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^{17}O NMR and ^{15}N NMR Chemical Shifts of Sterically-Hindered Amides: Ground-State Destablization in Amide Electrophilicity

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The structure and spectroscopic properties of the amide bond are a topic of fundamental interest in chemistry and biology. Herein, we report ^{17}O NMR and ^{15}N NMR spectroscopic data for four series of sterically-hindered acyclic amides. Despite the utility of ^{17}O NMR and ^{15}N NMR spectroscopy, these methods are severely underutilized in the experimental determination of electronic properties of the amide bond. The data demonstrate that a combined use of ^{17}O NMR and ^{15}N NMR serves as a powerful tool in assessing electronic effects of the amide bond substitution as a measure of electrophilicity of the amide bond. Notably, we demonstrate that steric destabilization of the amide bond results in electronically-activated amides that are comparable in terms of electrophilicity to acyl fluorides and carboxylic acid anhydrides.

The amide bond is a key linkage in peptides and proteins as well as one of the cornerstones of many biologically active compounds and natural products.[1,2] Deformations of the amide bond from planarity by steric repulsion are of utmost importance in nearly all areas of chemical research because distortions of this type may have tangible impacts on electronic and structural properties of amides.[3–8] The paramount importance of amides in every aspect of chemical science has led to extensive efforts to experimentally demonstrate distortion.[5a,8a] The distortion of amide bonds is notably present in enzymes, conformational relays and catalysis.[6–8] As a result, the development of efficient methods that determine electronic properties of amides[3a–f] is critical to scientists within both industry and academia because of the plethora of applications of amide bonds in their research.[1–8]

Typical amide bond is planar, and considered as one of the least reactive carboxylic acid derivatives as a consequence of $n_N \rightarrow \pi^*_{C=O}$ resonance (Fig. 1A).[3] However, distortions from planarity have a profound effect on the structural and electronic properties of amides (Fig. 1B-C).[4–6] A controlled degree of amide bond rotation can be successfully employed to modulate amide reactivity in synthesis, medicinal chemistry and conformational switching.[7] The ground-state amide bond destabilization mechanism in which the amide bond is twisted by steric repulsion between the N- and C-substituents has led to the development of N–C activation chemistry.[6a,c] The amide bond deformation by steric repulsion is analogous to the biomimetic activation of amides by which Nature affects the amide bond conformation by intermolecular steric interactions within the active site of enzymes.[8] Reliable methods to determine electronic properties of the amide bond are essential to processes involving the amide bond in chemistry and biology.[1,2,7,8] In this regard, ^{17}O NMR and ^{15}N NMR spectroscopy offer a broadly useful tool in experimental evaluation of bond electrophilicity;[9,10] however, despite the potential utility, ^{17}O and ^{15}N NMR spectroscopy have been rarely used to assess electronic properties of amides.

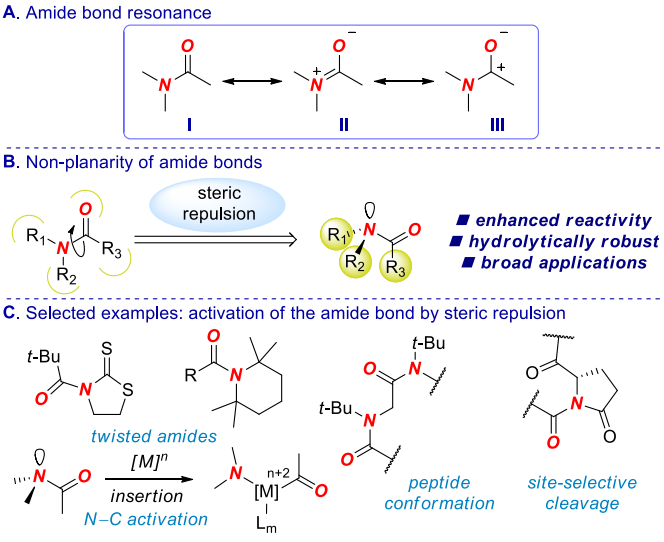

Fig. 1 (a) Amide bond resonance. (b) Activation of the amide bond by steric repulsion. (c) Selected examples.

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Herein, we report a blueprint for the use of ^{17}O NMR and ^{15}N NMR spectroscopy to determine electronic effects of the amide substitution in ground-state-destabilized amides as a measure of electrophilicity of the amide bond. Notably, we demonstrate that steric destabilization of the amide bond, using purely aliphatic substituents,[11,12] results in electronically-activated amides that are comparable in terms of electrophilicity to acyl fluorides and carboxylic acid anhydrides. We expect that the presented findings will result in a common application of ^{17}O and ^{15}N NMR spectroscopy to delineate electronic properties on activated amides in organic synthesis.

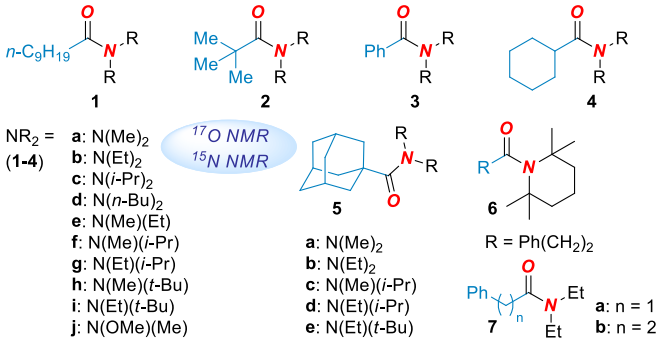

Fig. 2 Structures of amides employed in the current study.

The seminal study by Yamada demonstrated an excellent linear correlation between ^{17}O NMR chemical shifts and amide bond twist in a series of five N-acyl-1,3-thazolidine-2-thiones.[13] It was found that rotation around the N–C(O) axis led to a decrease of the charge density at the oxygen atom (i.e. disrupting amidic resonance), which could be quantitatively measured using ^{17}O NMR at natural abundance ($R^2 = 0.93$). ^{17}O NMR chemical shifts accurately measure π-electron density of the carboxylic acid derivatives, and are not affected by the electronic effect of distal substituents.[10,14]

Our interest in the chemistry of amides[6,12d,5f] inspired us to examine the use of ^{17}O and ^{15}N NMR spectroscopy to evaluate electronic properties of sterically-distorted amides in solution.

The ^{15}N NMR chemical shifts of the mentioned amides can be - in nearly all cases - determined via ^{1}H-^{15}N HMBC spectra. These measurements are now considered routine and easy to perform, also in a comparatively short time. Furthermore, the large chemical shift range of more than 1600 ppm renders ^{17}O NMR a sensitive tool in order to investigate the local chemical environment of the oxygen atom and therefore a valuable method for chemists. However, ^{17}O NMR recordings typically require high concentrations because of the low natural abundance of ^{17}O (0.037%). Moreover, it should be noted that with nuclei of low gyromagnetic ratio (like ^{17}O), an rf pulse will also excite acoustic waves in the metal of the probe ("acoustic ringing") which finally leads to baseline and phase distortions.[15] To partially overcome this short lived phenomenon, the simplest method is to add a delay (e.g. 100 μs) between the excitation pulse and the recording of the FID, which was applied in our study. All measurements have been performed using a "directly" detecting broadband observe (BBFO) probe.

In principle, ^{17}O NMR shifts represent a very sensitive measure of the charge density at the O atom of the carbonyl group, wherein an increase in shielding (smaller chemical shift) corresponds to the lower π-bond character of the C=O group.[9] As such, increasing sterics of the N-substituents (series **a** to **i**, Fig. 2) should lead to a more electrophilic amide bond and strong deshielding of the carbonyl oxygen.[9,13] Likewise, moving from the sterically-unhindered α-C-substituents to sterically-hindered substituents (series, **1** to **4**, Fig. 2) should result in larger chemical shifts due to diminished N–C(O) resonance.

Table 1 ^{17}O NMR Chemical Shifts for Amides in Series **1-4**[a]

Entry	δ(^{17}O) ppm **1**	δ(^{17}O) ppm **2**	δ(^{17}O) ppm **3**	δ(^{17}O) ppm **4**
a	335.0	347.0	347.6	325.2
b	335.0	346.0	352.8	323.0
c	349.0	357.0	365.0	326.9
d	327.0	349.4	354.0	324.7
e	333.9	345.1	351.2	324.5
f	336.3	340.7	351.2	321.8
g	338.0	347.8	356.1	323.0
h	362.2	379.5	384.1	356.8
i	367.0	385.0	388.6	347.6
j	333.7	349.0	350.0	330.7

[a]Recorded at 54.1 MHz in C_6D_6. Chemical shifts are referenced to external H_2O.

Table 2 ^{15}N NMR Chemical Shifts for Amides in Series **1-4**[a]

Entry	δ(^{15}N) ppm **1**	δ(^{15}N) ppm **2**	δ(^{15}N)[b] ppm **3**	δ(^{15}N) ppm **4**
a	95.2	93.4	104.9	94.2
b	124.6	122.5	134.4	123.7
c	139.4	128.9	149.3	141.2
d	121.0	119.0	130.0	119.2
e	110.3	107.5	120.1	107.9
f	117.2	117.8	127.2	116.0
g	133.4	132.2	144.1	131.9
h	119.9	115.8	127.3	118.5
i	136.0	133.0	145.2	135.7
j	187.6	186.8	186.6	185.8

[a]Recorded at 40.4 MHz in C_6D_6. Chemical shifts are referenced to external CH_3NO_2. [b]In MeOD-d^4.

Amides selected for the study are shown in Fig. 2. These amides have been selected on the basis of their synthetic accessibility and steric-destabilization range of the amide bond. In general, we selected four series of sterically-destabilized amides (**1-4**),[16] in which amide deformation would occur as a consequence of gradual C- and N-steric repulsion. Decanoyl group (**1**) has been selected as a model primary C-substituent to facilitate the synthesis of amides. Pivaloyl (**2**), benzoyl (**3**) and cyclohexyl (**4**) groups have been selected as model tertiary, aromatic and secondary C-substituents. In terms of N-substitution, we selected amides with gradually increasing steric hindrance covering the range from NMe_2 (**a**) to N(Et)(*t*-Bu) (**i**). In addition, NMe(OMe) amides (Weinreb amides) (**j**) have been selected for the study due to the importance of these amides in organic synthesis as ketone equivalents.[17] Three series of control compounds have been

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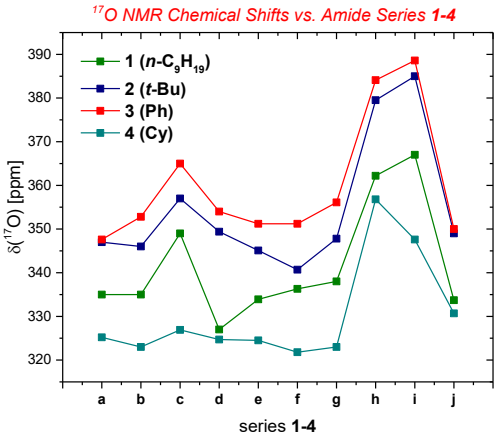

Chart 1 Plot of ^{17}O NMR chemical shifts vs. amide series **1-4**. Note that each curve represents δ(^{17}O) for one series of amides as a function of amide. See ESI for individual plots **1-4**.

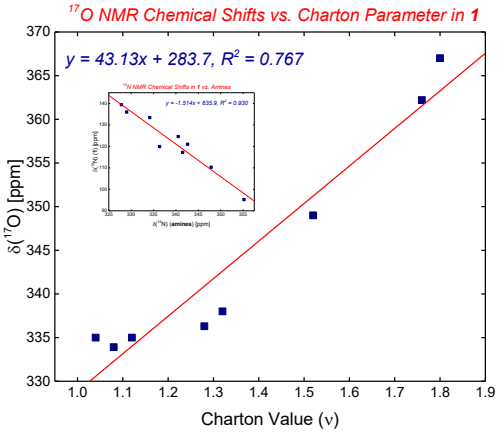

Chart 2 Plot of ^{17}O NMR chemical shifts in **1** vs. Charton Value (ν). Outlier: **1d**, δ(^{17}O) = 327 ppm. See ESI for additional plots. The inset shows plot of ^{15}N NMR chemical shifts in amide series **1** vs. ^{15}N NMR chemical shifts in amines. See ESI for additional plots.

selected (**5-7**). These compounds include extremely sterically-hindered C-adamantyl amides (**5**), representative extremely hindered N-TMP amide (TMP = 2,2,6,6-tetramethylpiperidinyl) (**6**),[18] and electronically-activated C-alkyl amides (**7**). It is worth noting that the selected amides (1) are among the most commonly used amides in organic synthesis, and (2) cover the range of steric-distortion that is synthetically-accessible by standard methods and are hydrolytically-robust.

^{17}O NMR spectra were recorded at 54.1 MHz in C_6D_6 solutions at 297 K and referenced against external H_2O. Additional details are provided in the ESI.

^{17}O NMR chemical shifts of amides in series **1-4** are listed in Table 1. For clarity ^{17}O NMR shifts of amides **5-7** are listed in Table 3. Chart 1 shows a graphical representation of ^{17}O NMR shifts vs. amide series **1-4**. The data in Table 1 provide a two-directional view of the changes in electrophilicity of the amide bond upon C- and N-substitution. Two points should be noted: (1) the effect of C-substituent is in the following order: C_9H_{19} < *t*-Bu < Ph, with amides in the cyclohexyl series being the least electrophilic likely due to conformational effects of the ring;

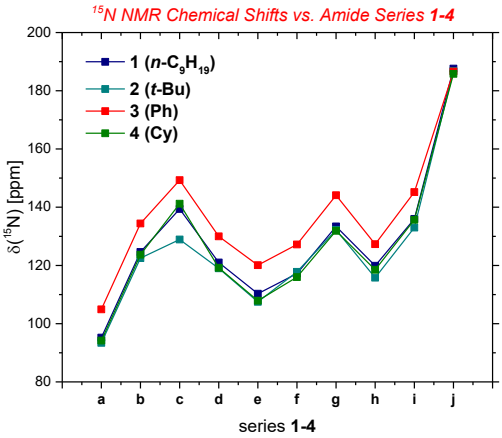

Chart 3 Plot of ^{15}N NMR chemical shifts vs. amide series **1-4**. Note that each curve represents δ(^{15}N) for one series of amides as a function of amide. See ESI for individual plots **1-4**.

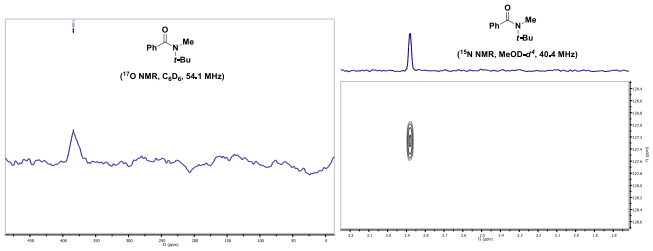

Chart 4 Representative ^{17}O NMR and ^{15}N NMR spectra.

(2) *more to the point, the data demonstrate an increase of electrophilicity upon N-substitution, which originates from steric interaction with N-substituents.* The extreme cases are amides **2h-i** and **3h-i** (379.5 ppm to 388.6 ppm), which can be compared with the available data for PhCOF (352.6 ppm) and PhCOOCOPh (386.4 ppm).[14] Thus, steric repulsion caused by N(Me)(*t*-Bu) and N(Et)(*t*-Bu) groups results in the amide bond electrophilicity that is comparable with acyl fluorides and carboxylic acid anhydrides, and this is achieved in the absence of activating N-carbonyl groups (cf. the most twisted Yamada's amide, 506 ppm).[13] Further, recent intriguing studies reported facile hydrolysis of N-sterically-hindered amides.[18] The present data suggest that these amides behave, electronically, as highly reactive acylating reagents (*vide infra*).

In addition to simply documenting the diminished resonance upon steric substitution, the ^{17}O NMR spectroscopy also allow to correlate the ^{17}O NMR shifts between each of the series studied (see ESI) and between the ^{17}O NMR shifts and Charton (ν) value (Chart 2 and ESI) using a classic evaluation of steric parameters developed by Charton.[19] This validates that the increased deshielding of the oxygen atom originates from steric demand of C- and N-substituents.

While ^{17}O NMR spectroscopy provides a sensitive probe for electronic properties of the amide bond, the use of ^{15}N NMR is less straightforward. Yamada was able to correlate rotation around the N–C(O) axis in N-acyl-1,3-thazolidine-2-thiones with ^{15}N NMR shifts by using correction vs. reference amines to eliminate inductive, steric and conjugative effects.[20] ^{15}N NMR shifts gave a good estimate of changes in the charge

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density at nitrogen, wherein $\Delta\sigma^{15}N$ decreased with increasing amide bond twist. Interestingly, we found that in the studied series of amides **1-4** (Table 2 and Chart 3), a plot of ^{15}N NMR shifts vs. ^{15}N NMR shifts of the reference amines gives an inverse linear correlation over the range of N-substituents studied for each series of compounds (Chart 2 and ESI). This indicates that the charge density at the nitrogen atom in series **1-4** follows the donor inductive effect of the N-substituent.[21]

To gain additional information, we analyzed three series of control compounds (Table ESI-1, **5-7**).

In summary, we have established the viability of ^{17}O NMR and ^{15}N NMR spectroscopy to experimentally determine the electronic properties of sterically-hindered amides. Our study provides a two-directional picture of the changes in electrophilicity of the amide bond upon C- and N-substitution. The study quantifies different contributions resulting from increasing steric distortion at the N- and C-atoms of the amide bond. The net result is that steric repulsion in simple acyclic amides furnishes electrophilic amide bonds with properties reminiscent to acyl fluorides and anhydrides rather than amide bonds. More generally, steric-distortion of acyclic amides has been utilized to great effect in the development of N–C activation methods. This mechanism of amide bond activation is also prevalent in controlling conformation of peptides, inducing site-selective peptide cleavage, and in medicinal chemistry. Our study clearly suggests that ^{17}O NMR and ^{15}N NMR spectroscopy should be commonly used in determining electronic properties of activated amides in organic synthesis.

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