Investigation of the Structure of Trimethylsilylated Secondary Amides by ^{13}C N.M.R. Spectroscopy

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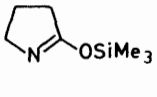
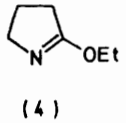
^{13}C N.m.r. spectroscopy has been shown to be a further valuable tool for investigating the position of silylation in trimethylsilylated secondary amides. Whereas most lactams are *N*-silylated and 2-hydroxypyridines *O*-silylated, acetanilides exist as a mixture of isomers.

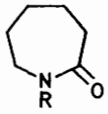
THE position of silylation of secondary amides has been the subject of several investigations in recent years.[1] The earlier studies have shown that whereas cyclic amides, such as pentano- and hexano-lactams, are trimethylsilylated on nitrogen, heteroaromatic amides, such as 2-hydroxypyridine and 2-hydroxypyrimidine, are exclusively *O*-silylated. These conclusions were based on i.r. and ^1H n.m.r. studies, although details of these findings have not been published. A similar study on bis(trimethylsilylated) primary amides [2] has shown that, with the exception of formamide, they all have the imidate form. Trimethylsilylated *N*-alkylformamides exist, in solution, in the amide form.[2] Silylated acetanilides form isomeric mixtures as shown by ^1H n.m.r. studies, with electron-withdrawing substituents on the aromatic ring strongly favouring the *O*-silylated form

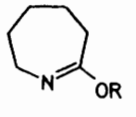

(1)


(2)

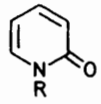

(3)


(4)


(5) R = H
(7) R = $SiMe_3$


(6) R = Et
(8) R = $SiMe_3$


(9) R = H
(10) R = $SiMe_3$
(11) R = Me


(12) R = Me
(13) R = $SiMe_3$

and electron-releasing substituents the *N*-silylated isomer.[3] In connection with studies on the oxidation of trimethylsilylated amides to hydroxamic acids [4] it was desired to clarify the position of silylation of a variety of secondary amides. The known sensitivity of the ^{13}C chemical shift of the carbonyl carbon atom to substituent effects [5] suggested the use of ^{13}C n.m.r. spectroscopy as a suitable structural probe.

The proton-noise-decoupled ^{13}C n.m.r. spectrum of trimethylsilylated 2-pyrrolidone showed five lines indicating that either only one of the two possible isomers [(1) or (2)] was present, or that rapid exchange between the two occurs. A comparison of the spectrum with those of 2-pyrrolidone (3) and its *O*-ethyl lactim ether (4) suggested that it was more in accord with the *N*-isomer (1) rather than the *O*-silylated form (2). In particular, the shift of the carbonyl carbon (183.7) was closer to that of the amide (179.8) than that of the imino-ether (173.4), in agreement with its reported structure [1] (Table 1). Similar results were obtained with ε-caprolactam (5) (carbonyl carbon shift 180.3), its *O*-ethyl imino-ether (6) (169.5), and its trimethylsilyl derivative (182.6), the latter value thus supporting the assigned structure (7) rather than the *O*-isomer (8).

By contrast to the former results, the silylation of 2-hydroxypyridine (9) leads exclusively to (trimethyl-

TABLE 1

^{13}C Chemical-shift values *

(*a*) Pyrrolidone and derivatives

	(1)	(3)	(4)
C(2)	183.7	179.8	173.4
C(3)	32.8	30.4	31.3
C(4)	21.7	20.8	23.2
C(5)	46.6	42.5	44.0

(*b*) ε-Caprolactam and derivatives

	(7)	(5)	(6)
C(2)	182.6	180.1	169.5
C(3)	37.4	37.0	32.5
C(4)	23.1	23.2	23.5
C(5)	29.4	29.8	27.9
C(6)	30.0	30.7	31.2
C(7)	44.1	42.8	48.7

(*c*) 2-Pyridone derivatives

	(10)	(9) [6]	(11) [6]	(12) [6]
C(2)	162.6	162.3	163.1	161.8
C(3)	112.4	119.8	110.5	119.1
C(4)	138.6	140.8	138.7	139.5
C(5)	116.4	104.8	116.7	104.8
C(6)	146.9	135.2	146.6	139.5

(*d*) 4-Quinolone and related compounds

	(14) [7]	(15) [8]	(18)	(16) [6]	(17) [6]
C(2)	139.5	150.0	151.3	139.8	150.7
C(3)	108.8	120.8	108.3	115.9	109.8
C(4)	177.2	135.7	159.1	175.7	164.9
C(4a)	125.9	128.0	124.0		
C(8a)	140.1	148.1	150.4		

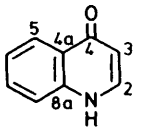
* See Experimental section for instrumental conditions.

silyloxy)pyridine (10), as shown by comparison of its ^{13}C n.m.r. spectrum with those of the *O*-, and *N*-methyl derivatives (11) and (12) (see Table 1). In these cases the 2-C atoms all exhibit similar shifts and the differentiation between isomers is more clearly revealed by the shifts of the remaining ring carbons at positions 3—6. Again the comparison agrees with the literature assignment as (10) rather than (13),[1] thus lending confidence to the reliability of the method.

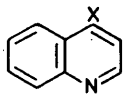
A brief survey of other heterocyclic systems was also made. A comparison of the spectra of trimethylsilylated 4-quinolone with those of the parent compound (14), quinoline (15), 4-pyridone (16), and 4-methoxypyridine (17) leads unambiguously to the assignment of the *O*-trimethylsilylated structure (18).

Comparisons were also made of a series of *p*-substituted acetanilides with their *O*-ethylimino-ethers and trimethylsilyl derivatives. In these cases mixtures of *N*- and *O*-silylated forms were observed. The chemical shifts of both the side-chain carbon atoms and also C(1) of the ring provided sensitive probes of structure (Table 2).

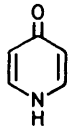
Assignments for the ring carbons of the *p*-substituted anilides are based on the use of substituent chemical-shift additivities given by Stothers.[9] Similar additivity



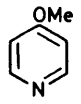
(14)



(15) X = H
(18) X = $OSiMe_3$



(16)



(17)

values for the imino-ether and *N*- and *O*-(trimethylsilyl)-acetamido-substituent were calculated from the observed spectra (Table 2) and are tabulated (Table 3).

Integration of the ^{13}C n.m.r. spectra (by gated de-

TABLE 2

^{13}C Chemical-shift values of acetanilide derivatives [a]

	p-$XC_6H_4NHCOMe$		*p*-$XC_6H_4N{=}C(Me)OEt$		*p*-$XC_6H_4N(SiMe_3)COMe$		*p*-$XC_6H_4N{=}C(Me)OSiMe_3$	
X = H	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
CO	169.5		161.1		176.6		160.0	
Me	24.2		16.2		23.3		17.1	
C(1)	138.2		149.3		142.7		149.0	
C(2)	120.4		121.2		128.9		120.8	
C(3)	248.8		129.0		129.7		129.7	
C(4)	124.2		122.8		127.3		122.7	
X = Cl								
CO	165.8		161.7		176.6		161.0	
Me	24.6		16.1		23.5		17.4	
C(1)	136.4	136.0 [b]	148.1	147.1	141.5	140.5	147.8	146.8
C(2)	121.1	121.5	122.7	122.3	129.6	130.0	122.5	121.9
C(3)	129.0	128.7	129.0	128.9	129.6	129.6	129.6	129.6
C(4)	129.0	129.8	129.0	128.4	133.2	132.9	129.6	128.3
X = OMe								
CO	169.0		162.1		176.9		168.2	
Me	24.2		15.1		23.2		17.2	
C(1)	131.4	130.2	143.0	141.3	135.7	136.7	140.3	141.0
C(2)	122.3	121.2	122.3	122.0	129.3	129.7	*c*	121.6
C(3)	114.2	114.2	114.6	114.4	115.3	115.1	*c*	115.1
C(4)	156.6	155.7	155.9	154.3	159.2	158.8	*c*	154.2
X = NO_2								
CO	169.9		161.5		*c*		160.8	
Me	24.6		16.6		23.0 [d]		17.7	
C(1)	145.4	144.1	155.3	155.2	*c*	148.6	155.3	154.9
C(2)	119.3	121.1	121.6	121.9	*c*	129.6	121.4	121.5
C(3)	125.1	123.5	125.1	123.7	*c*	124.4	124.8	124.4
C(4)		143.7		142.3	*c*	146.8	143.5	142.2

[a] See Experimental section for instrumental details. Substituted chemical shifts for X = Cl, OMe, and NO_2 taken from ref. 8, spectra 153, 248, and 157 respectively. [b] Calculated using the substituent chemical shifts in Table 3. [c] Signal not observed. [d] Trace signal only.

TABLE 3

Substituent chemical-shift values for ^{13}C chemical shifts of acetanilide derivatives, ArX

Ring position	X = NHCOMe [b]	N=C(Me)OEt	$N(SiMe_3)COMe$	$N{=}C(Me)OSiMe_3$
1	+9.5	+20.6	+14.0	+20.3
2	−8.3	−7.5	+0.2	−7.9
3	+0.1	+0.3	+1.0	+1.0
4	−4.5	−5.9	−1.4	−6.0

[a] Shift values, Δx, in p.p.m. (downfield shifts positive) from benzene, 128.7 p.p.m. from $SiMe_4$. [b] From ref. 8, spectrum no. 295, and our work.

TABLE 4

Isomer distribution in trimethylsilylated acetanilides

	% *N*-Si					Lit. K_{eq} [b]	
p-X [a]	Me	CO	C(1)	Average	K_{eq} (O–Si/N–Si)	[$^2H]_5$Pyridine	Other solvents
H($CDCl_3$)	72	73	73	73	0.37		
H([$^2H_5$]pyridine)	50	50	50	50	1.00	0.82	2.2 [c]
Cl	57	57	56	57	0.75	1.58	1.29 [d]
OMe	>96			>96	<0.04	0.17	
NO_2	trace			trace	>20	20	

[a] Measurements at 30 °C in $CDCl_3$. [b] Measurements at 0 °C, see ref. 3. [c] In CCl_4. [d] In PhCN.

coupling) afforded estimates of the proportions of *O*- and *N*-silylated forms. The reliability of these estimates could be gauged by the close agreement between values obtained from ^1H n.m.r. measurements (Table 4) and with literature values for K_{eq}, also obtained from ^1H n.m.r. measurements. Klebe reports [3] that a plot of log K_{eq} against Hammett σ constants gives a linear correlation with $\rho = +1.6$. Our own data for four points also suggest a linear relationship with ρ +2.5.

EXPERIMENTAL

^{13}C N.m.r. spectra were recorded on a JEOL JNM-FX 60 instrument in the Fourier-transform mode using a pulse angle of 45° and interval times of 1 s, except for integrations where longer interval times were used in a gated mode. All accumulations were carried out at ambient conditions with a probe temperature of 30 °C, using an internal solvent deuterium lock. Chemical shifts are quoted on the δ scale with respect to tetramethylsilane.

Spectra were recorded for analytically pure samples of the silylated materials or reference compounds. Silylation was carried out by standard methods, the products being redistilled several times before final, direct distillation into the n.m.r. sample tubes; 20—25% w/v solutions in deuteriochloroform were routinely used. Manipulation techniques followed those described by Schriver.[10] Literature methods were used for the preparation of the amides. The b.p.s of the trimethylsilylated amides are listed in Table 5.

TABLE 5

B.p.s of trimethylsilylated amides

(1) 51—52 °C at 2 mmHg (lit.,[a] 77—81 °C at 6 mmHg)
(7) 112—114 °C at 5.5 mmHg (lit.,[b] 111—111.5 °C at 16 mmHg)
(10) 77—78 °C at 20 mmHg (lit.,[c] 63 °C at 12 mmHg)
(18) 60 °C at 0.03 mmHg [d]
Trimethylsilyl derivatives of:
Acetanilide 105—106 °C at 15 mmHg (lit.,[e] 105 °C at 13 mmHg)
p-Chloroacetanilide 98 °C at 2 mmHg (lit.,[f] 61—62 °C at 0.2 mmHg)
p-Methoxyacetanilide 112—115 °C at 1.5 mmHg (lit.,[f] 75—76 °C at 0.2 mmHg)
p-Nitroacetanilide 135—140 °C at 1.0 mmHg (lit.,[f,g] 88—90 °C at 0.2 mmHg)

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