Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Natural Abundance Nitrogen-15 Spectra of the *cis* and *trans* Isomers of Secondary Alkylformamides†

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The ^{15}NMR chemical shifts were measured of a number of *N*-substituted formamides and acetamides at the natural abundance level. The ratios of the *cis* and *trans* isomers for several *N*-alkylformamides were also determined. Substituent effects on the ^{15}N chemical shifts of formamides are compared with those of some other nitrogen-containing compounds. There is a consistent pattern of behavior of the one bond spin–spin coupling constants [$^1J(^{15}NH)$] wherein the *trans* isomers of *N*-alkylformamides are larger than those of the *cis* isomers.

The amide group is a crucial structural element in proteins and many other biomolecules. Except in small-ring lactams and similar substances, the amide linkages of secondary amides are usually assumed to be exclusively in the *trans* configuration, although there is evidence to indicate that the difference in stability between the *cis* and *trans* isomers is often not very large.[1] A simple way to study *cis–trans* isomerism of amides is by NMR spectroscopy, but the proton NMR spectra of *N*-alkylformamides normally have complex line shapes. This is the result of a combination of line broadening of the H—N proton resonance by quadrupole relaxation of the ^{14}N nitrogen nuclei with spin–spin couplings involving formyl and H—N protons, which usually have similar chemical shifts. Without ^{14}N decoupling, it is not often easy to measure the *cis/trans* ratios of formamides from ^{1}H NMR spectra. Nonetheless, it has been reported, using proton spectra, that both *cis* and *trans* isomers can be detected for *N*-monosubstituted formamides,[2] while, with the *N*-alkylacetamides and the secondary amides of other higher aliphatic carboxylic acids, usually only the *trans* isomer can be observed.[1] For *N*-alkylformamides the percentage of the *cis* isomer increases somewhat as the size of the *N*-alkyl substituent increases, as expected for simple steric interactions between the *N*-alkyl substituent and the carbonyl oxygen.[2]

A number of ^{14}N chemical shifts of secondary amides have been determined,[3–6] but because the signals were generally broad, these spectra are not useful for measuring either *cis/trans* ratios, or the effect of structure on the nitrogen shifts of the different isomers. The ^{15}N shifts of both formamide and *N*-methylformamide have been measured,[7–9] but that of the *cis* isomer of *N*-methylformamide was not reported, probably because the proportion of the *cis* isomer is small and, at the low natural abundance level of ^{15}N, the sensitivity (about 1/50th that of ^{13}C) makes it difficult to obtain good signal-to-noise ratios.[10,11]

The ^{15}N chemical shifts of lactams are very informative about the *cis–trans* isomerism of these substances, with the changeover from *cis* to *trans* with increasing ring size occurring at the nine-membered ring.[12]

Because *N*-alkylformamides provide the only easily accessible open-chain amides for which the *cis–trans* isomers are both present in appreciable amounts, we have taken their ^{15}N NMR spectra to determine the substituent effects of the alkyl groups on the chemical shifts. The ^{15}N spectra of several *N*-alkylacetamides were also measured for comparison purposes.

EXPERIMENTAL

The secondary formamides used in this work were prepared by heating ethyl formate and the corresponding amines. The *N*-alkylacetamides were prepared from acetyl chloride and amines. All of the amides were distilled under reduced pressure and their purity checked by means of their ^{13}C NMR spectra.

The ^{15}N NMR spectra were recorded at the natural abundance level with a Bruker WH-180 spectrometer operating at 18.25 MHz, with 15–17 ml of sample in 25 mm o.d. Pyrex tubes. Quadrature detection was used for the Fourier transform mode with 8192 data points. The other parameters for full proton decoupling (4 W) were: spectral width, 6000 Hz; acquisition time, 1.493 s; pulse delay, 3 s; pulse width, 30 μs (corresponding to a pulse angle of 39°); and 100–500 transients. For the gated proton-coupled spectra, the corresponding figures were: 1000 Hz; 8.192 s; 0 s; 70 μs (90°), 8000–10000. The temperature of the

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samples was approximately 50 °C for the fully decoupled measurements and approximately 30 °C for the gated spectra. The chemical shifts are reported in ppm *upfield* from external 1.0 M $H^{15}NO_3$ in D_2O, contained in a coaxial 5 mm tube. The precision of the shifts was ±0.1 ppm and ±0.15 Hz for the coupling constants. The formamide spectra were taken either neat or in 10 M dimethyl sulfoxide which was dried by treatment with calcium hydride, while the acetamides were taken in chloroform solution.

RESULTS AND DISCUSSION

The ^{15}N NMR chemical shifts of formamide, acetamide, *N*-alkyl-substituted formamides and acetamides at room temperature are summarized in Table 1. All of the *N*-alkyl-substituted formamides showed two resonances, as expected for *cis* and *trans* isomers slowly interconverting about the CO—N bond.[1,13] The assignments of the resonances were made on the basis that the proportion of *cis* isomer is apparently invariably smaller than that of the *trans* isomer, as indicated by the ^3J(HH) (HCONH–) coupling obtained from proton NMR spectra.[1,14]

Cis/trans ratios

The *cis* isomer is present in *N*-methylformamide (**2**) to the extent of 8%, and increases to 11–18% for primary and secondary *N*-alkyl groups (**3–16**), and to about 22% when the alkyl group is tertiary (**17**, **18**). These proportions agree reasonably with those obtained from proton spectra (8% for **2**, 12% for **3**, and 18% for **17**).[2] The results can be easily rationalized as the result of increasing steric effects as the *N*-alkyl group increases in size and branching at the α carbon. However, the effects are much smaller than might be expected, especially for the *tert*-butyl and *tert*-pentyl groups, unless steric hindrance is reduced for the *trans* isomer by having the favored conformation for the alkyl groups staggered with respect to the carbonyl oxygen, as in **19**.

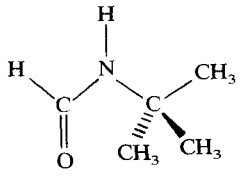

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Table 1. ^{15}N Chemical shifts of *N*-alkyl-substituted formamides and acetamides

	R	Concentration in $(CH_3)_2SO$	δ[a] *trans* (HNO_3)	δ[a] *trans* [$(CH_3)_4NCl$)]	δ[a] *cis* (HNO_3)	δ[a] *cis* [$(CH_3)_4NCl$)]	Δδ (ppm)	% of *cis* isomer[b]
1	H	Neat	262.4 (269.0)[c]	70.4 (63.8)[c]			—	—
2	CH_3–	Neat[d]	265.6 (269.8)[c]	67.2 (63.0)[c]	267.6	65.2	2.0	8
3	CH_3CH_2–	Neat	247.7	85.1	248.8	84.0	1.1	12
4	$CH_3CH_2CH_2$–	Neat	250.8	82.0	252.2	80.6	1.4	14
5	$CH_3CH_2CH_2CH_2$–	Neat	250.9	81.9	252.3	80.5	1.4	14
6	$CH_3CH_2CH_2CH_2CH_2$–	Neat	250.8	82.0	252.3	80.5	1.5	12
7	$(CH_3)_2CHCH_2$–	Neat	252.8	80.0	254.4	78.4	1.6	12
8	$(CH_3)_3CCH_2$–	Neat	255.0 (259.3)[e]	77.8 (73.5)[e]	256.6	76.2	1.6	11
9	$C_6H_5CH_2$–	10 M	251.6 (254.2)[e]	81.2 (78.6)[e]	252.9	79.9	1.3	13
10	$C_6H_5CH_2CH_2$–	Neat	252.4	80.4	253.8	79.0	1.4	14
11	$(CH_3)_2CH$–	10 M	234.1	98.7	235.7	97.1	1.6	14
12	$CH_3CH_2(CH_3)CH$–	Neat	236.8	96.0	238.7	94.1	1.9	16
13	$CH_3CH_2CH_2(CH_3)CH$–	10 M	236.9 (239.6)[e]	95.9 (93.2)[e]	238.7	94.1	1.8	14
14	$(CH_2)_2CH$–	10 M	246.3	86.5	249.2	83.6	2.9	18
15	$(CH_2)_4CH$–	Neat	237.6	95.2	239.9	92.9	2.3	12
16	$(CH_2)_5CH$–	Neat	236.6	96.2	237.3	95.5	0.7	14
17	$(CH_3)_3C$–	Neat[d]	230.8	102.0	228.8	104.0	−2.0	22
18	$CH_3CH_2(CH_3)_2C$–	Neat	233.0 (239.4)[e]	99.8 (93.4)[e]	230.6	102.2	−2.4	22

[a] Shifts were measured in ppm with respect to external 1.0 M $H^{15}NO_3$ (upfield shifts positive) in D_2O and converted to the $(CH_3)_4$ ^{15}NCl (2 m in H_2O) scale (downfield shifts positive) by the relationship $\delta[(CH_3)_3{}^{15}NCl)] = 332.8 - \delta$ ($H^{15}NO_3$). The parenthetical values are the chemical shifts of the corresponding acetamides.

[b] The precision of the population ratios is ±1%.

[c] 1.5 M in $CHCl_3$.

[d] The chemical shifts of the *cis* and *trans* isomers and the *trans*/*cis* ratios were found to be the same in the neat samples as in 10 M dimethyl sulfoxide solution.

[e] 4.5 M in $CHCl_3$.

^{15}N NMR chemical shifts of the *trans* and *cis* isomers of *N*-alkylformamides

The data in Table 1 show that the ^{15}N shifts of the *cis* isomers of the *N*-alkyl derivatives **2–16** are at higher fields than those of the *trans* isomers, but at lower fields for **17** and **18**, which have tertiary alkyl groups. Interestingly, similar trends are observed for the methyl proton signals of the *cis* isomers of **2**, **3**, **11** and **17**. Those of **2**, **3** and **11** are at lower fields than of the *trans* isomers, while **17** is at higher fields.[2] Furthermore, the formyl hydrogen resonance of the *cis* isomers of **2** and **3** are at higher field than those of the *trans* isomer, while with **17** the opposite is true.[15] The simplest explanation of all this would be that the assignments of the *cis* and *trans* configurations of **17** are reversed, and this substance (and **18**) is actually 22% *trans* and 78% *cis*. Although facile, this explanation is at variance with the ^{3}J[H(CO)H(N)] couplings, the larger of which is associated with the predominant isomer.[14]

A possible difference between the *cis* isomers of **2–16** and **17–18** is that there could also be a change in the preferred alkyl conformation of the *cis* isomer with respect to the formyl hydrogen in **17** and **18**. However, this does not agree with the relatively smooth sequence of *cis* ^{15}N shifts for **2**→**3**→**11**→**17** (Fig. 1). There is a rather larger discontinuity in the sequence of *trans* shifts for the same amides when the change from *trans*-**11**→*trans*-**17** is encountered, and thus it would appear that *tert*-alkyl substituents produce a special change in the ^{15}N shifts of *trans*-*N*-substituted formamides.

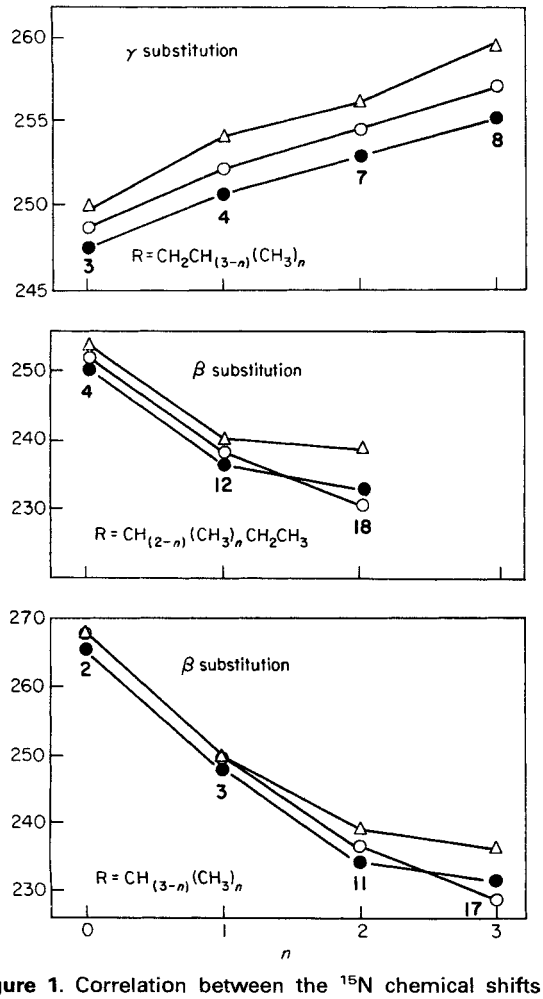


Figure 1. Correlation between the ^{15}N chemical shifts of *N*-alkylformamides and acetamides and the number (*n*) and placement of β, γ methyl substituents in the *N*-alkyl group: △ = CH_3CONHR; ● = *trans*–HCONHR; ○ = *cis*-HCONHR.

Substituent effects on ^{15}N chemical shifts of *N*-alkylformamides

The α-, β- and γ-substituent effects of methyl or phenyl groups on the ^{15}N chemical shifts of *N*-alkylformamides and some *N*-alkylacetamides are summarized in Table 2. A positive sign for the substituent effect corresponds to an upfield (shielding shift). The δ- and ε-substituent effects are all less than 0.7 ppm and are omitted from the table.

For both the *cis* and *trans* isomers of *N*-alkylformamides, α and γ substitution results in shielding, while β substitution results in deshielding.

The data in Table 2 indicate that substituent effects for *cis* isomers of *N*-alkylformamides are generally not much different from those for the *trans* isomers, except for the β-effect changes for **11**→**17** and **12**→**18**. The general relationship between the ^{15}N chemical shifts and the number of β-substituted methyl groups on the *N*-alkyl groups of formamides and acetamides is best seen from Fig. 1. For both series, where R, the *N*-alkyl group, changes from $-CH_3$→$-CH_2CH_3$→

Table 2. ^{15}N NMR shift changes produced by substitution of methyl or phenyl groups on *N*-alkylformamides

Effect	Δδ, ppm[a] Number of substituents 1	2	3
α	+3.4 +5.2 (1→2) (+0.8)		
β	−17.9 −18.8 (2→3) (−19.0)	−13.6 −13.1 (3→11) (−11.3)	−3.3 −6.9 (11→17) (−2.3)
	−14.0 −14.7 (2→9) (−14.0)	−14.0 −13.5 (4→12) (−13.9)	−3.8 −8.1 (12→18) (−0.9)
		−13.9 −13.6 (5→13) (−14.7)	
γ	+3.1 +3.4 (3→4) (+5.0)	+2.0 +2.2 (4→7) (+2.0)	+2.2 +2.4 (7→8) (+3.1)
	+2.7 +3.0 (11→12) (+2.4)		
	+2.2 +1.8 (17→18) (+3.8)		
	+4.7 +5.0 (3→10) (+6.9)		

[a] The upper and lower figures are for the *trans* and *cis* isomers, respectively, and those in parentheses are for the corresponding acetamides.

$CH(CH_3)_2 \rightarrow -C(CH_3)_3$ and from $-CH_2CH_2CH_3 \rightarrow CH(CH_3)CH_2CH_3 \rightarrow C(CH_3)_2CH_2CH_3$, the chemical shifts of the *cis*-formamides are most strongly affected by methyl substitution (deshielding) and those of the (*trans*)-acetamides are least influenced. This is surprising, because the *cis* isomers of formamides are the ones which are expected to have the *smallest* steric repulsion. Furthermore, the magnitude of the change for each added β-methyl substituent becomes smaller with increasing number of methyl groups ($18.8 \rightarrow 13.1 \rightarrow 6.9$ ppm). The general overall pattern of the β shifts suggests that, for these amides, the normally deshielding β effect is partially compensated by a shielding steric effect which becomes more important as more β substituents are introduced.

The γ-substituent effect is an upfield effect which also diminishes after the first methyl is substituted, but not the second, going from $+3.1 \rightarrow +2.0 \rightarrow +2.2$ ppm for the *trans* isomer and $+3.4 \rightarrow +2.2 \rightarrow +2.4$ ppm for the *cis* isomer. The γ effect has more the appearance of a steric effect, because it is somewhat larger for acetamides than for formamides (Table 2).

A substantial *upfield* ^{15}N shift change of 14.3 ppm has been noted for the change from $(CH_3)_2CH—NH_2$ to $(CH_2)_2CH—NH_2$.[10] This change is apparently too large to be a ring-current effect operating for the cyclopropyl group but not the isopropyl group. It is also not in the normal direction for either an inductive or conjugative effect, at least of the type normally associated with nitrogen connected to carbon–carbon double bonds. When the amines are converted to the corresponding formamides, there is a correspondingly large upfield shift difference, not much smaller than for the amines themselves, independently of whether the *trans* (12.2 ppm) or the *cis* (13.5 ppm) isomer is involved. Because of the sizable conjugation between amide nitrogens and their associated carbonyl groups, it seems unlikely that an electron-accepting conjugative influence of a cyclopropyl ring could be very important in competition with the carbonyl group. In this situation, it seems likely that the differences in ^{15}N shifts between isopropylamine-cyclopropylamine and the respective geometrical isomers of **11**→**14** have their origin in the same mechanism.[10]

The data of Table 2 show that phenyl substitution parallels methyl substitution in producing a β effect which is deshielding (**2**→**9**) and a γ effect which is shielding (**3**→**10**) for both *cis* and *trans* isomers. However, the β effect of phenyl is about 4 ppm smaller and the γ effect about 2 ppm larger than produced by methyl groups.

Comparison of the substituent effects for *N*-alkylformamides and other nitrogen-containing compounds

Although β-, γ- and ε-substituent effects on ^{15}N chemical shifts resulting from methyl substitution show the same trends for *N*-alkylformamides and *N*-alkylacetamides (the β and ε effects being deshielding and the γ effect shielding, see Table 3), the α effects of methyl substitution for formamide (+3.4 and +5.2 ppm, respectively, for *trans* and *cis* isomers) is opposite to the reported difference of −2.4 ppm for acetamide.[16] However, this value was obtained by comparing shifts of acetamide (**20**) and *N*-methylacetamide (**21**) at different concentrations, and when the comparison is made with each at 1.5 M in chloroform, the α effect of methyl substitution is small, but definitely shielding (+0.8 ppm).

It is interesting to compare substituent effects produced by various methyl substitutions on ^{15}N chemical shifts of amides with those reported for other nitrogen-containing compounds, and on the ^{13}C shifts of hydrocarbons, as given in Table 3. It will be seen that methyl substitution in the α position is deshielding for nitrogen shifts of amines,[10] imines,[17] hydrazines[18] and ammonium ions.[8,10] One exception[21] for the amines is with piperidines, where substitution of an axial *N*-methyl produces a shielding of +20.2 ppm, while equatorial substitution is deshielding by −2.2 ppm. These substitutions change secondary to tertiary nitrogen, while we are concerned here with primary to secondary. Moreover, the α effect on ^{13}C chemical shifts of hydrocarbons[19] is also deshielding. In contrast, the α effect for amides is shielding, even though the β and γ effects are in the same direction as for the other compounds listed in Table 3. The α effects on ^{14}N chemical shifts of ureas and thioureas appear to be shielding, but the inaccuracies in the shifts are too large, because of line broadening, to permit detailed discussion.[20a] Recently, α effects on

Table 3. Substituent effects on ^{15}N, ^{14}N and ^{13}C NMR chemical shifts by a methyl group[a]

Compound		Nucleus	α	β	γ	δ	ε	Reference
Amine	RNH_2	^{15}N	−8.7[b]	−18.2[b]	+2.7[b]	−3.0[b]	+1.8[b]	10
	RNHMe		−6	−22				
	RCH_3	^{13}C	−9.09[b]	−9.40[b]	+2.49[b]	−0.31[b]	−0.11[b]	19
Ammonium ion	$RNH_3Cl^{\ominus}$	^{14}N	−3.5	−15	+11	+0.2		46
		^{15}N		−14.7	+2.3			22
Hydrazine	$RNHNH_2$	^{15}N	−3.6[b]	−24.8[b]				18
			−6.8					
Imine	R'MeC=NR	^{15}N	−8.1	−15.3				17
Acetamide	CH_3CONHR	^{15}N	−2.4	−19.0	+5.0	+0.1	−0.3	16
			+0.8					This work
Formamide	HCONHR (*trans*)	^{15}N	+3.4	−17.9	+3.1	+0.1	−0.1	This work
	HCONHR (*cis*)		+5.2	−18.8	+3.4	+0.1	0.0	This work

[a] Positive values denote shifts to higher fields.
[b] Figures obtained by linear regression analysis.

Table 4. $J(^{15}NH)$ spin–spin coupling constants for neat formamides, in Hz

	Compound	^1J(NH) trans	^1J(NH) cis	^2J(NHCOH) trans	^2J(NHCOH) cis	^2J(NCH) trans	^2J(NCH) cis	^2J(NCCH$_3$) trans	^2J(NCCH$_3$) cis
2	$HCONHCH_3$	93.8	90.2	15.6	15.1	1.4	1.4		
3	$HCONHC_2H_5$	92.2		15.1					
5	$HCONH(CH_2)_3CH_3$	92.2[a]	89.8[a]	15.0[a]	14.3[a]				
11	$HCONHCH(CH_3)_2$	92.4		15.3					
17	$HCONHC(CH_3)_3$	92.3	86.6	14.7	14.5			2.5	2.9

[a] From ^{1}H spectra.[38]

^{15}N chemical shifts of ureas have been reported to be upfield.[20b]

Substantial success has been obtained in correlating the substituent effects on ^{15}N NMR chemical shifts with ^{13}C chemical shifts of correspondingly constituted hydrocarbons.[10,12,17,18,21–23] For amides, the corresponding compounds would be aldehydes for formamides and ketones for other amides. The changes in ^{13}C chemical shifts of the methyl carbons of acetaldehyde and acetone produced by substitution of a methyl group on the α carbon are −5.5 ppm and −5.8 ppm, respectively.[24] These deshielding α effects are, thus, also opposite to those observed for amides.

The chemical shifts of nitrogen nuclei are usually considered to be dominated by the paramagnetic screening term in the Ramsey equation.[25,26] This term can be expected to be modified by (1) inductive effects resulting from alkyl substitution;[27,28] (2) substituent-induced distortions of the α—β bonds;[10,29,30] (3) steric effects;[21] (4) conjugation effects;[10,31] (5) substituent-induced polarizations of the lone-pair electrons;[10,21] and (6) intermolecular interactions with hydrogen bonding and solvent effects.[4–6,17,21,22,32] The only one of these effects which, on detailed analysis, seems capable of explaining the upfield α shift is intermolecular hydrogen bonding. It is known that the chemical shifts of amide nitrogens move toward lower fields as the result of intermolecular hydrogen bonding,[6,17] and it is certainly reasonable to expect that the degree of hydrogen bonding will be greater for primary amides ($R'CONH_2$) than for secondary amides (R'CONHR). That hydrogen bonding might produce a greater effect for amides than the other compounds listed in Table 3 is a consequence of having both good hydrogen donating (NH) and hydrogen accepting (CO) groups.

Effects of hydrogen bonding, concentration, and changes in solvent on ^{15}N NMR chemical shifts of amides will be discussed in more detail in a later paper.

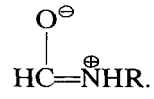
^{15}N—H coupling constants in formamides

The couplings between ^{15}N and ^{1}H [^1J(NH)] are known to be influenced by the degree of *s* character of nitrogen orbitals contributing to the N—H bond.[14,28,33] It is interesting from this standpoint to determine the differences between the ^{15}N—H coupling of the *trans* and *cis* isomers of *N*-alkylformamides, and this has been possible for a few formamides, as the data in Table 4 show.

For formamide itself, $^1J(^{15}NH)$ for the N—H proton *trans* to the C=O bond is reported to be larger than for the *cis* N—H proton (except in water solution).[14,34–37] The same trend of $^1J(^{15}NH)$ for the protons *trans* (93.8 Hz) and *cis* (90.2 Hz) to the C=O bond was observed for the *N*-methylformamide stereoisomers. With larger *N*-alkyl groups (**3**, **5**, **11** and **17**), the *trans* couplings become slightly smaller. The one-bond coupling for the *cis* isomers of **3** and **11** could not be measured because of signal overlaps arising from the simultaneous presence of couplings corresponding to ^1J(NH), ^2J(NCO*H*), ^2J(NC*H*) and $^3J(NCH_3)$, and also because the proportions of the *cis* isomer are small. Values for ^2J(NC*H*) and $^3J(NCH_3)$ of the *trans* isomers of **3** and **11** could not be determined either because of their small values or line broadening. A ^{1}H NMR study of **5** showed ^1J(NH) of the *cis* isomer to be 2.4 Hz smaller than that of the *trans* isomer.[38] The difference becomes more than twice as large (5.7 Hz) for **17**.

Alei and co-workers report for amines[39] and ammonium ions[40] that methyl substitution on the nitrogen produces an increase in the one bond N—H coupling constants. The same trends are seen for *N*-alkyl substitution on formamide isomers. The rather small ^1J(NH) of the *cis* isomer of **17**(86.6 Hz) could reflect a steric interaction between the *tert*-butyl group and the formyl hydrogen, but, surprisingly, there is almost no effect on the corresponding one bond coupling for the *trans* isomer, where a rather large steric effect should arise from the *tert*-butyl · · · carbonyl oxygen interaction. In general, the values of ^2J(NCO*H*) and ^2J(NC*H*) are unexceptional.

The three bond NCC*H* couplings for **17** (2.5 Hz and 2.9 Hz for *trans* and *cis* isomers, respectively) are larger than those for ^2J(NCH) which fits the general trends for saturated systems.[33,41–44] The magnitudes of these three bond couplings are similar to the values reported for ammonium compounds[45] and probably reflect the importance of the dipolar resonance structure



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