4. Electrophilicity scale of acyclic twisted and activated amides.

electrophilic carbonyl groups that range between that of acid anhydrides and acid chlorides. Furthermore, we have demonstrated that a wide range of electrophilic amides with gradually varying carbonyl electrophilicity are available by steric and electronic tuning of amide bond properties. The amide bond twisting in common acyclic amides has major implications in organic synthesis, biochemistry, structural chemistry and biology. Studies directed toward the development of new methods for activating amide bonds, study of the reactivity of various classes of amides and their characterization are currently underway.

Acknowledgements

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Keywords: ^{17}O NMR • twisted amides • transition-metal-catalysis • cross-coupling • N–C(O) activation

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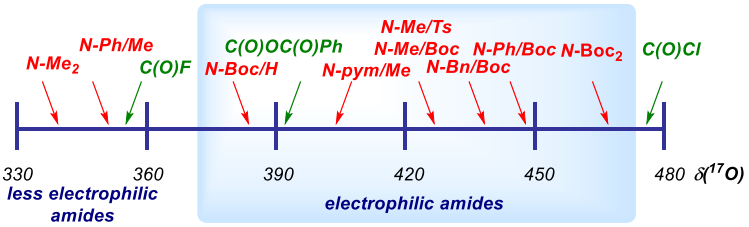
[21] a) Note that amides do not need to be tertiary in order to be useful in N–C cleavage reactions. For a recent study, see ref. 13. b) We have been unable to record *N,N*-Ts/Ac and *N,N*-Ts/Boc amides. These amides are insufficiently stable to record the data. c) Compound **16**, *N,N*-4-CO_2Et-2-py/H (5-CO_2Et pyridine numbering) was selected as the 5 isomer rather than the 3 isomer because it is fully conjugated with the amide nitrogen. Ethyl group has been selected rather than *t*-Bu because it is more general and to facilitate the measurement. We have been unable to measure ^{17}O NMR due to low solubility.

[22] For recent elegant studies of amide distortion by peripheral metal coordination, see: S. Adachi, N. Kumagai, M. Shibasaki, *Chem. Sci.* **2017**, *8*, 85.



We report electrophilicity scale by exploiting ^{17}O NMR and ^{15}N NMR chemical shifts of acyclic twisted and destabilized acyclic amides that have recently received major attention as precursors in N–C(O) cross-coupling and electrophilic activation. Most crucially, acyclic twisted amides feature electrophilicity of the carbonyl group that ranges between that of *acid anhydrides and acid chlorides*.

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Electrophilicity Scale of Activated Amides: ^{17}O NMR and ^{15}N NMR Chemical Shifts of Acyclic Twisted Amides in N–C(O) Cross-Coupling