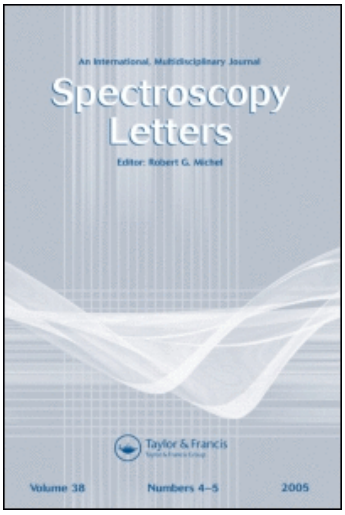

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^{1}H and ^{13}C NMR Chemical Shifts and N-Substituent Effects of Some Unsymmetrically N,N-Disubstituted Acetamides

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^{1}H AND ^{13}C NMR CHEMICAL SHIFTS AND N-SUBSTITUENT EFFECTS OF SOME UNSYMMETRICALLY N,N-DISUBSTITUTED ACETAMIDES

KEY WORDS: ^{1}H and ^{13}C NMR assignments of Amides, Unsymmetrical Amides

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ABSTRACT: The ^{1}H and ^{13}C NMR chemical shift assignments of a series of (*E*)- and (Z)-N,N-Dialkylacetamides [$CH_3C(O)NR^1R^2$, with R^1/R^2= Me/Et (1), Me/*n*-Bu (2), Et/*n*-Bu (3), Et/*t*-Bu (4), Me/Hydroxyethyl (5), Et/Hydroxyethyl (6), Et/Acetylhydroxyethyl (7)] are reported. The ^{1}H chemical shifts for the N-substituents of the amides 1-7 recorded in benzene-d_6 and in chloroform-d_1 are in agreement with the Hatton and Richards (ASIS) and Paulsen-Todt models, respectively. The ^{13}C chemical shifts for the N-substituents of compounds 1-3 were compared with data of the corresponding symmetrical amides, and the results can be explained by the reciprocal steric compression effect of one

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N-substituent on the other. The validity of this explanation is confirmed by ^{13}C spin-lattice relaxation time (T_1) measurements.

INTRODUCTION

Although N,N-dialkyl aliphatic amides have been studied extensively by ^{1}H and ^{13}C NMR spectroscopy[1-6], there is a lack of ^{1}H and ^{13}C NMR data for unsymmetrically N,N-disubstituted amides in the literature[1,7,8].

Symmetrical N,N-Dialkylamides are known to exhibit different chemical shifts for the carbon atoms in *syn*- and *anti*-position to the oxygen of the carbonyl group[2-4]. Levy and Nelson[3] attributed these different values to the steric compression effect of the carbonyl oxygen atom on the *syn* carbon atoms leading to an upfield shift, in addition to the electric field shielding effect due to the oxygen atom[1]. Fritz *et. al.*[4] explained the differences between the *syn*- and *anti*-carbon shielding effect by comparison with those of olefins. In a previous work[6], we also concluded that major contribution to the differences of chemical shift values of the *syn*- and *anti*-N-alkyl groups of N,N-diethylacetamides, in comparison with N,N-dialkylformamides, can be derived from *trans*- and *cis*-olefin effects[4], respectively. The differences between the chemical shifts of the N-alkyl carbons of α-mono-substituted N,N-diethylacetamides are caused by the *trans*- and *cis*-olefin effect and the direct or indirect steric compression effect[6].

In this work the ^{1}H and ^{13}C NMR spectra of seven unsymmetrically substituted N,N-dialkylacetamides [$CH_3C(O)NR^1R^2$, with R^1/R^2= Me/Et (1), Me/*n*-Bu (2), Et/*n*-Bu (3), Et/*t*-Bu (4), Me/Hydroxyethyl (5), Et/Hydroxyethyl (6), Et/Acetylhydroxyethyl

(7)] were recorded. Proton and carbon resonances for *syn*- and *anti*-N-substituents of the (*E*)- and (*Z*)-isomers were assigned through a series of homo- and heteronuclear COSY experiments, as well as by DEPT 90° and 135°. The proton resonances thus obtained for *syn*- and *anti*-N-alkyl-substituents will be applied to the theories of aromatic solvent induced shifts (ASIS)[9] and the Paulsen-Todt model[10]. The *syn*- and *anti*-N-alkyl-substituent carbon resonances will be analyzed in comparison with the data of the corresponding symmetrical N,N-dialkylamides.

RESULTS AND DISCUSSION

^{1}H NMR

The ^{1}H NMR experiments were performed in chloroform-d_1 and benzene-d_6 solutions. In chloroform-d_1 the proton resonances of (*E*)- and (*Z*)-N-substituted amides were partially superimposed. In Table 1 the ^{1}H chemical shifts of the N,N-dialkylacetamides 1-7 are listed.

When benzene-d_6 is used as solvent, the N-C(1) proton resonances of the *anti*-N-substituents are shifted by 0.18-0.65 ppm upfield relative to the *syn*-N-substituents. However, the N-C(1) proton resonances of the *anti*-N-substituents are shifted by 0-0.12 ppm downfield in relation to the *syn*-N-substituents (except for the compound 3) when chloroform-d_1 is used as solvent. In benzene-d_6 the N-C(2) proton resonances of the *anti*-N-substituents are shifted upfield in comparison with the *syn*-N-substituents. However, in chloroform-d_1 the tendency for the N-C(2) protons is reversed.

TABLE 1

^{1}H Chemical shifts[a] of N,N-dialkylacetamides 1-7.

Compd.	Isomer	α-CH_3		N-C^1		C^2		C^3		C^4	
		C	*B*	*C*	*B*	*C*	*B*	*C*	*B*	*C*	*B*
1 Me	*Z*	2.08	1.66	2.98	2.16						
Me	*E*	2.06	1.71	2.91	2.65						
Et	*Z*			3.42	3.20	1.10	0.86				
Et	*E*			3.33	2.55	1.18	0.56				
2[b] Me	*Z*	2.10	1.79	3.0	2.7						
Me	*E*	2.10	1.79	2.9	2.3						
n-Bu	*Z*			3.4	3.2	1.5	1.3	1.3	1.2	0.9	0.8
n-Bu	*E*			3.3	2.7	1.6	1.3	1.3	1.2	0.9	0.8
3[b] Et	*Z*	2.04	1.82	3.23	2.91	1.2	0.9				
Et	*E*	2.04	1.82	3.35	3.34	1.1	1.0				
n-Bu	*Z*			3.27	3.30	1.5	1.4	1.3	1.1	0.92	0.78
n-Bu	*E*			3.24	2.78	1.6	1.3	1.3	1.1	0.98	0.78
4 Et	*Z*	2.12	-	3.37	-	1.18	-				
Et	*E*	-		-	-	-	-				
t-Bu	*Z*			-	-	1.18	-				
t-Bu	*E*			-	-	-	-				
5 Me	*Z*	2.08	1.79	3.10	2.66						
Me	*E*	2.12	2.04	2.92	2.84						
CH_2CH_2OH	*Z*			-	3.45	-	3.63				
CH_2CH_2OH	*E*			-	3.12	-	3.77				
6 Et	*Z*	2.11	1.79	3.52	2.95	1.20	0.78				
Et	*E*	2.11	2.02	3.41	3.35	1.11	1.03				
CH_2CH_2OH	*Z*			3.48	3.40	3.72	3.78				
CH_2CH_2OH	*E*			3.48	3.12	3.72	3.62				
7 Et	*Z*	2.11	-	3.52	2.85	1.20	0.75				
Et	*E*	2.12	-	3.41	3.24	1.11	0.97				
CH_2CH_2OAc	*Z*			3.56	3.39	4.21	4.16			2.06	-
CH_2CH_2OAc	*E*			3.56	3.00	4.21	3.87			2.06	-

[a] In ppm downfield from TMS. Solvents, *C* =Chloroform-d_1, *B* =Benzene-d_6.
[b] Values taken from 2-D NMR spectra.

At 80 MHz the protons attached to the N-C(3) and N-C(4) exhibit practically the same chemical shift in both solvents. The proton chemical shifts for the N-substituents of the amides 1-7 recorded in benzene-d_6 are as expected from literature[9]. Normally, the aromatic solvent induced shift (ASIS)[9] of the

anti-N-substituent is upfield and larger than that of the *syn*-N-substituent due to the formation of a collision complex between the aromatic ring and the nitrogen as has been reported by Hatton and Richards[9].

On the other hand, the chemical shift differences observed in chloroform-d_1 are explained satisfactorily by applying the Paulsen-Todt model[10]. This model explains the differences of proton chemical shifts in N-substituted amides with respect to the position occupied in space by each proton or group of protons relative to the plane of the carboxamide group. This plane determines zones out-of-plane and in-plane of larger shielding or deshielding, according to the distance and location relative to the carboxamide group.

In agreement with the steric model established for unsymmetrical amides[1], compound **4** seems only to occur in the Z-form. Furthermore it is shown that in the other acetamides the bulkier N-substituent preferentially occupies the position *syn* to the carbonyl oxygen[1,3].

^{13}C NMR

In Table 2 the ^{13}C chemical shifts of compounds **1-7** are listed.

The homo- and heteronuclear COSY experiments allowed the assignment of upfield resonances for N-C(1) and N-C(2) carbons to the respective *syn*-N-substituent group. Compound **4** exhibits only one ^{13}C NMR signal, corresponding to the (Z)-isomer, where the N-*t*-butyl group is in *syn* position to the carbonyl oxygen.

The *syn*-N-substituents are shielded in relation to the *anti*-N-substituents, for the carbons N-C(1) (2.3-3.6 ppm) and

TABLE 2

^{13}C Chemical shifts[a] of N,N-dialkylacetamides 1-7.

Compd.		Isomer	α-CH_3[b]	C=O	N-C^1	C^2	C^3	C^4
1	Me	*Z*	21.63	169.81	35.20			
	Me	*E*	20.80		32.39			
	Et	*Z*			41.89	12.07		
	Et	*E*			45.09	13.17		
2	Me	*Z*	20.22	169.44	34.92			
	Me	*E*	19.84		31.93			
	n-Bu	*Z*			46.01	28.24	18.82	12.64
	n-Bu	*E*			49.43	29.35	18.82	12.64
3	Et	*Z*	19.94	167.70	41.64	12.66		
	Et	*E*	19.72		38.84	11.51		
	n-Bu	*Z*			43.38	28.66	18.76	12.36
	n-Bu	*E*			46.72	29.88	18.60	12.36
4	Et	*Z*	24.48	170.88	40.38	16.69		
	Et	*E*	-	-	-	-		
	t-Bu	*Z*			56.58	28.84		
	t-Bu	*E*			-	-		
5	Me	*Z*	20.78	170.69	36.07			
	Me	*E*	20.45		32.48			
	CH_2CH_2OH	*Z*			49.53	59.17		
	CH_2CH_2OH	*E*			52.01	58.32		
6	Et	*Z*	19.50	169.34	43.09	12.15		
	Et	*E*	20.01		38.91	11.04		
	CH_2CH_2OH	*Z*			46.40	58.31		
	CH_2CH_2OH	*E*			48.66	57.97		
7	Et	*Z*	19.04	169.93[b]	43.26	12.19		
	Et	*E*	19.04	170.39[b]	40.07	10.97		
	CH_2CH_2OAc	*Z*			43.48	60.13	166.56	18.92
	CH_2CH_2OAc	*E*			45.78	60.13	166.56	18.92

[a] In ppm downfield from TMS. Solvent, chloroform-d_1.

[b] These *Z*/*E*-assignments are interchangable.

N-C(2) (0-1.3 ppm). On the other hand, the shielding differences of the respective N-C(3) and N-C(4) carbons between the *syn*- and *anti*-N-substituents are neglectable.

The chemical shift data for the unsymmetrical N,N-dialkylacetamides **1-3** were analyzed in comparison with the data of the corresponding symmetrical N,N-dialkylacetamides[11]. This analysis led to a determination of the $\Delta\delta C(1)$ and $\Delta\delta C(2)$ values, which represent the effects of each N-substituent in the unsymmetrical acetamide in relation to the corresponding N-substituent in the symmetrical acetamide, i.e. $\Delta\delta C(1,2) = \delta C(1,2)_{[UNSYMM.AMIDE]} - \delta C(1,2)_{[SYMM.AMIDE]}$.

Table 3 shows that the $\Delta\delta C(1)$ values decrease for *syn*- and *anti*-N-CH_3 (i.e., the methyl carbon is shielded, compounds 1,2) with the size of the carbon chain of the other N-substituent (shielding effect). A similar trend is observed for *syn*- and *anti*-N-CH_2CH_3 and N-$CH_2CH_2CH_2CH_3$ substituents. Thus, we conclude from the $\Delta\delta C(1)$ values that the shielding effect of N-substituents on N-CH_3 decreases in the series *n*-Bu(2) > Et(1). For N-CH_2CH_3 the order is *n*-Bu(3) > Me(1). For N-$CH_2CH_2CH_2CH_3$ the order is the same where the Et>Me compounds are 3,2. The results obtained from $\Delta\delta C(1)$ data can be explained by the reciprocal steric compression effect of one N-substituent on the other which leads to a shielding of the carbon atom[3].

Another trend was observed for the $\Delta\delta C(2)$ values. For N-CH_2CH_3 substituents, we observed the following order of the shielding effect: *n*-Bu(3) > Me(1), for the N-$CH_2CH_2CH_2CH_3$ substituent Me(2) > Et(3) . The results obtained from $\Delta\delta C(2)$ data for N-CH_2CH_3 can be explained also by the reciprocal steric compression effect between the N-substituents. The N-$CH_2CH_2CH_2CH_3$ substituent shows a different behavior. This behavior could be

TABLE 3

$\Delta\delta C^1$ and $\Delta\delta C^2$ values[a] for Amides 1-3.

1st N-Substituent		Compound/2nd N-Substituent	
		$\Delta\delta C^1$	
		1/Et	2/*n*-Bu
CH_3	*syn*[b]	-2.19	-2.65
	anti	-1.91	-2.19
		1/Me	3/*n*-Bu
CH_3-CH_2	*syn*	1.93	-1.12
	anti	2.54	-0.58
		2/Me	3/Et
$CH_3CH_2CH_2CH_2$	*syn*	0.56	-2.07
	anti	1.05	-1.66
		$\Delta\delta C^2$	
		1/Me	3/*n*-Bu
CH_3CH_2	*syn*	-1.30	-1.54
	anti	-1.03	-1.86
		2/Me	3/Et
$CH_3CH_2CH_2CH_2$	*syn*	-2.25	-1.83
	anti	-2.10	-1.57

[a] In ppm. Compared were $\Delta\delta(C^{1,2})$ values of the 1st-N-substituent and $CH_3C(O)N(1^{st}\text{-Substituent})_2$. See also footnote 11 and text.

[b] *syn*: Refers to the position of the 1st N-substituent relative to the carbonyl oxygen.

explained by the sum of β-effect and γ-effect from the methyl group of the *n*-butyl carbon chain and the N-methyl group, respectively, which can be larger than the sum of β-effect and γ-effects from the methyl group of the *n*-butyl carbon chain and the N-methylene carbon, respectively. The presence of a δ-effect

TABLE 4

^{13}C Spin-lattice relaxation times (nT_1)[a] of the N-*n*-butyl substituent of the N,N-dialkylacetamides 2 and 3.

Compound	R^1	N-C^1	C^2	C^3	C^4
2	Me	3.8	4.6	6.4	12.0
3	Et	3.4	4.0	5.8	10.5

[a] In seconds. n = number of protons attached to each carbon.

from the methyl group of the N-Ethyl carbon chain and the conformational effects could also be considered.

^{13}C spin-lattice relaxation time (T_1) values provide an information about the mobility of the carbon chain[12]. Table 4 shows the nT_1 (n = number of protons attached to each carbon multiplied by T_1) of the N-*n*-butyl substituent for compounds 2 and 3. These results confirm the reciprocal steric compression effect of one N-substituent on the other as mentioned above because all nT_1 values of carbon-13 of the N-*n*-butyl substituent of compound 2 (N-CH_3) are larger than the corresponding ones of compound 3 (N-CH_2CH_3).

EXPERIMENTAL

Compounds

The compounds 1-7 have been synthesized from the respective N,N-disubstituted amine and acetyl chloride[8].

Spectra

^{1}H NMR spectra were recorded on a BRUKER AC-80 spectrometer at 80 MHz. For the measurements 0.1M solutions in chloroform-d_1 or benzene-d_6 containing 0.1 % tetramethylsilane (TMS) as internal reference and 5mm o.d. sample tubes were used. The conditions were as follows: deuterium internal lock, T = 308 K, pulse width 4.7 μs, flip angle 90°, acquisition time 4.1 s, spectral width 1000 Hz, delay time 1.0 s, number of transients 16, and number of data points 8192.

^{13}C NMR spectra of 0.5M solutions in chloroform-d_1 or benzene-d_6 containing 0.1 % TMS as internal reference were recorded in 5mm o.d. sample tubes on a BRUKER AC-80A spectrometer in FT mode at 20.15 MHz. The conditions were as follows: deuterium internal lock, probe temperature T = 308 K, pulse width 1.6 μs, flip angle 30°, acquisition time 0.8 s, spectral width 5000 Hz, delay time 1.3 s, number of transients 6000, data points 8192.

The DEPT experiments were performed employing the pulse sequences, D1-90°(^{1}H)-D2-180°(^{1}H), 90°(^{13}C)-D2-P0(^{1}H), 180°(^{13}C) -D2-FID; delay time 1 s; 1/2 J(CH) = 3.3 ms; phase angle 90° at 16.8 μs and 135° at 25.2 μs. The other acquisition parameters were the same as for the ^{13}C NMR spectra.

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

Heteronuclear chemical shift correlated spectra were obtained by using a composite pulse sequence delay with decoupling in both dimensions. A 1s relaxation delay was used, and the delay times $\Delta_1 = 0.5/J_{CH} = 3.5$ ms and $\Delta_2 = 0.25/J_{CH} = 1.75$ ms. The $90^{o}(^{1}H)$ pulse was 16.8 μs and the $90^{o}(^{13}C)$ pulse was 4.8 μs. The spectral width in the t_2 domain was 893 Hz and in the t_1 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.

The ^{13}C spin-lattice relaxation time (T_1) measurements were performed using the Fast Inversion-Recovery Fourier Transform (FIRFT) technique[13]. The delay between the repetition of the sequence was 1 s with up to 12 variables delay times, ranging from 1 ms to 15 s. T_1 relaxation times were determined on a BRUKER Aspect 3000 computer applying a nonlinear three-parameter-fit[14,15].

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