17O NMR and 15N NMR Chemical Shifts of Sterically-Hindered Amides: Ground-State Destabilization in Amide Electrophilicity

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Electronic Supplementary Information

Table of Contents

1. Additional Data Referred to from the Manuscript
2. 17O NMR Chemical Shift Measurement
3. 15N NMR Chemical Shift Measurement
4. Additional Plots Referred to from the Manuscript
5. Representative 17O NMR and 15N NMR Spectra

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To gain additional information, we next decided to analyze three series of control compounds (Table ESI-1). First, since adamantyl group represents one of the most sterically-hindered C-substituents,\textsuperscript{5b} we prepared and analyzed a series of representative C-adamantyl amides (entries 1-5). As expected, the presence of an adamantyl results in strong deshielding of the carbonyl oxygen, which is attributed to increased rotation around the N–C(O) bond (up to 8 ppm, a plot of $^{17}$O NMR(adamantyl) vs. $^{17}$O NMR(pivaloyl) gives a linear correlation, $R^2 = 0.98$). Along the same lines, N-TMP is the most sterically-hindered alkyl substituent that has been used to twist amide bonds.\textsuperscript{16} We found that the use of a simple C-primary substituent in combination with N-TMP group results in a highly electrophilic carbonyl (entry 6, 398.2 ppm). This can be compared with the analogous N-Et\textsubscript{2} amide (entries 7-8), which shows a remarkable $\Delta \sigma^{17}$O of 66.8 ppm. Indeed, the unique electrophilic reactivity of N-TMP amides has been well demonstrated, and future studies will likely expand the growing utility of this class of sterically-destabilized amides.
Table ESI-1. $^{17}$O NMR and $^{15}$N NMR Chemical Shifts for Amides in Series 5-7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Series</th>
<th>$\delta^{(17\text{O})}$ ppm</th>
<th>$\delta^{(15\text{N})}$ ppm</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>Ad</td>
<td>350.3</td>
<td>93.9</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>Ad</td>
<td>347.6</td>
<td>123.7</td>
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<tr>
<td>3</td>
<td>5c</td>
<td>Ad</td>
<td>348.1</td>
<td>116.9</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>Ad</td>
<td>350.5</td>
<td>133.0</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>Ad</td>
<td>393.0</td>
<td>132.6</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>TMP</td>
<td>398.2</td>
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<tr>
<td>7</td>
<td>7a</td>
<td>PhCH$_2$</td>
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<td>126.1</td>
</tr>
<tr>
<td>8</td>
<td>7b</td>
<td>Ph(CH$_2$)$_2$</td>
<td>331.4</td>
<td>126.1</td>
</tr>
</tbody>
</table>

*Recorded at 54.1 MHz in C$_6$D$_6$. Chemical shifts are referenced to external H$_2$O. *Recorded at 40.4 MHz in C$_6$D$_6$. Chemical shifts are referenced to external CH$_3$NO$_2$. Ad = adamantyl; TMP = 2,2,6,6-tetramethylpiperidinyl.
17O NMR Chemical Shift Measurement

17O NMR spectra were recorded on Bruker Avance III 400 spectrometer (400 MHz for 1H, 54.1 MHz for 17O) from approximately 1.0 M C₆D₆ solutions at 297 K using a “directly” detecting broadband observe (BBFO) probe, unless stated otherwise. Referencing was performed against external H₂O (0 ppm, coaxial capillary) by measuring the difference between the water 17O shift and the spectrometer values. For the 17O NMR spectra 10 000 to 300 000 scans were accumulated (pulse width 90°, acquisition time 0.15 s, relaxation delay 0.2 s, spectral width 500 ppm) and Fourier transformed after a 200 Hz line broadening by exponential multiplication. To decrease acoustic ringing a pre-scan delay DE = 100 μs was used in the pulse sequence.
**15N NMR Chemical Shift Measurement**

15N NMR spectra were recorded on Bruker Avance III 400 spectrometer (400 MHz for 1H, 40.4 MHz for 15N) from approximately 1.0 M C6D6 solutions at 297 K using a “directly” detecting broadband observe (BBFO) probe, unless stated otherwise. The spectra were either taken via one-pulse experiments (inverse gated decoupling, digital resolution 1 Hz/data point, 15 s relaxation delay, 8192 scans) or via gradient-selected 15N, 1H HMBC spectra (2048×32 data matrix, 16 ppm spectral width for 15N). Referencing was performed against neat, external nitromethane (0 ppm, coaxial capillary) by measuring the difference between the nitromethane 15N shift and the spectrometer values. The reported values are referenced against nitromethane and given according to IUPAC by adding -380.5 ppm to the referenced spectrometer value for C6D6.
Chart ESI-1. Plot of $^{17}$O NMR chemical shifts in amide series 1 vs. amide series 2. Outlier: 1d, $\delta(^{17}\text{O}) = 327$ ppm.

Chart ESI-2. Plot of $^{17}$O NMR chemical shifts in amide series 1 vs. amide series 3. Outlier: 1d, $\delta(^{17}\text{O}) = 327$ ppm.

Chart ESI-3. Plot of $^{17}$O NMR chemical shifts in amide series 2 vs. amide series 3.
**Chart ESI-4.** Plot of $^{17}$O NMR chemical shifts in amide series 2 vs. Charton Value (v).

Outlier: 2f, $\delta(^{17}$O) = 340.7 ppm.

**Chart ESI-5.** Plot of $^{17}$O NMR chemical shifts in amide series 3 vs. Charton Value (v).

**Chart ESI-6.** Plot of $^{15}$N NMR chemical shifts in amide series 2 vs. $^{15}$N NMR chemical shifts in amines.
**Chart ESI-7.** Plot of $^{15}$N NMR chemical shifts in amide series 3 vs. $^{15}$N NMR chemical shifts in amines.

**Chart ESI-8.** Plot of $^{15}$N NMR chemical shifts in MeOD-$d^4$ vs. $C_6D_6$ in 3.
Chart ESI-9. Plots of $^{17}$O NMR chemical shifts vs. amide series 1-4 showing $\delta^{(17)O}$ as a function of individual amides 1-4.
Chart ESI-10. Plots of $^{15}\text{O}$ NMR chemical shifts vs. amide series 1-4 showing $\delta^{(15}\text{O})$ as a function of individual amides 1-4.
Figure ESI-1. $^{17}$O NMR Spectrum of N,N-Dibutyl-2,2-dimethylpropanamide.
Figure ESI-2. $^{15}$N NMR Spectrum of $N,N$-Dibutyl-2,2-dimethylpropanamide.
**Figure ESI-3.** $^{17}$O NMR Spectrum of $N$-Ethyl-$N$,2,2-trimethylpropanamide.
Figure ESI-4. $^{15}$N NMR Spectrum of $N$-Ethyl-$N,2,2$-trimethylpropanamide.
Figure ESI-5. $^{17}$O NMR Spectrum of $N$-tert-Butyl-$N$-methylbenzamide.
Figure ESI-6. $^{15}$N NMR Spectrum of $N$-tert-Butyl-$N$-methylbenzamide.
Figure ESI-7. $^{17}$O NMR Spectrum of N,N-Dimethylcyclohexanecarboxamide.
Figure ESI-8. $^{15}$N NMR Spectrum of $N,N$-Dimethylcyclohexanecarboxamide.
**Figure ESI-9.** $^{17}$O NMR Spectrum of $N$-Methyl-$N$-(propan-2-yl)cyclohexanecarboxamide.
Figure ESI-10. $^{15}$N NMR Spectrum of N-Methyl-N-(propan-2-yl)cyclohexanecarboxamide.