^{13}C–^{15}N Coupling constants in a series of twisted amides: relationships with C(O)–N twist angles

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For a series of ^{15}N-labelled amides 1a–e with increasing C(O)–N twist angles, the one-bond ^{13}C–^{15}N coupling constants decrease, whereas the two-bond ^{13}C–^{15}N coupling constants increase.

It is well-documented that amides have planar geometry due to the partial double bond character of the C(O)–N bond resulting from amide resonance.[1] However, a number of peptides, proteins and enzymes have been proved by X-ray analysis to contain non-planar deformation in the amide moiety.[2] Furthermore, Schreiber and his colleagues have recently suggested that the orthogonally orienting α-keto amide groups of the immunosuppressive agent FK506 and rapamycin may mimic the twisted amide transition-state of peptide substrates of FKBP rotamase.[3] Such twisted structures are of significant interest in relation to their biochemical functions. Synthetic twisted amides have also received considerable attention with regard to their structure and reactivity.[4,5]

The principal method for studying the non-planarity of amide bonds in solution is ^{13}C, ^{15}N and ^{17}O NMR spectroscopy.[6,7] Although C–N coupling constants[8] seem to be another promising parameter for elucidation of amide deformation about the C(O)–N bond, no investigations have been reported. Here we describe the relationships between C(O)–N twist angles and $^1J_{C,N}$ and $^2J_{C,N}$ values in a series of twisted amides.

A series of twisted amides 1a–e,[7]‡ enriched to 99% with ^{15}N, was synthesized *via* several steps from commercially available [^{15}N] glycine and [^{15}N] leucine. The C–N coupling constants of 1a–e were measured at 100.04 MHz using ^{13}C NMR spectroscopy. Table 1 shows the $^1J_{C,N}$ and $^2J_{C,N}$ values, and the previously reported C(O)–N twist angles τ and the χ_N values,[7,9] $^1J_{C(O),N}$ lies in the range of 2.5–7.8 Hz in CDCl$_3$, and 3.2–7.9 Hz in [^{2}H$_6$]DMSO. The plots of $^1J_{C(O),N}$ *versus* τ are a little scattered, but a rough correlation exists between them, as shown in Fig. 1(*a*). Thus, as the twist angle increases, the $^1J_{C(O),N}$ value decreases. By assuming the Fermi contact mechanism to be dominant, it has been reported that $^1J_{C,N}$ depends on the percentage s-character of the C and N atoms.[10] However, there are no clear-cut relationships between the $^1J_{C(S),N}$ and $^1J_{C4,N}$

values and the χ_N value, which represents the extent of pyramidalization of the N atom. These suggest that the contribution of the contact term to $^1J_{C(O),N}$ is not predominant in this case. Therefore, the orbital and dipolar terms,[11] which depend upon the p-electron distribution, may be the dominant factors governing $^1J_{C,N}$. The importance of the effect of the p-electron distribution on $^1J_{C,N}$ has been reported in substituted anilines: steric inhibition of nitrogen lone-pair delocalization in *N,N*-dimethylaniline derivatives reduces the $^1J_{C,N}$ value.[12] A similar explanation can be applied to the present case. Thus, rotation about the amide bond causes a decrease in the C–N double bond character resulting from amide resonance; consequently, the $J_{C,N}$ decreases. When [^{2}H$_6$]DMSO was used as the NMR solvent, the slope changed, becoming somewhat gentler compared to that in CDCl$_3$. This is because the polar solvent easily stabilizes the canonical form **II** (Scheme 1).

The $^2J_{C7,N}$ values are in the range 5.6–7.1 Hz, which is much narrower than that of $^1J_{C(O),N}$. On the other hand, $^2J_{C5,N}$ was not observed for any of the amides. In contrast to the relationship between $^1J_{C(O),N}$ and τ, the $^2J_{C7,N}$ value increases with increasing the twist angle, as shown in Fig. 1(*b*). It has been assumed that $^2J_{C,N}$ depends on the dihedral angle between the lone pair orbital and the Cα–Cβ bond. For example, $^2J_{C,N}$ of quinuclidine, whose dihedral angle is 180°, is only 0.2 Hz, whereas that of propylamine is 1.2 Hz.[13] Because the dihedral angle of the series of amides decreases with increasing C(O)–N twist angle, as shown in Fig. 2, the present results may also be

1a R^1 = Me, R^2 = R^3 = H
b R^1 = Bn, R^2 = R^3 = H
c R^1 = R^2 = R^3 = Me
d R^1 = Bu^t, R^2 = R^3 = H
e R^1 = Bu^t, R^2 = Bu^i, R^3 = H

Table 1 $J_{C,N}$ values, χ_N and twist angle τ

Compound	$^1J_{C(O),N}{}^a$ /Hz	$^1J_{C(O),N}{}^b$ /Hz	$^1J_{C(S),N}{}^a$ /Hz	$^1J_{C4,N}{}^a$ /Hz	$^2J_{C7,N}{}^a$ /Hz	χ_N (°)	τ (°)
1a	7.8	7.9	8.9	10.2	5.8	11.9	20.1
1b	7.5	7.6	8.7	10.0	5.6	13.4	10.2
1c	7.0	7.1	8.7	6.9	6.0	12.2	36.5
1d	2.9	3.5	9.1	7.8	7.1	29.5	74.3
1e	2.5	3.2	9.1	6.8	6.7	31.4	65.5

^{a} In CDCl$_3$. ^{b} In [^{2}H$_6$]DMSO.

ascribed to the directional effect of the nitrogen lone pair orbital.

Kainosho and Nagao reported[14] that the ^{13}C–^{15}N coupling constant between the Phe-97 carbonyl carbon and the ser-98 nitrogen in *Streptomyces* subtilisin inhibitor is unusually small, and they explained that it is a result of the non-planarity of peptide bonds in β-sheets and α-helices. The present result seems to support their hypothesis.
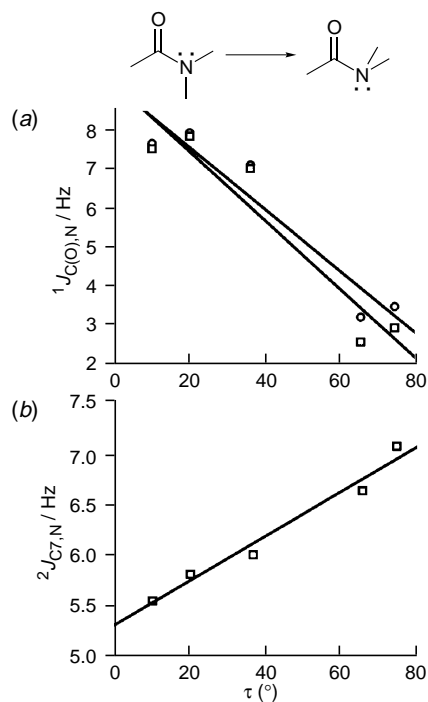
Fig. 1 Plots of (*a*) $^1J_{C(O),N}$ ($\square$ = in CDCl$_3$, $\bigcirc$ = in [^{2}H$_6$]DMSO) and (*b*) $^2J_{C7,N}$ *vs.* τ
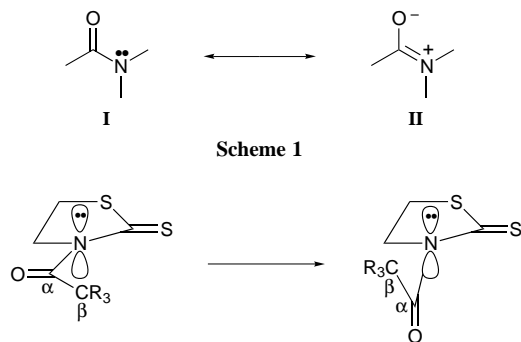
Scheme 1

Fig. 2

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