Effect of the Orientation of Substituents on the Chemical Shifts of ^{13}C

IV†—^{13}C NMR Spectra of *N,N*-Diisopropylamides and -thioamides

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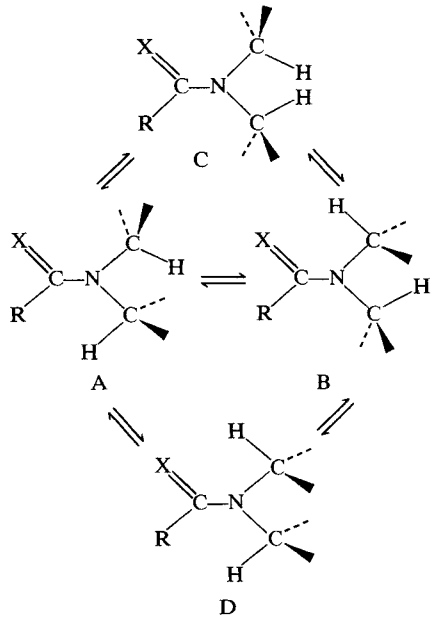
***N,N*-diisopropylamides and -thioamides show hindered rotation around the N—CH bonds, and the presence of mixtures of conformational isomers can be demonstrated at temperatures below 273 K in solution. ^{1}H and ^{13}C NMR spectra of these conformers are measured and assigned. The ^{13}C data serve to study through-space effects on ^{13}C chemical shifts, which strongly depend on the conformations of the isopropyl groups. For amides, a through-space shielding of the *N*-methine carbons is found to exist only for conformers in which the methine hydrogen atom is spatially close to the oxygen atom. Chemical shift differences between amides and thioamides can be rationalized in terms of through-bond and through-space contributions, and serve for a better understanding of the shift differences in *N,N*-dialkylamides and -thioamides.**

INTRODUCTION

N,N-diisopropyl compounds RC(X)N(isopropyl)$_2$ (X = O, S, Se; R = H, CH_3, OCH_3, SCH_3, $SeCH_3$) have been thoroughly investigated by ^{1}H NMR spectroscopy.[1–8] These studies were mainly concerned with the analysis of the conformation of the isopropyl groups, which show hindered rotation around the N—C bonds in a temperature range easily accessible by NMR for most compounds. The results of the ^{1}H NMR studies at variable temperature[7,8] and of molecular mechanics calculations[6–8] can be summarized as follows.

Molecular mechanics calculations result in four conformers of low energy, as shown in Scheme 1 (conformer D is actually a mixture of rapidly racemizing enantiomers, in which the methine C—H bonds form an angle of about + and −25°, respectively, with the (thio)amide plane.[7] The representation in Scheme 1 corresponds to the effective symmetry seen in the NMR spectra). Up to three of these conformers have been observed in the ^{1}H NMR spectra at low temperature and assigned the conformations A, B and D. No evidence for the presence of conformer C has been found. The free energy of activation of the conformational interconversion is *c.* 33 kJ mol^{-1} for *N,N*-diisopropylformamide (**1**), and above 49 kJ mol^{-1} for the other compounds. Two conformers have been observed in the spectrum of amide **2** (Table 1), for example, at 200 K and in the spectrum of thioamide **10** at 250 K, which have been assigned the conformations A and B. The ratio of A to B depends on the size of substituent R relative to that of the C=X group.



Scheme 1. Low energy conformations and possible exchange routes of *N,N'*-diisopropyl(thio)amides.

The following order of sizes has been deduced.[7,8]

$$H < CH_3O < C{=}O < CH_3 < CH_3S < C{=}S$$

As a rule, the conformer in which the methine H is eclipsed by the larger group (R or C = X) is the more stable. The presence of three conformers (A, B and D) has, as yet, only been observed[7,8] in compounds with two large groups, namely SCH_3 and C=S, or $SeCH_3$ and C=Se. It has been shown,[8] furthermore, for these compounds that the conformational interconversion from A to B occurs not by a synchronous rotation of

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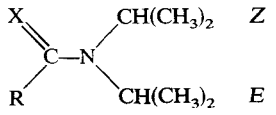
Table 1. Compounds investigated



R	X=O	X=S
H	1	9
CH_3	2	10
CH_3CH_2	3	11
$CH_3CH_2CH_2$	4	12
∅-CH_2	5	13
$(CH_3)_2CH$	6	14
CF_3	7	15
$(CH_3)_3C$	8	16

both isopropyl groups, but by a stepwise process from A via D to B (see Scheme 1).

To our knowledge, there are no systematic ^{13}C NMR studies of diisopropylamides and -thioamides. In continuation of our work on the ^{13}C NMR spectra of *N,N*-dialkylamides[9] and -thioamides,[10] we have measured the 360 MHz ^{1}H NMR and the 90.5 MHz ^{13}C NMR spectra of the 16 compounds listed in Table 1. We were interested in the effect of the substituents R on the conformational equilibrium and especially in the ^{13}C chemical shifts of the individual conformers. These chemical shifts are strongly dependent on the orientation of the substituents in the different conformers. Strong through-space effects are, moreover, expected for the C=X groups. A study of these effects should further the interpretation of the chemical shift differences between amides and analogous thioamides.[10]

RESULTS

The ^{1}H and ^{13}C chemical shifts of the compounds studied are collected in Tables 2–5. The data are given for the lowest temperature in $CDCl_3$ solution. Missing data indicate that the corresponding signals were not observed due to low intensity or overlap with other signals. The assignments have been verified in most cases by homo- and heteronuclear decoupling experiments. In some cases, the temperature dependence of the spectra could be used for the signal assignments (see below). Where prior investigations of the ^{1}H NMR spectra were available,[2,7] our assignments are in agreement with those published. We were able, however, to show the presence of one additional conformer in the low temperature spectra of **10**, **13** and **14**, compared with previous results,[2,7] presumably due to the higher field employed.

DISCUSSION

Conformational equilibria of the amides 1–8

The equilibria observed in the amides can be discussed solely in terms of the two conformers A and B. We leave open the question whether the *E*-isopropyl groups have fixed conformations in A and B, or whether the equilibria A⇋C and B⇋D are strongly biased towards A and B, respectively. The observation of hindered rotation of the *E*-isopropyl groups in thioamides (see below) also favours fixed conformations in amides, at least for larger R substituents.

At approximately 213 K, compounds **2**, **3** and **4** show ^{1}H and ^{13}C signals for the two conformers A and B in a ratio of 96:4, in complete agreement with ^{1}H results for **2** in Ref. 7 (in Ref. 6 the equilibrium mixture of **2** in CCl_4 solution and at 279 K is described as approximately 85% A and 15% D. Our low temperature results are not compatible with this conformational assignment). The isobutyramide **6** also shows signals for A and B at 213 K, but in a ratio of 91:9, indicating that $CH(CH_3)_2$ is a 'smaller' substituent than CH_3. At higher temperatures the spectra show the expected exchange broadenings, which follow the

Table 2. ^{1}H chemical shifts of the *N,N*-diisopropylamides 1–8 in $CDCl_3$[a]

Compound	T(K)[b]	Conformer[c]	Ratio[d] (%)	δ (CH-Z)	δ (CH-E)	δ (CH_3-Z)	δ (CH_3-E)	δ (R)
1	203	[e]	[e]	4.32 (b)	3.65	1.26	1.32	8.20
2	203	A	96	3.37	3.97	1.41	1.21	2.13
		B	4	5.08	3.64	1.12	(1.40)	2.19
3	203	A	96	3.37	4.06	1.42	1.20	2.37, 1.11
		B	4	5.12	3.62			
4	203	A	96	3.36	4.04	1.41	1.20	2.30, 1.62, 0.97
		B	4	5.11	3.61	1.10	(1.38)	
5	213	A	99	3.34	3.95	1.43	0.99	3.73, 7.2–7.4
		B	1	5.16				
6	223	A	91	3.32	4.10	1.41	1.22	2.74, 1.11
		B	9	5.10	3.60	(1.1)	(1.4)	
7	223	A	100	3.57	4.17	1.44	1.27	
8	213	A	100	3.31	4.36	1.39	1.21	1.27

[a] δ-Value in ppm (±0.01 ppm) at 360 MHz, TMS as internal standard, concentration 20 mg ml^{-1} solvent, missing values indicate that the corresponding signals were not observed due to low intensity or overlap with other signals, values in parentheses have been obtained by double resonance experiments, (b): broad signal.
[b] Temperature in K, as read from the scale of the variable temperature unit; the temperature of the probe may vary by up to 3 K.
[c] See Scheme 1.
[d] Ratio of the conformers in per cent obtained by integration, reproducibility ±1%.
[e] Mixture of conformers, see text.

Table 3. ^{13}C chemical shifts of the *N,N*-diisopropylamides 1–8 in $CDCl_3$[a]

Compound	T(K)[b]	Conformer[c]	δ (CH-Z)	δ (CH-E)	δ (CH_3-Z)	δ (CH_3-E)	δ (C=O)	δ (R)
1	220	[e]	43.39	46.26 (b)	20.03	23.37 (b)	161.65	
2	213	A	45.27	50.04	20.33	20.49	169.67	24.53
		B	44.73	43.34		22.76		
3	213	A	45.32	48.31	20.51	20.51	172.46	28.08, 9.28
		B		43.22		22.95	174.63	29.22, 10.86
4	213	A	45.36	48.57	20.51	20.58	171.91	37.33, 18.43, 14.07
		B	44.52	43.30		23.15	173.68	38.14
5	213	A	45.58	49.55	20.16	20.16	169.95	43.36, 135.41, 128.56, 128.30, 126.41
6	213	A	45.47	48.21	20.58	20.80	175.87	31.35, 19.51
		B	44.34	43.11	20.03	23.02	178.25	33.42, 20.03
7[d]	223	A	47.15	49.17	19.34	20.32	155.25	116.23
				(3.7)			(34.2)	(288)
8	223	A	46.43	48.17	20.35	20.50	176.49	39.29, 28.13

[a] δ Values in ppm (±0.02 ppm) at 90.53 MHz, TMS as internal standard, concentration 100 mg ml^{-1} solvent, (b): broad signal.
[b] Temperature in K, as read from the scale of the variable temperature unit; the temperature of the probe may vary by 3–5 K.
[c] See Scheme 1.
[d] Values in parentheses: *J*(CF)
[e] Mixture of conformers; see text.

rules established by Anet and Basus[11] for two site equilibria with very unequal populations. In particular, the exchange broadening of the major signals allows an estimation of the chemical shifts of the corresponding minor signals. This is useful in cases where the signals of the minor conformer cannot be observed because of low intensity or overlap with intense signals. Thus, we can establish that the chemical shifts of the methyl groups of the *Z*-isopropyl group in **2**, **3** and **4** are very similar for the A and B conformers. Also, we conclude from the exchange broadenings observed in **5** (where at low temperature only the ^1H signal for the *Z*-methine H of B can be observed) that about 1% of conformer B is present in equilibrium with A. On the other hand, no measurable broadening is observed in the variable temperature spectra of **7** and **8** below 273 K, indicating that less than 0.3% of B (or another conformer) is present in equilibrium with A.

For the formamide derivative **1**, the conformational process cannot be slowed down sufficiently to observe two species in $CDCl_3$ solution. However, selective broadening of the *Z*-methine ^1H and the *E*-methine ^{13}C signals (these signals are expected to have the largest shift differences between A and B conformers) at 203 K indicates an equilibrium giving A and B in approximately equal amounts, as had been found for **1** at lower temperature.[7] The slow exchange limit is approached in a ^{13}C spectrum in acetone-d_6 at 160 K. Here, two sets of broadened signals are observed for the carbons of the *E*-isopropyl group at 50.7 and 43.5 ppm (CH) and 24.4 and 21.2 ppm (CH_3). The *Z*-isopropyl group gives rise to a broad signal at 43.5 ppm and a sharp signal at 20.1 ppm. Inspection of

Table 4. ^1H chemical shifts of the *N,N*-diisopropylthioamides 9–16 in $CDCl_3$[a]

Compound	T(K)[b]	Conformer[c]	Ratio[d]	δ (CH-Z)	δ (CH-E)	δ (CH_3-Z)	δ (CH_3-E)	δ (R)
9	203	B	>99	5.71	3.91	1.26	1.36	9.38
10	213	A	21	3.90	4.43	1.74	1.29	2.71
		B	78	6.18	4.05	1.24	1.48	2.83
		D	1	6.01	4.59			
11	213	A	24	3.88	4.38	1.74	1.32	2.90, 1.27
		B	74	6.20	4.04	1.23	1.48	2.92, 1.42
		D	2	5.98	4.53			
12	213	A	25	3.88	4.34	1.73	1.31	2.84, 1.67, 1.03
		B	73	6.19	4.03	1.23	1.47	2.84, 1.90, 1.03
		D	2	5.99	4.50			
13	208	A	71	3.83	4.28	1.77	0.98	4.37, 7.2–7.4
		B	25	6.28	4.17	1.31	1.55	4.34, 7.2–7.4
		D	4	6.04	4.43	1.48	(1.30)	4.47, 7.2–7.4
14	223	A	3	3.92	4.63	1.74		3.05
		B	97	6.26	4.05	1.23	1.49	3.35, 1.32
15	213	A	99	4.06	4.62	1.71	1.35	
		D	1	5.61				
16	213	A	99	3.91	4.88	1.74	1.32	1.43
		D	1	6.08	5.07			

[a–d] See footnotes of Table 2.

Table 5. ^{13}C chemical shifts of the *N,N*-diisopropylthioamides 9–16 in $CDCl_3$[a]

Compound	T (K)[b]	Conformer[c]	δ (CH-Z)	δ (CH-E)	δ (CH_3-Z)	δ (CH_3-E)	δ (C=S)	δ (R)
9	203	B	48.54	48.34	19.04	24.20	183.67	
10	213	A	50.50	55.42	18.65	19.54	196.43	36.64
		B	55.10	48.89	18.97	22.18	199.35	33.36
		D	54.27	53.77	21.13		197.15	
11	213	A	50.67	54.84	18.73	19.86	202.45	41.44, 13.81
		B	54.66	48.91	18.99	22.65	206.41	36.72, 16.11
		D	54.17	52.95	21.20	22.26	204.90	38.70, 14.47
12	213	A	50.70	55.00	18.77	19.94	201.40	50.38, 22.80, 14.23
		B	54.61	48.89	19.04	22.75	204.93	45.66, 25.40, 14.12
		D	54.14	53.09	21.25	22.28	203.54	47.53, 23.54
13	223	A	50.73	55.86	18.46	19.28	197.42	54.76, 136.07, 128.69, 127.21, 126.67
		B	54.87	49.11	19.17	23.03	201.94	48.58, 138.87, 128.48, 128.33, 126.33
		D	54.30	53.98	21.10	21.88		51.87
14	223	A	50.88	53.12	20.09	19.20		37.82, 23.22
		B	54.02	48.67	18.99	22.59	212.02	38.02, 23.79
15[d]	213	A	52.09	56.76	17.59	19.82	178.89	116.84
				(4.6)			(32.9)	(279)
		D			21.08	22.57		
16	213	A	52.18	54.64	19.05	19.92	209.23	44.36, 31.20
		D			21.73	22.80		32.01

[a–d] See footnotes of Table 3.

Table 3 shows that these values are in good accord with the shifts in the A and B conformers of the other amides, for instance **2**.

Conformational equilibria of the thioamides 9–16

The two compounds with 'small' R substituents, **9** and **14**, consist of A and B conformers only, but with B as the main conformer. While in **14** separate signals for A can be observed at low temperature, **9** shows only one set of sharp signals at 203 K for conformer B. At higher temperature, some of the signals of **9** show exchange broadening, indicating the presence of about 1–2% of A in equilibrium. The spectra of **10–13** show signals for A and B in comparable amounts. In addition, they show low intensity signals for a third conformer (these signals were not detected in previous investigations of **10**[2,7] and **13**[2]). In agreement with the assignments for *N,N*-diisopropyl-*S*-methyl dithiocarbamate[7] and the corresponding diseleno derivative,[8] we assign conformation D to these conformers.

An interesting result is obtained from the variable temperature spectra of **10–12**, which contain B as the major conformer: upon increasing the temperature, the signals of the major conformer B broaden, while the signals of A remain sharp. This broadening arises from exchange between B and D by rotation of the *E*-isopropyl group (see Scheme 1). This process, therefore, must have a lower barrier than that for the rotation of the *Z*-isopropyl group. This result corroborates that interconversion between A and B does not occur by synchronous rotation of both isopropyl groups, but is a stepwise process, as had already been stated for other compounds.[8]

Compounds **15** and **16** show signals for two species only. The predominant species is conformer A, while the chemical shifts of the minor species are compatible only with the presence of conformer D.

Additional line broadenings are observed in the ^{1}H spectra of **16** above 290 K due to *E–Z* isomerization. The methyl signals of the isopropyl groups coalesce at about 313 K, leading to a $\Delta G^{\ddagger}$ of 61.5 KJ mol^{-1}. For the amide **8**, coalescence of the methyl signals occurs at 335 K, resulting in a $\Delta G^{\ddagger}$ value of 67.5 KJ mol^{-1}. These values are significantly higher than those of corresponding *N,N*-dimethyl derivatives [54.3 (C=S) and 49.7 (C=O) KJ mol^{-1}].[12] In contrast to the usual behaviour, the barrier for the amide **8** is higher than that of the thioamide **16**. Very probably, the relatively high barriers result from a destabilization of the transition state by steric interactions of the bulky alkyl groups.

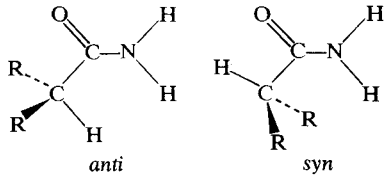
The ratios of the conformers of the compounds investigated are summarized in Table 6. If the substituents are ordered according to the A/B ratio, the following order of their 'effective size' is obtained:

$$H \approx C{=}O < CH(CH_3)_2 < CH_3 \approx C_2H_5 \approx n\text{-}C_3H_7 < C{=}S < \text{benzyl} < CF_3 \approx C(CH_3)_3$$

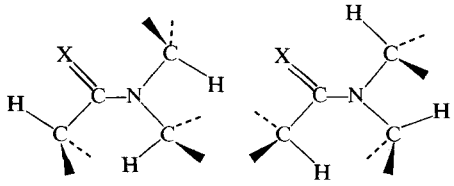
Table 6. Equilibrium ratios of conformers A, B and D in compounds 1–16

No.	R	R	% A	% B	% D
1	H	O	50±20	50±20	0
6	$(CH_3)_2CH$	O	91	9	0
2	CH_3	O	96	4	0
3	CH_3CH_2	O	96	4	0
4	$CH_3CH_2CH_2$	O	96	4	0
5	Ø-CH_2	O	99	1	0
7	CF_3	O	100	0	0
8	$(CH_3)_3C$	O	100	0	0
9	H	S	1	99	0
14	$(CH_3)_2CH$	S	3	97	0
10	CH_3	S	21	78	1
11	CH_3CH_2	S	24	74	2
12	$CH_3CH_2CH_2$	S	25	73	2
13	Ø-CH_2	S	71	25	4
15	CF_3	S	99	0	1
16	$(CH_3)_3C$	S	99	0	1

Obviously, not only the volume of a substituent is important for its effective size. Very probably, the conformational equilibrium with respect to the C—C=X bond in the different conformers also plays a role. Two conformers, (*anti* and *syn*), are discussed for



amides with R = H and R = CH_3. The *anti* conformers are observed in the solid state.[13,14] The *syn* conformers, however, have been found in *ab initio* and empirical force field calculations[13] for acetamides to be the most stable, and have been found to participate in the conformational equilibrium in solution for isobutyramide.[14] It is quite probable that **6** and **14** exist solely as A *syn* and B *anti* conformers, and that



the unusual behaviour of the isopropyl group is caused by the relative stability of these 'interlocking' conformers. The similar effective sizes of the methyl, ethyl and propyl groups indicate that these substituents can adopt conformations in which the interactions with the *E*-isopropyl groups and the C=X are nearly equal. This is obviously not the case for the benzyl group because of the sterically more demanding phenyl ring. While the concentrations of A and B show a monotonic behaviour with increasing size of R, this is not the case for the D conformers of the thioamides. Here the concentration reaches a maximum for R = benzyl.

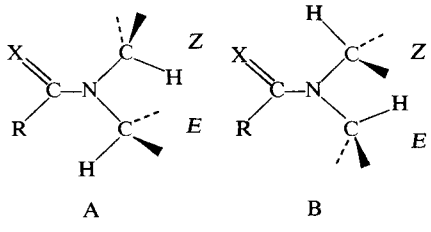
^{13}C Chemical shifts

The conformational assignments given in the previous paragraph can be made with the very characteristic ^{1}H chemical shifts alone.[7,8] In particular, the chemical shifts of the *Z*-isopropyl protons show a strong dependence on conformation because of the substantial through-space deshielding of protons spatially close to the C=X group.[12] This deshielding is larger for C=S than for C=O. The signals of the *E*-isopropyl protons are much less dependent on conformation, indicating that differences in through-space effects of the other groups are not pronounced. By connecting the ^{1}H and ^{13}C chemical shifts through the usual assignment procedures we arrive at a body of unambiguous ^{13}C chemical shifts, whose dependence on conformation can now be studied in terms of differences in through space effects on ^{13}C chemical shifts. The discussion is restricted to the chemical shifts of the *N*-isopropyl groups, and centres on the shifts of the methine carbons since they show the largest differences between conformers. The two representative compounds **2** and **10** are first discussed, followed by the effect of other substituents R on the chemical shifts.

With respect to the chemical shifts of the methine carbons, we will mainly concentrate on two questions. First, is there a significant through-space effect of the C=X group on the chemical shifts of the *Z*-methine carbons, does it depend on the conformation of the *Z*-isopropyl group and is it different for C=O and C=S compounds? Second, do any other significant through-space effects determine the chemical shifts of the methine carbons and what is their origin and spatial dependence?

The second question is treated first by studying the chemical shifts of the *E*-methine carbons, for which the through-space effect of the C=X should be much less pronounced than for the *Z* carbons. A large difference of 6.7 ppm for **2** and 6.5 ppm for **10** is noted between the chemical shifts of the *E*,A and *E*,B carbons (nomenclature: e.g. *E*,A: carbon of the type discussed in the *E* position in conformer A).

We interpret these differences as arising from differences in γ *gauche* effects[15] of the methyl groups of the *Z*-isopropyl group and γ *syn* effects[16] of the (thio)acetyl methyls: for *E*,B carbons, the γ *gauche* effect causes a substantial shielding, while it is small or absent for the *E*,A carbon. On the other hand, the γ



syn effect only operates on the *E*,A carbon, since for the *E*,B carbon the necessary H,H interaction is absent. From the chemical shift differences observed we conclude that the γ *gauche* effect on the *E*,B carbons is much stronger than the γ *syn* effect on the *E*,A carbons. The magnitude of the γ *gauche* effect can be estimated from the chemical shifts of the *N*-methyl carbons in the *N*-methyl-*N*-isopropyl derivatives **17** and **18** (see Fig. 1). These compounds exist as mixtures (approximately 1:1) of *E* and *Z* isomers in $CDCl_3$ solution. The conformation of the isopropyl groups is preferentially, if not exclusively, as shown in the formulae. This follows from ^{1}H[7] and ^{13}C chemical shifts (see Table 7) at variable temperatures. The *N*-methyl carbons in both isomers of **17** and **18** are shielded by more than 9 ppm with respect to the corresponding carbons in the *N*,*N*-dimethyl derivatives.[9,10] We consider this value to be an upper limit for the γ *gauche* effect in **2** and **10**, while the value of approximately 6.5 ppm should be a lower limit (negligible γ *syn* effect on the *E*,A carbons in **2** and **10**). A shielding effect of the same magnitude is also expected to be present for the *Z*,A carbons, since they have the analogous spatial relationship to the *E*,A methyl groups as the *E*,B carbons to the *Z*,B methyl groups.

The second question is therefore answered in the

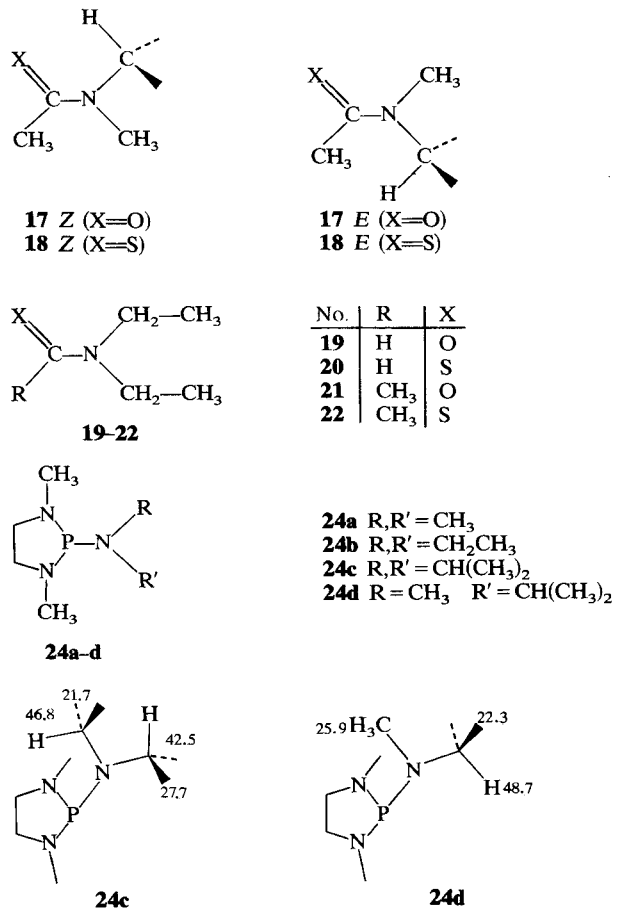


Figure 1. Structures of compounds **17–24** and ^{13}C chemical shifts in **24c** and **24d**.

affirmative: there is, indeed, a substantial through-space influence of the methyl groups of the isopropyl group on the chemical shifts of the methine carbons in a favourable spatial disposition. The first question can now be treated by considering the shift differences between *Z*,A and *Z*,B methine carbons. If a through-space (γ *anti*) effect of the (thio)acetyl methyl groups on these carbons is neglected, the differences consist of the—already mentioned—γ *gauche* effect on the *Z*,A carbons and the differences in the through-space effect of the C=X groups on the *Z*,A and *Z*,B carbons. In **2**, δ(*Z*,A) − δ(*Z*,B) is 0.5 ppm, indicating that the difference in the through-space effects of the C=O group on the *Z*,A and *Z*,B carbons is of the same magnitude as the γ *gauche* effect (6.5–9 ppm), with the *Z*,B carbon being more strongly shielded than the *Z*,A carbon. Quite obviously, a strong dependence of the through-space effect on the conformation of the *Z*-isopropyl group exists, at least for C=O. Shielding is only observed for the *Z*,B carbon, whose hydrogen points towards the oxygen atom. The spatial proximity of a hydrogen atom to the oxygen atom is, therefore, considered as a necessary condition for the existence of a substantial shielding effect, which we call a γ *syn* effect of the oxygen atom. For **10**, δ(*Z*,A) − δ(*Z*,B) is −4.6 ppm, 5 ppm smaller than in **2**. It is, therefore, concluded that the C=S group in **10** exerts a smaller shielding on the *Z*,B carbon by this amount.

From the rather small shift differences between *E*,B and *Z*,A carbons in **2** and **10** (less than −2 ppm), it is further concluded that the through-space effects of C=O and C=S on the *Z*,A carbons are small (possibly slightly deshielding) and similar in both compounds.

The results for **2** and **10** can now be summarized: substantial γ *gauche* effects exist of the appropriate isopropyl methyls on the *E*,B and *Z*,A carbons of about the same magnitude in **2** and **10**. The γ *syn* effect of the (thio)acetyl group on the *E*,A carbons is probably small and equal for **2** and **10**, as is the γ *syn* effect of the heteroatom X on the *Z*,A carbon. A large shielding effect is only observed for the *Z*,B carbon in **2**; in **10** this effect is smaller by 5 ppm.

A comparison of the chemical shifts of corresponding carbons in **10** and **2** confirm these results. The chemical shift differences for the *E*,B, the *E*,A and the *Z*,A carbons are about 5.5 ppm. This value is considered as arising from differences in through-bond effects of C=S vs C=O, which should only depend on the type and number of bonds between X and the carbon atom in question, and it is also taken as representative for the through-bond differences in other amide/thioamide pairs. The chemical shift difference for the *Z*,B carbons is 10.4 ppm, consisting of the through-bond and through-space contributions in approximately equal amounts.

Since the chemical shifts of the methine carbons in the amides **1**, **3–8** and in the thioamides **11–16** do not differ by more than 2 ppm from the corresponding shifts in **2** or **10**, they are not discussed further. The shifts for the thioformamide **9**, however, show a different behaviour. As seen in Table 5, the *Z*,B chemical shifts for **9** and **10** differ by more than 6.5 ppm, while the *E*,B shifts are very close. The chemical shifts of the

Table 7. ^{13}C Chemical shifts of compounds 17–22[a]

Compound	δ (Zα-C)[b]	δ (Eα-C)[b]	δ (Zβ-C)[c]	δ (Eβ-C)[c]	δ (C=X)	δ (CH_3)
17 *Z*	43.61	28.98	19.44	—	170.05	22.41
17 *E*	25.52	48.82	—	20.38	169.77	21.52
18 *Z*	52.29	32.50	18.74	—	198.88	33.48
18 *E*	34.55	53.06	—	20.09	198.09	31.98
19	36.66	41.85	12.80	14.91	162.23	—
20	42.33	50.77	11.21	14.43	186.84	—
21	40.04	42.94	13.12	14.22	169.64	21.37
22	47.99	46.69	11.21	13.17	198.10	32.13

[a] δ Values in ppm, internal standard TMS, solvent $CDCl_3$. **17** and **18** were measured at 90.53 MHz; data for **19–22** from Refs. 9 and 10.

[b] N—$CH<$ for **17** and **18**, N—CH_2— for **19–22**.

[c] N—$CH(CH_3)_2$ for **17** and **18**, N—CH_2—CH_3 for **19–22**.

A conformer of **9** cannot be directly observed; they can, however, be estimated from line broadenings in the region of intermediate exchange.[11] Thus, it is estimated that the *Z*,A and *Z*,B methine carbons have a shift difference of less than ±1 ppm, while for the *E*,A and *E*,B carbons a difference of +10 (±2) ppm is estimated. Evidently, the through-space shielding of the *Z*,B carbon by the C=S group is larger by about 5 ppm in **9** than in **10**. The thioformyl compound, therefore, shows an effect similar to that found in amides and differs strongly from the other thioamides. Possibly, bond angles in the thioamide skeleton (S=C—N and C—N—C angles) are somewhat larger in **9** than in **10** because of steric interaction of the CH_3 with the *E*-isopropyl group in **10**. (Differences of about 1–3° have been found for the pair *N*-methylformamide/*N*-methylacetamide.[13]) Since differences in angles and the ensuing difference in distance between the sulphur atom and the methine hydrogen cannot be very large, the through-space effect of the C=S must depend very strongly on geometrical factors if we adopt this explanation.

As expected, the chemical shifts of the methyl carbons β to nitrogen show less dependence on conformation. The largest shift differences (about 2 ppm) are again observed for the *E* carbons. The main contribution to these differences is the γ *gauche* shielding of the *E*,A methyl carbons by the *Z*,A methine. An analogous shielding is expected for the *Z*,B methyl carbons. The small differences between *Z*,A and *Z*,B shifts are accounted for by assuming a through-space shielding of the *Z*,A methyls by the C=X, which is slightly larger for the C=S than for the C=O group. Since, in general, the chemical shifts in the thioamides are smaller by 0.5–1 ppm, we assume that a difference in through-bond effects of this magnitude exists between thioamides and corresponding amides.

No shielding γ *gauche* effect is expected to influence the chemical shifts of the methine carbons in the D conformers of the thioamides **10–13** and **15–16**. Indeed, the *Z*,D methine shifts in **10–13** (the signals for the methine carbons could not be localized with certainty in **15** and **16**) are very close to the *Z*,B shifts, and also the *E*,D shifts are closer to the *E*,A than to the *E*,B chemical shifts. From the small shift difference between *Z*,D and *E*,D methine carbons we can conclude that the through-space effect of the C=S on the *Z*,D shift is similar to the through-space effect of the R group on the *E*,D shift. The chemical shifts for the methyl carbons in the isopropyl group are intermediate between the shifts of the A and B conformers, indicating the absence of shielding by either γ *gauche* effects of the methine carbons or through-space effects of the C=S groups.

Applications

The *N*-isopropyl groups have proven to be good probes to study through-space effects on ^{13}C chemical shifts because of their well defined conformations. The existence of *gauche* shieldings on methine (or *N*-methyl) carbons by the methyl groups of a geminal isopropyl group should not be confined to the compounds studied here and can be used to explain apparent anomalies in chemical shifts in other compounds. An example from the recent literature may serve to illustrate this point.[17]

In 2-diethylamino-1,3-dimethyl-1,3,2-diazaphospholane (**24b**) (see Fig. 1) the CH_2 carbon of the *E*-ethyl group is deshielded by 2.6 ppm with respect to the *Z* carbon, while in the diisopropyl derivative **24c** the *E*-methine carbon is shielded by 4.3 ppm. This is in full agreement with the conformation of the isopropyl groups shown in Fig. 1, which has been also adopted by the authors in Ref. 17 for other reasons. In the *E* isomer of the *N*-methyl-*N*-isopropyl compound **24d** the methine carbon is deshielded by 6.2 ppm with respect to the corresponding carbon in **24c**, which is, in our opinion, only explainable by a change in the preferred conformation of the *E*-isopropyl group, as depicted in Fig. 1. This conclusion is supported by the significant shielding of 11.5 ppm of the *N*-methyl carbon with respect to the *Z*-methyl carbon in **24a**, by the significant upfield (low frequency) shift of the *E*-isopropyl methyl carbons on going from **24c** to **24d** (the methyl carbons in **24c** are strongly deshielded, presumably by a through-space effect of the lone pair on phosphorus), and by the change in the two bond coupling of the *E*-methine carbon with phosphorus.[17]

The finding that the through-space shielding of the *Z*-methine carbons by C=O or C=S is dependent on the methine hydrogen orientation has, to our knowledge, no precedent and is difficult to explain by existing mechanisms of through-space shielding. We suggest that through-space interactions of the lone pair orbitals on oxygen or sulphur with C—H bond orbitals contribute to this shielding. Further work is in progress to study this effect in other systems. The results can be applied to understand better the chemical shifts in *N*,*N*-dialkyl(thio)amides, for which the four *N*,*N*-diethyl compounds **19–22** (see Fig. 1 and Table 7) serve as examples. For these compounds the chemical shifts of the N—CH_2 carbon atoms showed trends which were difficult to explain, as becomes apparent by analysing the chemical shift data in terms of three types of shift differences: first, differences between *Z* and *E* chemical shifts for the individual compounds; second, shift differences between (thio)acetyl and the corresponding (thio)formyl compounds. These differences formally correspond to methyl substituent effects on γ situated carbons; and, third, shift differences between thioamides and corresponding amides.

For the thioformyl compound **20** the difference between the *Z*- and *E*-CH_2 shifts is −8.4 ppm, while for **22** it is +1.3 ppm. This large change results from a deshielding of the *Z*-CH_2 by 5.7 ppm and a shielding of the *E*-CH_2 by −4.1 ppm on going from **20** to **22**. The deshielding of the *Z* carbon is analogous to the deshielding of the *Z*,B methine carbon in the pair **10/9** and is also caused by a diminished through-space shielding of the thioacetyl vs the thioformyl group (the condition for efficient through-space shielding, spatial proximity of a hydrogen atom of the CH_2 to C=X, is fulfilled for these compounds[18]). The shielding of the *E* carbon is caused by the expected γ *syn* effect of the thioacetyl methyl group (no shielding was observed for

the *E*,B carbons of the pair **10/9**, because of the unfavourable geometry for a γ *syn* effect).

For amides **19** and **21** the differences between the *Z* and *E* carbon shifts are both negative (−5.2 and −2.9 ppm, respectively), signifying a shielding effect of the C=O group in **21**, which is larger than the γ effect of the acetyl methyl group. However, the differences between **21** and **19** appear anomalous; for the *Z* and for the *E* carbons deshielding effects of 3.4 and 1.1 ppm, respectively, are observed.

The value for the *Z* carbons indicates that—in analogy to thioamides—the shielding by the formyl group is stronger than by the acetyl group. To explain the positive value for the *E* carbon in **19**, we assume that this carbon is shielded by a 'γ *anti* effect' of the oxygen atom[23] in **19**, a shielding which is not present in the thioformyl compound **20** and in the acetamide **21**. The magnitude of this shielding effect is such that it compensates for the γ *syn* effect of the acetyl methyl in **21**. The assumption of a γ *anti* effect also helps to explain the differences for the *E* carbons in the pair **20/19**, which is 8.9 ppm and considerably larger than the difference for the *Z* carbons (5.7 ppm) in this pair. The differences in the pair **22/21** are 8 ppm for the *Z* carbons and 3.8 ppm for the *E* carbons. To account for these differences, we assume that approximately 5.5 ppm arise from the difference in through bond contributions to the chemical shift, as was deduced for the diisopropyl compounds **10** and **2**. The value for the *Z* carbons in the pair **20/19** can be fully accounted for by the through-bond contributions, while the value for the *E* carbons arises from the additional differences in γ *anti* effects in **19** and **20**. For the pair **22/21**, the difference for the *Z* carbons is accounted for by the better through-space shielding of these carbons by C=O vs C=S, while the smaller value for the *E* carbons might reflect a stronger γ *syn* effect of the thioacetyl methyl group as compared with the acetyl methyl group.

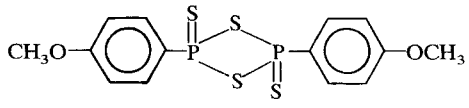
EXPERIMENTAL

^{1}H NMR spectra were run at 360 MHz and ^{13}C spectra at 90.5 MHz, both in the Fourier transform mode, on a Bruker HX-360 NMR spectrometer. 32 K data points were used for the accumulations of the free induction decays, resulting in a digital resolution of 0.22 Hz for ^{1}H and 1.3 Hz for ^{13}C spectra.

Elementary analyses were carried out by NOVO Microanalytical Laboratory, NOVO Industry A/S, DK-2880 Bagsvaerd, Denmark, supervised by Dr Rolf E. Amsler, and were in all cases in accordance with the calculated figures.

Compounds **1–4**[5] and **17**[7] were used as received. Compounds **5**,[20] **6**[21] and **7**[22] are known, and were prepared by standard methods from diisopropylamine and the appropriate acid chloride (**7** from the corresponding anhydride). **8**: m.p. 49–51 °C.

The thioamides **9–16** and **18** were quantitatively formed from the amides by means of 2,4-bis(4-methoxyphenyl)-1,3,4,2-dithiadiphosphetane-2,4-disulphide (**25**).[10,19] *N,N*-diisopropylpivaloylthioamide (**16**) needed a reaction temperature of 140 °C (xylene as solvent) and a reaction time of 24 h. The thioamides



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9,[7] **10**,[20] **13**[20] and **14**[2] are known. **11**: b.p. 73 °C/0.05 Torr, **12**: b.p. 76–78 °C/0.05 Torr, **15**: m.p. 63 °C, **16**: m.p. 63 °C, **18**; b.p. 120 °C/12 Torr.

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