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THE CONFORMATIONAL DEPENDENCE OF $^{15}N^{13}C$ SPIN SPIN COUPLING CONSTANTS

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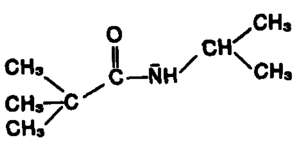
Abstract—2-Azabicyclo(2.2.2)octan-3-one **1**, N-isopropylpivaloylamide **2** and 4-azatricyclo(4.3.1.$1^{3,8}$)undecan-5-one **3** have been prepared with a ^{15}N label. The amides were reduced to the corresponding amines 2-azabicyclo(2.2.2)octane **4**, N-isopropyl-N-neopentylamine **5** and 4-azatricyclo(4.3.1.$1^{3,8}$)undecane **6**. The ^{13}C spectra of these compounds and their hydrochlorides were measured and the $^{15}N^{13}C$ spin coupling constants interpreted in terms of their conformational dependence.

The spin coupling constants of the ^{13}C nucleus to nuclei other than hydrogen are of increasing current interest.[1] It was hoped to develop the $^{15}N^{13}C$ spin coupling[2–4] into a new conformational probe with some importance for biological material.[5] Very recently several papers dealt with the theoretical calculation of these coupling constants.[6–8] After the first experimental results, however, it soon was realized[9,10] that vicinal $^{15}N^{13}C$ spin coupling constants in saturated systems were hardly capable of resolution although a theoretical study for the peptide linkage[11] predicted a Karplus type[12] behaviour of the vicinal $^{15}N^{13}C$ spin coupling constants with values between 2,0 and 3 Hz.

One of the possible reasons for the observed absence of vicinal coupling constants in amides[10] could have been a rotational or conformational averaging in the molecules so far studied. We have initiated a study where the ^{15}N label of an amide linkage is part of a relative rigid system and have therefore synthesized the *cis*- and *trans*-amides **1** and **2** together with 4-azatricyclo(4.3.1.$1^{3,8}$)undecan-5-one (4-azahomoadamantan-5-one) **3** where the exact conformation of the amide linkage is not known *a priori*.

1



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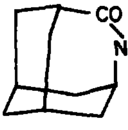
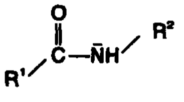


3

Furthermore we have reduced these molecules to their corresponding amines **4**, **5** and **6**. The choice of the molecules **1** and **2** was determined by the fact that these compounds have been standard models for the *cis*- and *trans*-amide linkage already used in IR spectroscopy.[13]



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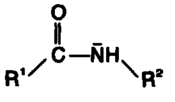
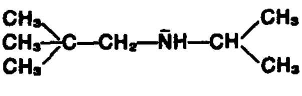


cis

We were interested whether $^{1}J_{^{15}N\text{–}CO}$ would reflect the difference between *cis*- and *trans*-amides. Compounds **1** and **2** have only one distinguishable C atom that displays a vicinal spin coupling constant across the amide linkage. Therefore we include in this study, **3** where several C atoms of a rigid system could show long range spin coupling constants.

In the amines **4–6** the polarizing effect of the CO group is no longer present. Besides quinuclidine[5] and 1-azaadamantane[14] no other azabicyclic amines have been examined for conformational dependence of the $^{15}N^{13}C$ spin coupling constants in amines. For all the compounds reported here the free bases as well as their hydrochlorides were measured and the effect of protonation on the spin coupling constants was studied.

4



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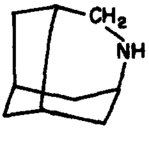

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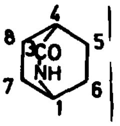
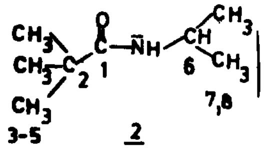
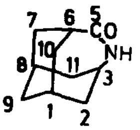
RESULTS AND DISCUSSION

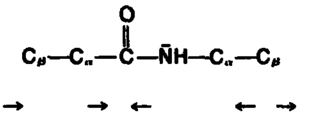
1. ^{13}C *chemical shifts*. The ^{13}C chemical shifts of the amides **1–3** and their hydrochlorides are given in Table 1. To our knowledge no systematic ^{13}C study of amides and their protonation shifts has been published; ^{13}C chemical shifts of lactames were reported by Williamson and Roberts.[15] The chemical shifts of **1** have already been published.[16] The assignment of the amide resonances is straightforward for all C atoms using standard techniques except for the relative assignment of the C atoms being in β position to the CO group and the C atoms β to the NH group in **1** and **3**. The assignment for **1** by van Binst and Tourwe[16] was based on a comparison with the chemical shifts of bicyclo(2.2.2)octan - 2 - one and is corrobated by the protonation shifts found in this work. Protonation shifts turned out to be identical in direction and similar in magnitude for all three amides. The CO group is deshielded by about 3–4 ppm. A similar downfield shift is true for the C atom α to the NH group. The C atoms α to the CO group and β to the NH group are shielded and the C atom β to the CO group still

Table 1. ^{13}C chemical shifts and ^{15}N^{13}C spin coupling constants of the amides 1–3 and their hydrochlorides in CDCl$_3$[a]

		$>$C=O	α-NH	α-C=O	β-NH	β-CO		
		C-3	C-1	C-4	C-6/7	C-5/8		
 1	δ	178.4 (181.0)	47.3 (48.5)	37.6 (33.8)	27.5 (25.9)	23.9 (23.3)		
	J	12.1 (16.2)	7.5 (6.3)	5.1 (2.5)				
		C-1	C-6	C-2	C-7/8	C-3/4/5		
 2	δ	177.2 (181.9)	41.1 (46.8)	38.5 (38.8)	22.8 (21.1)	27.6 (26.9)		
	J	13.2 (18.8)	9.5 (6.3)	6.5 (2.3)	0.4			
		C-5	C-3	C-6	C-2/11	C-7/10	C-1/8	C-9
 3	δ	182.2 (186.2)	45.9 (48.5)	41.5 (38.0)	36.6 (33.8)	30.1 (29.5)	27.3 (26.4)	35.1 (33.8)
	J	12.3 (15.1)	8.3 (7.2)	7.0 (3.5)				

a) Chemical shifts in ppm vs Me$_4$Si, spin coupling constants in Hz, values in parentheses for the hydrochlorides.

experiences a minor upfield effect. This pattern as visualized in formula 7 is remarkable in view of the dis-



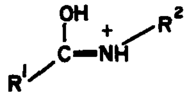
$$C_\beta—C_\alpha—\overset{O}{\overset{\|}{C}}—\bar{N}H—C_\alpha—C_\beta$$

7

cussion on protonation sites for amides.[17] We have carried out a model INDO calculation for propionicacid-N-ethylamide using the program of Dobosh and Ostlund[18] which shows that the total valence electron density of the carboxyl C atom is diminished by O-protonation and enhanced by N-protonation.

In principle the same findings and difficulties hold for the amines (Table 2). The relative assignment of the C atoms being in β and γ position to the NH group was solved for 4 by Morishima *et al.*[19] by contact shift measurements. Our assignment for 6 is based on incremental shifts of the NH group and use of the chemical shift data of tricyclo(4.3.1.1^{3,8})undecane (homoadamantane).[20] Due to the small shift differences in the hydrochlorides the relative assignment between these C atoms in 4 and 6 is only tentative. Finally it is interesting to note that on protonation the CH$_2$ group α to the NH group is shielded by about 2–5 ppm whereas the CH group α to the N is deshielded by about 1 ppm, an effect already clarified by Morishima *et al.* for 2-methylpiperidine.[21]

2. ^{15}N^{13}C *spin spin coupling constants*. The spin coupling constants for the amides and amines are given in Tables 1 and 2, respectively. From the values of the neutral amides in the first column of Table 1 it is clearly seen that ^{1}J ^{15}N^{13}C spin coupling constants do not significantly reflect the difference between a *cis*- and *trans*-amide. O-protonation enhances the coupling

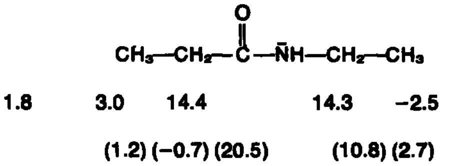


$$\overset{OH}{\overset{|}{C}}{}^{+}{=}NH{-}R^2 \quad R^1{-}$$

8

constants of the carboxyl group as expected from formula 8. The $^1J_{NCH}$ value to the CH group is about one quarter the $^1J_{NCO}$ coupling constant. Here protonation decreases all values even further. The protonation effect seems to be strongest for the *trans*-amide. $^2J_{NC}$ coupling constants across the amide linkage are about half of the values for $^1J_{NCO}$ to the carboxyl group, on protonation these couplings are halved again. $^2J_{NC}$ to the C atoms β to the NH group are hardly capable of resolution. Vicinal coupling constants are not found for any of the amides. This clearly suggests that conformational or rotational effects are not responsible for the observed absence of these values in other amides.[10]

Our INDO calculation of the Fermi contact contribution to the ^{15}N^{13}C spin coupling constants in propionic-acid-N-ethylamide yielded the values in Hz given in formula 9, where the spin coupling constants in paren-

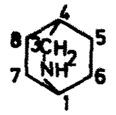
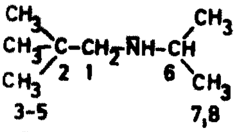
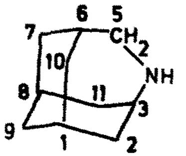


$$CH_3—CH_2—\overset{O}{\overset{\|}{C}}—\bar{N}H—CH_2—CH_3$$

9

thesis are for the O-protonated form. A comparison with the mean values of our experimental results demonstrates that the order of magnitude, but more important the effect of protonation, are correctly represented by the calculation for $^1J_{NCO}$, $^1J_{NCH_2}$ and $^2J_{NCOCH_2}$. Cal-

Table 2. ^{13}C chemical shifts and $^{15}N^{13}C$ spin coupling constants of the amines 4-6 and their hydrochlorides in $CDCl_3$[a]

		$-CH_2-N-$	$-CH-N-$	β-NH	β-NH	γ-NH		
		C-3	C-1	C-4	C-6/7	C-5/8		
 4	δ	46.9	43.4	24.4	26.9	24.7		
		(44.7)	(44.7)	(22.4)	(22.8)[c]	(22.4)[c]		
	J	2.5	2.6					
		(-[b])	(-[b])					
		C-1	C-6	C-2	C-7/8	C-3/4/5		
 5	δ	59.9	49.5	31.2	23.0	27.8		
		(54.3)	(51.3)	(30.5)	(18.3)	(27.5)		
	J	3.5	4.2	1.6	2.6	1.0		
		(4.3)	(3.6)			(0.8)		
		C-5	C-3	C-6	C-2/11	C-7/10	C-1/8	C-9
 6	δ	53.4	50.1	33.2	39.2	37.3	26.7	35.9
		(50.5)	(51.5)	(30.3)	(35.8)	(33.6)	(25.5)	(33.9)
	J	3.4	3.1					
		(3.7)	(3.5)					

a) Chemical shifts in ppm vs Me_4Si, spin coupling constants in Hz, values in parentheses for the hydrochlorides. b) ot observed due to isochronism of the signals. c) relative assignment tentative.

culation of the N-protonated form did not yield satisfactory results.

In the amines 4-6, the coupling constants are in the usual order as reported for other amines[1] and are somewhat enhanced by protonation. The only molecule in this investigation which shows vicinal coupling constants is neopentyl-isopropylamine 5 with values similar to n-propylamine.[5]

CONCLUSIONS

In this work we have demonstrated that for rigid compounds $^{15}N^{13}C$ values, in comparision to $^{13}C^{13}C$ spin coupling constants[1,23] are not very well suited as a conformational probe since vicinal spin coupling constants are difficult to resolve. Geminal and one bound spin coupling constants, however, do give some information especially in comparing of the neutral with the protonated compounds.

EXPERIMENTAL

All compounds described here were prepared by standard procedures in the literature with the difference that due to the cost of the labelled material these procedures had to be scaled down and suitably modified. Reduction of the amides was best achieved using the dimethylsulfide-borane reagent. The hydrochlorides were prepared directly in the NMR tube by bubbling dry HCl gas through the soln. The ^{13}C spectra were obtained on a Varian XL-100-15 spectrometer equipped with a 16 K 620 L computer and a Varian disc system. Thus, 32 K FT spectra were usually obtained with no exponential filtering and with a digital resolution of less than 0.2 Hz/point. Where no coupling constants are given, the values are lower than 0.4 Hz. Spectra were normally taken three times in rather dilute solns of $CDCl_3$ due to the limited amount of material.

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