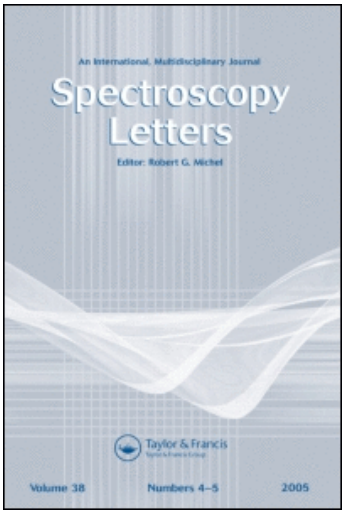

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^{13}C NMR Chemical Shifts Substituent Effects of (*E*)- and (*Z*)-N-ethyl-N-Methylamides

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^{13}C NMR CHEMICAL SHIFTS SUBSTITUENT EFFECTS OF (*E*)- AND (*Z*)-N-ETHYL-N-METHYLAMIDES.

KEY WORDS ^{13}C NMR of Amides
(*E*)- and (*Z*)-N-Ethyl-N-methylamides
^{13}C NMR Substituent Effects

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ABSTRACT

Carbon-13 NMR chemical shifts of a series of (*E*)- and (*Z*)-N-ethyl-N-methylamides [RC(O)NEtMe, R= H, Me, Et, *i*-Pr, *t*-Bu, CF_3, $ClCH_2$, Cl_2CH, Cl_3C, $BrCH_2$, Br_2CH, Br_3C and ICH_2] are reported. The α-carbon and carbonyl carbon chemical shifts are correlated with the empirical α-substituent effect and Charton's electrical parameter (σ_I), respectively. The N-alkyl carbon resonances were attributed mainly to the γ- and δ-effects of R.

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INTRODUCTION

Although aliphatic N,N-dialkylamides have been extensively studied by ^{13}C NMR spectroscopy[1-4] there is a lack of ^{13}C NMR data for the N-ethyl-N-methylamides in the literature. In this work the ^{13}C NMR spectra of 13 compounds were recorded, and *syn*- and *anti*-N-substituents carbon resonances for (*E*)- and (*Z*)-isomers were assigned through a series of homo- and heteronuclear COSY experiments, as well as DEPT 90° and 135°, and using proton chemical shifts[5]. The ^{13}C chemical shifts are discussed in terms of substituent electronic and steric effects, and empirical relationships between the α-effect of the substituent and the α-carbon resonance are examined. The N-alkyl carbon resonances are analyzed in terms of γ- and δ-effects of the substituent.

RESULTS AND DISCUSSION

Assignments

The resonance signals of the *syn*- and *anti*-N-alkyl groups in (*E*)- and (*Z*)-isomers of N-ethyl-N-methylamides **1-13** could be unambiguously assigned as a result of homo- and heteronuclear COSY experiments, DEPT 90° and 135° [5]. To select non-superimposed signals, chloroform-d_1 and benzene-d_6 were used as solvents.

TABLE 1

^{13}C NMR chemical shifts[a] of N-Ethyl-N-methylamides 1-13.

Compd.	α-CH_nX_{3-n}		C=O[b]		N-CH_3		N-CH_2		N-C-CH_3	
	Z	*E*	*Z* / *E*		*Z*	*E*	*Z*	*E*	*Z*	*E*
1	-	-	161.9	162.1	33.6	28.6	38.5	43.9	11.6	13.8
2	21.6	20.6	169.8		35.2	32.2	41.8	45.0	12.0	13.1
3	26.8	26.0	173.2		34.5	32.6	42.3	44.3	12.3	13.5
4	30.1	29.8	176.3	177.3	34.5	32.9	42.3	44.0	12.0	13.8
5	38.5	38.5	176.8		35.1	35.1	44.4	44.4	12.5	12.5
6	116.4	116.4	157.4		34.4	34.1	44.9	44.8	11.1	13.1
7	40.8	40.2	164.8	165.0	33.8	31.9	42.0	43.8	10.9	12.5
8	65.3	64.8	162.3	162.8	34.8	33.7	44.1	44.6	11.4	13.2
9	92.7	92.7	160.6		37.6	36.0	47.1	47.1	11.2	12.6
10	26.3	25.5	166.1	166.2	35.2	32.8	42.8	45.1	11.5	13.2
11	35.8	34.7	162.8	163.3	35.5	33.9	44.2	45.2	11.3	13.2
12	28.4	28.4	159.3		36.4	36.4	47.0	47.0	11.6	11.6
13	-3.2	-4.9	168.3	170.9	36.0	33.4	43.4	46.0	11.4	13.1

[a] In ppm, downfield from TMS. Solvent $CDCl_3$. The chemical shifts of the β-carbon for the compounds 3-5 are: 9.6(*Z*) and 9.2(*E*); 19.4(*Z*) and 18.8(*E*); 28.1(*Z*) and 28.1(*E*) (ppm).

[b] The chemical shifts of the *Z* and *E* isomers cannot be unambiguously assigned.

Within 20°-130°C, the influence of both the solvents and the temperature on the isomeric equilibrium can be omitted[5].

These experiments allowed the assignment of the upfield resonances to the (*E*)-N-CH_3 and (*Z*)-N-C-CH_3 groups for the N-Ethyl-N-methylamides 1-4,6-11,13 (Table 1). The compounds 5,12

show superimposed ^{13}C NMR signals for *syn*- and *anti*-N-substituents at room temperature. It was also attributed the upfield resonance signals for the (*Z*)-N-CH_2 group of amides 1-4,7,8,10,11,13, and for amides 5,6,9,12 the (*Z*)- and (*E*)-N-CH_2 groups exhibit superimposed ^{13}C NMR signals for *syn*- and *anti*-N-substituents at room temperature (Table 1).

α-Carbon and Carbonyl Carbon

The substituent effects on the α-carbon and carbonyl carbon chemical shifts in carbonyl compounds should correspond to the complex contribution of the electronic, steric and magnetic anisotropy effects of the substituents[1-3].

The relationships of ^{13}C NMR data of α-carbon to the substituent effects shows to deviations from linearity on increasing the atomic number of the halogen-substituent. This fact was attributed to a diamagnetic contribution to the chemical shift due to the magnetic anisotropy of the halogen atom[6,7]. The same relationships for atom substituents of the 1st row of the periodic table also showed deviations from linearity. This deviation can be explained by an orbital interaction[6,7,11].On the other hand, for α-alkyl carbons of α-alkylamides the differences of the chemical shifts depend mainly on steric effects[4].

A similar deviation from linearity was observed when the α-carbon chemical shift of a series of α-hetero-substituted

N,N-diethylamides were plotted against Pauling's electronegativities and electronic parameters defined by Taft, Charton, and Inamoto[4].

In this work, the same trend is shown for α-carbon chemical shifts already observed for N,N-diethylamides when these values were plotted *versus* the electronic and steric parameters mentioned above. Therefore, the α-carbon chemical shifts of the N-ethyl-N-methylamides under investigation correlate with the empirical α-effect of the Y substituents (effect of Y on the chemical shifts of the substituted methanes[8], cf. Table 3). The plot of α_Y values *versus* α-carbon chemical shifts shows a good correlation (for (*E*) and (*Z*) plots, r=0.995). Thus, the chemical shift of α-*CHnX*3-n carbons of the isomers (*E*) and (*Z*) of N-ethyl-N-methylamides 2-13 can be predicted by using Eq. 1 and 2.

$$(E)\delta_{CHnX3\text{-}n} = 0.86\ \alpha_Y + 16.34 \qquad (1)$$

$$(Z)\delta_{CHnX3\text{-}n} = 0.85\ \alpha_Y + 17.19 \qquad (2)$$

n = 1,2, or 3.

The difference between the (*E*) and (*Z*) α-carbon chemical shifts is caused by the considerable steric compression effect[2] in the (*E*)-isomer exerted by the N-ethyl group on the R group

leading to an upfield shift in relation to the (*Z*)-isomer. This evidence could be confirmed through the similarity of the angular coefficients of Eq. 1 and the corresponding equation for N,N-diethylamides[4]: $\delta_{\alpha-CH2} = 0.88\ \alpha_Y + 17.22$ (r=0.989).

Substituent effects on the carbonyl carbon chemical shifts have been extensively studied[9-12]. Stothers and Lauterbur[9] attributed the observed upfield shift of chloroacetone carbonyl carbon to the inductive effect of the chlorine atom, which reduces the polarization of the carbonyl group double bond. These explanation can be extended to the (*E*)- and (*Z*)-isomers of the α-halo-amides 6-13 presented here. Charton's electrical parameter[13] (σ_I) (cf. Table 2) shows a linear correlation (for (*E*) and (*Z*) plotting, r=0.948 and r=0.977, respectively) with the carbonyl carbon chemical shifts when the data for the alkylamides 2,4,5 are omitted (Eq. 3 and 4).

$$(E)\delta_{C=O} = -38.8\ \sigma_I + 173.8 \qquad (3)$$

$$(Z)\delta_{C=O} = -37.5\ \sigma_I + 173.0 \qquad (4)$$

The carbonyl carbon chemical shifts of α-alkyl N-ethyl-N-methylamides(2-5) show straight dependence on the bulkness of the α-alkyl substituent.

The difference between the (*E*) and (*Z*) carbonyl carbon chemical shifts for some α-mono- or α,α-di-substituted amides

TABLE 2

The α effect[a] (α_Y), Charton's electronic (σ_I) and steric (ν_s) parameters[b] for some substituents.

Y	α_Y	R	σ_I	ν_s
H	0	Me	-0.01	0.52
Me	8.0	Et	-0.01	0.56
Me_2	18.2	*i*-Pr	0.01	0.76
Me_3	27.3	*t*-Bu	-0.01	1.24
F_3	-	F_3C	0.40	0.91
Cl	26.1	$ClCH_2$	0.17	0.60
Cl_2	55.2	Cl_2CH	0.28	0.81
Cl_3	79.7	Cl_3C	0.36	1.38
Br	11.2	$BrCH_2$	0.20	0.64
Br_2	22.6	Br_2CH	0.28[c]	0.89
Br_3	13.4	Br_3C	0.35[c]	1.56
I	-19.5	ICH_2	0.17	0.67

[a] In ppm. ^{13}C chemical shift data for substituted methanes, Ref. 8, p.199.

[b] Charton's electronic parameter from Ref. 13a, p.143, and steric parameter from Ref. 13b, p.269.

[c] Calculated from Ref.13b, p.231.

can be explained on the basis of the conformational analysis of several mono-substituted N,N-diethylamides by IR spectroscopy, which gave evidence for a *cis* and *gauche* equilibrium of the YCH_2-C(O) conformers[14]. Thus, it was expected that asymmetrical

N-substituents have an effect on the *cis/trans* conformer equilibrium and that these changes are reflected by different effects on the (*E*) and (*Z*) carbonyl carbon magnetic neighborhood.

N-Ethyl and N-Methyl Carbons

In comparison with N-ethyl-N-methylamides reported here, the (*E*)-CH_3 and the (*Z*)-N-CH_2 groups are shielded for about 3-5ppm and 2-5ppm, relative to the (*Z*)-CH_3 and the (*E*)-N-CH_2 groups, respectively.

N,N-Dialkylamides are known[2] to exhibit different chemical shifts for the *syn*- and *anti*-carbon atoms to the oxygen atom of the carbonyl group. Levy and Nelson[2] attributed these differences to the steric compression effect of the carbonyl oxygen atom on the *syn*-carbon atoms leading to an upfield shift, in addition to the electrical field shielding effect due to the oxygen atom[1].

Fritz *et. al.*[3] explained the differences between *syn*- and *anti*-carbon shielding by comparison with olefins. The α-methylene carbon in a *trans*-olefin is deshielded by 5.7ppm in comparison with a *cis*-olefin; this deshielding effect is small for a β-carbon and vanishes for a γ-carbon atom.

As previously found, the major contribution to the differences in chemical shift values of the *syn*- and *anti*-N-alkyl groups for N,N-diethylamides in relation to N,N-dialkylformamides were derived from *trans*- and *cis*-olefin effects[3,4], respectively.

The differences between the N-alkyl carbon chemical shifts of the α-mono-substituted N,N-diethylacetamides were attributed similarly to the *trans*- and *cis*-olefin effect and the steric compression effect[4].

The chemical shift data of N-ethyl-N-methylamides **1-13** described here were similarly analyzed and led to an estimation of the *trans*- and *cis*-γ effects of the R group on the *syn*- and *anti*-N-substituents, respectively; the values are presented in Table 3. The corresponding δ effects on the *syn*- and *anti*-N-C-CH_3 groups are also included.

Table 3 shows that the *trans*-γ effects of the (*E*)-N-CH_3 and the (*Z*)-N-CH_2 groups have similar values (3.3 - 8.6 ppm) while the *cis*-γ effects of the (*Z*)-N-CH_3 and the (*E*)-N-CH_2 groups display values between 0-4.0 ppm. There is a close resemblance of *trans*-γ effects of (*Z*)-N-CH_2 and *cis*-γ effects of (*E*)-N-CH_2 with *trans*-γ effects of the *syn*-N-CH_2 and *cis*-γ effects of the *anti*-N-CH_2 of N,N-diethylamides previously studied[4](corresponding to compounds 1-3,7,10,13). This shows that the ^{13}C chemical shifts of N-substituents of the N-ethyl-N-methylamides 1-13 behave like two series of compounds: N,N-dimethylamides and N,N-diethylamides.

The order for the *trans*-γ and the *cis*-γ effects was similar to that previously observed[4]. This suggests the predominance of the γ-effect as established in olefins[3]. However, it was also observed that the differences of the *cis*-γ effect of the

TABLE 3

Gamma (γ) and delta (δ) effects[a] on the N-CH_3, N-CH_2-, and N-C-CH_3 carbon chemical shifts for *Z* and *E* isomers of compounds 1-13.

		N-CH_3		N-CH_2		N-C-CH_3	
		Z	*E*	*Z*	*E*	*Z*	*E*
R	Compound	*cis*-γ[b]	*trans*-γ	*trans*-γ	*cis*-γ	*trans*-δ	*cis*-δ
H	1	0	0	0	0	0	0
Me	2	1.6	3.6	3.3	1.1	0.4	-0.7
Et	3	0.9	4.0	3.8	0.4	0.7	-0.3
i-Pr	4	0.9	4.3	3.8	0.1	0.4	0
t-Bu	5	1.5	6.5	5.9	0.5	0.9	-1.3
F_3C	6	0.8	5.5	6.4	0.9	-0.5	-0.7
$ClCH_2$	7	0.2	3.3	3.5	-0.1	-0.7	-1.3
Cl_2CH	8	1.2	5.1	5.6	0.7	-0.2	-0.6
Cl_3C	9	4.0	7.4	8.6	3.2	-0.4	-1.2
$BrCH_2$	10	1.6	4.2	4.3	1.2	-0.1	-0.6
Br_2CH	11	1.9	5.3	5.7	1.3	-0.3	-0.6
Br_3C	12	2.8	7.8	8.5	3.1	0	-2.2
ICH_2	13	2.4	4.8	4.9	2.1	-0.2	-0.7

[a] In ppm. The γ-effect refer to the observed alterations of N-CH_3 and N-CH_2- chemical shifts, and the δ-effect refer to the observed alterations of N-C-CH_3 chemical shifts, using N-ethyl-N-methylformamide (1) as reference compound.

[b] The *cis*- and *trans*- effects are effects of the R group on *anti*- and *syn*-carbon atoms to oxygen of the carbonyl group, respectively.

(*Z*)-N-CH_3 and (*E*)-N-CH_2 groups depend on the steric effect of R within the series of mono-, di- or tri-substituted compounds, as well as the α-chlorinated and α-brominated series. On the other hand, the differences of the *trans*-γ effects on the (*E*)-N-CH_3 and (*Z*)-N-CH_2 groups have surprisingly shown a narrow correlation with Charton's steric parameter[13] of R throughout the series of compounds **2-13**. The existence of this type of correlation may suggests an indirect steric interaction (*'gear effect'*)[15].

The *cis*-δ and *trans*-δ effects exhibit small values between -2.2 and -0.9ppm, which are apparently randomized. This could be explained by the sum of the competitive effects already mentioned which contribute to the chemical shift differences of the N-C-CH_3 groups, according to the position on space of these groups in relation to the magnetic anisotropy of the carboxamide plane[16].

EXPERIMENTAL

Compounds

N-Ethyl-N-methylamides **1-13** were prepared as described previously[5].

Spectra

The ^{13}C NMR spectra were recorded at 20.15 MHz on a BRUKER AC-80A spectrometer in the FT mode (0.5M solution in $CDCl_3$, 0.1%

TMS as internal standard), in a 5mm i.d. sample tube. The conditions were as follows: deuterium internal lock, probe temperature 35°C, pulse width 1.6μs, flip angle 30°, acquisition time 0.8s, spectral width 5000Hz, pulse repetition time 1.3s, number of transients 6000, data points 8K.

The DEPT experiments were recorded using the pulse sequence D1-90°(^{1}H)-D2-180°(^{1}H), 90°(^{13}C)-D2-PO(^{1}H), 180°(^{13}C)-D2-FID; recycle delay 1/2 J(CH) = 3.3ms; phase angle 90° at 16.8μs and 135° at 25.2μs. The other acquisition parameters were the same as for the ^{13}C NMR spectra.

Homonuclear chemical shift correlation (COSY 45) experiments were carried out by using the pulse sequence delay 90°-t_1-45°-acquisition; the relaxation delay was 1s, the 90° pulse was 4.5 μs, and 1s relaxation delay was used. A total of 16 transients were collected per time unit; 256 time increments were applied to characterize the t_1 domain and 1024 points were used to characterize t_2, and a zero filling once in the t_2 domain was applied.

Heteronuclear chemical shift correlated spectra were obtained by using the pulse sequence delay 90°(^{1}H)-$t_{1/2}$-Δ_1-90°(^{1}H)-90°(^{13}C)-Δ_1-acquisition with decoupling in both dimensions. A 1s recycling delay was used, and the delay times Δ_1 = 3.5ms and Δ_2 = 1.75ms. The 90°(^{1}H) pulse was 16.8μs and the 90°(^{13}C) pulse was 4.8μs. The spectral width in the t_2(carbon) domain was 893 Hz and in the t_1(proton) domain 332 Hz;

4096 points were used in the t_2 domain and 256 time increments defined the resolution of the t_1 domain; a total of 300 transients were applied per increment.

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