¹⁵N and ¹³C NMR Study of Acylated Hydrazines. The Instability of Trifluoroacethydrazide in the Solid State*

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Trifluoroacethydrazide is unstable even in the solid state with respect to hydrazonium N,N'-ditrifluoroacetyl hydrazinate, as shown by ¹⁵N and ¹³C NMR spectroscopy. The ¹H, ¹³C and ¹⁵N NMR data and rotamer distributions of formyl-, acet- and trifluoroacet-hydrazide and of N,N'-diformyl-, N,N'-diacetyl- and N,N'-ditrifluoroacetyl-hydrazine are reported and compared with the results of earlier investigations. A conformational dependence is observed for ¹J(NH) and ²J(NH) in the formylhydrazides and of ¹J(NH), ²J(NH) and ³J(NH) in the N,N'-diformylhydrazines. The conformational dependence of ²J(CH) in formamide, reported in the literature, however, could not be confirmed.

KEY WORDS ¹⁵N NMR Hydrazides ¹⁵N-¹H coupling constants ¹³C-¹H coupling constants Rotamer distribution

INTRODUCTION

Trifluoroacethydrazide (1) reacts with phosgene to give 5-trifluoromethyl-1,3,4-oxadiazolone (3) (Scheme 1), which is a useful starting material for heterocyclic synthesis by means of ring transformation.^{1,2} Compound 1 can be prepared by analogy with known methods³⁻⁶ from ethyl trifluoroacetate and hydrazine hydrate and purified by distillation (b.p. 76 °C/12 Torr). During the distillation the distillate solidified to a low-melting crystalline solid (m.p. 39–40 °C). On standing at room temperature for several days, however, the low-melting hydrazide 1 was transformed into a rock-hard solid 2 of

* Dedicated to Professor W. von Philipsborn on the occasion of his 60th birthday.

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identical elemental composition, m.p. 132–134 °C, which gave no 3 on reaction with phosgene. Heating this compound above its melting point, however, or even better redistillation, with almost no loss of material, yielded again pure 1. Compound 2 is the hydrazonium salt of N,N'-ditrifluoroacetylhydrazine (4), as shown below by ¹⁵N and ¹³C NMR spectroscopy. This paper describes the structural analysis of 1 and 2 and an NMR investigation of the acylated hydrazines 4–8 (Scheme 2) studied in this context and in continuation of our work on the ¹³C NMR spectra of amides.⁷

RESULTS AND DISCUSSION

Scheme 2 shows the investigated compounds together with the numbering system used in Tables 1 and 2. The well investigated amides 9-11 were measured as reference compounds. Table 1 lists the ¹H, ¹³C and ¹⁵N



Scheme 1

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Scheme 2. Compounds investigated. Numbering system as used in Tables 1 and 2. For clarity, only the observed rotamers of 5 and 7 are drawn individually.

NMR chemical shifts, the rotamer distributions of the rotamerically non-uniform compounds and references to earlier investigations. Table 2 contains the coupling constants measured. In the case of the amides 9–11 the data are generally restricted to coupling constant values not previously reported.

Trifluoroacetylated hydrazines 1, 2 and 4

As already stated, trifluoroacethydrazide (1) is unstable even in the solid state and has to be freshly prepared for measurement. The ¹⁵N NMR chemical shifts compare well with those of formylhydrazide (5) and acethydrazide (6), proving the presence of an amide and an amine N atom. In the ¹³C NMR spectrum, the carbonyl chemical shift is well outside the range given by the corresponding data of 4 and 2. Neither the rotamer distribution nor the J(NH) value could be measured owing to fast exchange. An ¹⁹F chemical shift has been reported⁸ for 1. The stable N,N'ditrifluoroacetylhydrazine (4) shows only one ¹⁵N NMR signal at 124.2 ppm, indicating rapid rotameric exchange. Similarly, the N,H exchange is fast on the NMR time scale. Kalikhman and co-workers^{8–10} reported 100% Z,Z rotamer population in DMSO and CDCl₃ (¹H, ¹⁹F and ¹³C NMR).

Compound 2 possesses a narrow ¹⁵N NMR signal at 48.6 ppm and a broad ($\Delta v_{1/2} \approx 30$ Hz), difficult to observe peak at 174.9 ppm in DMSO- d_6 solution. It is the hydrazonium salt of 4 on the basis of the following arguments. Admixture of hydrazonium sulphate (48.3 ppm in DMSO- d_6) to a solution of 2 does not result in the appearance of a new peak in the ¹⁵N NMR spectrum. The broad peak at 174.9 ppm results from averaging the chemical shifts of the two different nitrogen atoms in the anion (see formula A) by proton exchange, which is not fast enough, however, to lead to

| Table 1. ¹ H, ¹³ C | C and ¹⁵ N cher | nical shifts | in DMS | 0-d ₆ | | | | | | | | | | |
|--|----------------------------|----------------|--------------|------------------|--------------|------------------|----------------------------------|----------------|--------------|--------|------|-------|------|--------------------------------------|
| Compound Hydrazides | Percentage of rotamer | ۍ ۲ | н. | C-2 | H-2 | N-3 | н-3 | N-4 | H-4 | C-5 | н.5 | C-6 | 9-H | Previous investigations (Ref.) |
| (Z)-5 (F)-5 | 80 | | | 160.06 166.92 | 7.99 8.01 | 135.48 132.27 | 9.03 8.66 | 50.66 53.98 | 4.25 4.41 | | | | | 13 |
| (Z) - 6 (E) - 6 | 97 97 97 | 20.56 19.47 | 1.73 1.90 | 169.20 174.92 | | 131.48 129.34 | 8.93 8.12 | 53.78 59.58 | 4.13 4.38 | | | | | 13, 31 |
| - | | 117.3 | | 157.1 | | 136.4 | | 56.7 | | | | | | |
| N,N'-Diacylhydrazines | | | | | | | | | | | | | | |
| (Z'Z)-1 | 65 | | | 159.20 | 8.00 | 129.31 | 10.02 | 129.31 | 10.02 | 159.20 | 8.00 | | | 9, 10, 13 |
| (Z,E)-7 | 31 | | | 161.72 | 8.13 | 130.55 | 10.02 | 128.12 | 9.41 | 166.98 | 7.90 | | | |
| (E,E)-7 | 4 | | | 167.19 | 8.11 | 132.34 | 9.77 | 132.34 | 9.77 | 167.19 | 8.11 | | | |
| 8 -(Z'Z) | 87 | 20.48 | 1.83 | 168.22 | | 128.74 | 9.66 | 128.74 | 9.66 | 168.22 | | 20.48 | 1.83 | 9, 10, 16, 17 |
| (Z,E)- 8 | 13 | 20.48 | 1.85 | 169.28 | | 132.77 | 9.66 | 129.08 | 8.85 | 174.29 | | 19.16 | 1.75 | |
| (E,E)- 8 | ~ 0.5 | 19.61 | 1.86 | 174.14 | | 134.83 | 9.25 | 134.83 | 9.25 | 174.14 | | 19.61 | 1.86 | |
| 4 | | 115.5 | | 155.3 | | 124.2 | | 124.2 | | 155.3 | | 115.5 | | 8, 9, 10 |
| 2 | | 117.7 | | 153.5 | | 174.9 | | 174.9 | | 153.5 | | 117.7 | | |
| | | | | | | 48.6 | | 48.6 | | | | | | |
| Amides | | ç. | н-1 | C-2 | Н-2 | N-3 | н-3 | C-4 | H.4 | | | | | |
| 6 | | | | 163.61 | 7.97 | 112.06 | 7.19/7.45 | | | | | | | e.g. 14, 18, 19, 23, 30 |
| (Z)-10 | 93 7 | | | 161.98 165 42 | 8.00 | 108.36 | (11 syn/11 anti) 7.85 7 AA | 24.15 27.40 | 2.58 | | | | | 14, 18, 2226 |
| (Z)-11 | ∿98.5 | 22.39 | 1.77 | 170.00 | 60.1 | 104.17 | 7.79 | 25.51 | 2.53 | | | | | 18, 23, 24, 27–29 |
| (E)-11 | ~ 1.5 | 20.05 | 1.83 | 172.55 | | 102.41 | 7.01 | 29.07 | 2.67 | | | | | |

¹⁵N AND ¹³C NMR STUDY OF ACYLATED HYDRAZINES

| Compound Hydrazides | C-2,H-2 | C-2,H-3 | N-3,H-2 | N-3,H-3 | | | Comments |
|--------------------------|--------------|------------------------|-------------------------|---------------|----------------|----------------|---------------------------------------|
| (Z)-5 (E)-5 | 191.0 190 | 9.3 5.3 | 18.3 12.0 | 101.6 96.2 | | | J(HH) cf. lit. ¹³ |
| () - | C-1,C-2 | C-1,N-3 | C-2,N-3 | N-3,H-3 | | | |
| (Z)- 6 | 51.0 | 10.1 | 12.3 | 101 | | | Data for (E)-6 n.d. |
| | C-1.F | C-2.F | | | | | |
| 1 | 287 | 36 | | | | | Rapid NH exchange J(NH) n.d. |
| N,N'-Diacylhydrazides | C-2,H-2 | C-2,H-3 | C-5,H-4 | C-5,H-5 | | | |
| $(7.7)_{-7}$ | 196 | q | q | 196 | | | |
| (Z, E) - 7 | 197 | 10 | 35 | 195 | | | |
| (E,E)-7 | 197 | 5 | 5 | 197 | | | |
| . , | | N-3.H | | | N | -4,H | |
| (<i>7 7</i>)- 7 | 101.6 (H-3) | 22.0 (H-2) · 4.0 | (H-5) · 2 5 (H-4 | 4) | Values ident | tical to N-3 H | |
| (Z.E)-7 | 102.2 (F | -3): 22.0 (H-2 | (): 2.2 (H-4) | ., 99 (H-4 | 4): 12.5 (H-5) | : 3.5 (H-3): 3 | .5 (H-2) |
| (E,E)- 7 | 98 (H- | 3); 12.5 (H-2); | ; 2.5 (H-4) | (| Values ident | tical to N-3,H | |
| | C-1,N-3 | C-2,N-3 | N-3,H-3 | N-3,H-4 | N-4,H-3 | N-4,H-4 | |
| (7.7)-8 | 11.2 | 12.2 | 100.9 | 28 | 28 | 100.9 | Data for (<i>E.E</i>)- 8 n d |
| (Z,E)- 8 | n.d. | n.d. | 101.5 | ~1.5 | 3.9 | 98.7 | J(NH), J(NC), cf. lit. ¹⁷ |
| | C-1,F | C-2,F | | | | | |
| 4 | 287 | 37 | | | | | cf. lit. ¹⁰ |
| 2 | 285.5 | 34 | | | | | |
| Amides | C-2,H-2 | C-2,H-3 _{syn} | C-2,H-3 _{anti} | C-2,N-3 | | | |
| 9 | 186.4 | 2.8 | 2.8 | 13.5 | | | J(HH), J(NH), cf. lit. ¹⁴ |
| | C-2,H-2 | C-2,H-3 | C-2,H-4 | C-4,H-2 | C-4,H-3 | C-4,H-4 | |
| (Z)-10 | 190 | 3.8 | 3.8 | 5 | 2.8 | 137.5 | J(HH), J(NH), cf. lit. ¹⁴ |
| (E)-10 | 186.5 | ~ 0 | 5 | 2.0 | 2.8 | 137.5 | (Z)-10: all J, cf. lit. ²⁶ |
| | C-1,C-2 | C-1,N-3 | C-1,H-3 | C-2,N-3 | C-4,N-3 | | |
| (Z)-11 | 50.7 | 9.8 | 0 | 14.4 | 11 | | (Z)-11: J(CH), cf. lit. ¹⁸ |
| (E)-11 | n d | nd | 5 | nd | n d | | 1 ((NH)) of 10+ 29 |

Table 2. Coupling constants in DMSO- d_6

a narrow average signal. The NH chemical shift in the slow exchange limit is estimated to be about 135 ppm (from the chemical shift of 4 after correcting for the replacement of NH—C by N=C). This results in a chemical shift of about 215 ppm for the deprotonated N atom, indicating that the negative charge largely resides at the oxygen atom, as depicted in A.



In a mixture of 37 mol-% 2 and 63 mol-% 4, two narrow peaks appear at 48.4 ppm (for the hydrazonium cation) and 141.4 ppm, the latter representing the average chemical shift for the nitrogen atoms in 4 and its anion and indicating rapid exchange between these species (the average chemical shift calculated from the shifts of 2 and 4 is 142.7 ppm).

On addition of one equivalent of CF₃COOH to a sol-

ution of 2, narrow peaks are observed at 48.2 and 124.2 ppm, corresponding to a mixture of hydrazonium trifluoroacetate and 4. Addition of CH₃COOH to solutions of 2 does not lead to protonation of the anion, but to an increase of the exchange rate, as evidenced by an appreciable sharpening of the signal at 174.9 ppm. Hence the acid strength of 4 must be intermediate between those of CH₃COOH and CF₃COOH. Indeed, in aqueous solution a pK_a of 3.8 was determined for 4. Addition of one equivalent of NaOH to an aqueous solution of 4 leads to a slightly broadened ¹⁵N NMR signal at 177 ppm, again indicating formation of the anion and rapid proton exchange.

Similarly, a mixture of 2 and 4 shows only the averaged spectrum of one species in the ¹³C NMR spectrum. Finally, the reduction of the ²J(CF) in 2 vs. 4 (34 vs. 37 Hz) is also indicative of salt formation in the presence of a strong base.¹¹

Mass spectral studies proved the presence of N,N'ditrifluoroacetylhydrazine in 2 by a weak molecular ion at m/z 224 in the electron impact mode and strong signals at m/z 223 (M – H), 447 (223 + 4) and 469 (223 + Na salt of 4) in the negative-ion fast atom bombardment mode.

The transformation of 1 to 2 implies a disproportionation of 1 into 4 and hydrazine, followed by salt formation to 2. Acethydrazide disproportionates in acetic acid solution to N,N'-diacetylhydrazine by a reaction of second-order in acethydrazide.¹² In our hands, addition of CF₃COOH to a solution of formylhydrazide (5) or acethydrazide (6) in DMSO- d_6 results in the formation of the corresponding N,N'-diacylhydrazine, as shown by the appearance of the ¹⁵N NMR signals of 7 and 8, respectively, and proved by the admixture of authentic 7 or 8, respectively. The instability of 1 at room temperature explains the different melting points reported³⁻⁵ for 1 and also some of the negative results obtained by using it as a reagent. Indeed, there are only a few reports on 1 as a reagent, which is not surprising in view of its transformation to 2 under normal conditions.

Hydrazides 5 and 6

Formylhydrazide (5) is a mixture of 80% Z and 20% E rotamers in DMSO- d_6 , in agreement with the ¹H NMR study by Bouchet et al.¹³ In our hands, the exchange of the NH₂ protons was always fast on the NMR time scale. In contrast, the exchange of the amide protons was slow in dry DMSO- d_6 , but faster for the Z than for the *E* rotamer. The ${}^{1}J(NH)$ and ${}^{2}J(NH)$ values show the well known conformational dependence¹⁴ for formamides: ${}^{1}J = 101.6 (Z)$ and 96.2 (E) Hz, ${}^{2}J = 18.3 (Z)$ and 12.0 (E) Hz. The difference in the ^{2}J values is much larger than, for example, in N-methylformamide (10) $[^{2}J = -15.7 (Z) \text{ and } -13.6 (E) \text{ Hz}]^{.14}$ The ¹⁵N chemical shift of the NH_2 group shows a γ -effect of 3.3 ppm caused by the carbonyl oxygen atom, similar to that of the N-methyl carbons in the N-methylformamide (10) (3.33 ppm).

Acethydrazide (6) is also a mixture (97% Z, 3% E), as already reported by Bouchet et al.13 The signals of the E rotamer could be identified unequivocally in the 1 H, ¹³C and ¹⁵N NMR spectra, similarly to the spectra of N-methylacetamide (11), where 1.5% of the E rotamer was detected (see the section Amides 9-11 below). ${}^{1}J(NH)$ could only be measured for the Z rotamer. Its value, 101 Hz, is similar to that of (Z)-5. The ${}^{2}J(NC)$ coupling constant was measured from satellite signals in the ¹³C and ¹⁵N NMR spectra: ${}^{2}J(NC) = 10.1$ Hz, which is slightly larger than the analogous coupling constant in 11, 9.8 Hz. The isotope effect on the chemical shifts in ¹³CH₃CO¹⁵NHNH₂ is very small, as opposed to the isotopomer $CH_3^{13}CO^{15}NHNH_2$, where $^{1}J(CN) = 12.3$ and the isotope effect is -2 Hz for both nuclei. The chemcal shift difference between the NH₂ N atoms in the two rotamers is 5.8 ppm, which is larger than the difference for the N-methyl C atoms in the Nmethylacetamides (11) (3.6 ppm). This difference represents the unequal y-effects caused by the carbonyl O atom and by the methyl group.

N,N'-Diacylhydrazines 7 and 8

Diformylhydrazine (7) consists of 65% Z,Z, 31% Z,E and 4% E,E rotamers, in agreement with the results of

Bouchet et al.¹³ and in disagreement with all of those of Kalikhman and co-workers.^{9,10} The NH exchange is slow in dry DMSO- d_6 , allowing the measurement of all J(NH) values in the ¹⁵N NMR spectrum. In the Z,Erotamer the coupling constants can be measured directly, since the proton spectrum is first order. Further, ${}^{3}J(H-3,H-4)$ (as observed from the ${}^{15}N$ satellites of the H-4 signal) and ${}^{5}J(H-2,H-5)$ (as seen from the ¹³C satellites of the formyl protons of all rotamers) are ca. 0 Hz, owing to the orthogonal arrangement¹⁵ of the two amide moieties. The observed J(NH) values of (Z,E)-7 are listed in Table 2. The conformational dependence of ${}^{2}J(NH)$ (Z 22 Hz, E 12.5 Hz) is even stronger than that observed in 5. Further, only the trans N atom couples with the formyl proton three bonds away $[{}^{3}J(N-4,H-2) = 3.5 \text{ Hz } vs. {}^{3}J(N-3,H-5) \approx 0 \text{ Hz}]$, similar to the analogous ${}^{3}J(HH)$ value $[{}^{3}J(H-4,H-5) = 10.5$ Hz vs. ${}^{3}J(H-2,H-3) \approx 0$ Hz; see also Refs. 13 and 14]. The J(NH) coupling patterns discussed for (Z,E)-7 are repeated in the symmetrical rotamers, (Z,Z)-7 and (E,E)-7. The ¹³C NMR spectrum of (Z,E)-7 has been assigned by selective proton decoupling, thereby ascertaining the assignments of the long-range couplings given in Table 2. Again, both ${}^{3}J(C-2,H-4)$ and ${}^{3}J(C-5,H-3)$ are ca. 0 Hz owing to the orthogonal arrangement of the two amide moieties. The situation is similar in the two symmetrical rotamers, since their proton-coupled ¹³C NMR spectra show no AA'X character. The Z/E ratio Z, Z/(Z, E/2) $\approx (Z, E/2)/(E, E) \approx 4$ is very similar to that of 5, indicating little interaction between the amide moieties due to the orthogonal arrangement¹⁵ (we are indebted to a referee for a pertinent comment.)

N,*N'*-Diacetylhydrazine (8), in turn, consists of 87% *Z*,*Z*, 13% *Z*,*E* and *ca*. 0.5% *E*,*E* rotamers. Kalikhman and co-workers^{9,10} reported 95% *Z*,*Z* and 5% *E*,*E* in CDCl₃ (¹H NMR) and 100% *Z*,*Z* in DMSO- d_6 (¹³C NMR). Kapkan *et al.*,¹⁶ in agreement with our data, found 86% *Z*,*Z* and 14% *Z*,*E*. The data for (*Z*,*Z*)-8 isotopically enriched with ¹⁵N have been collected by Khasapov *et al.*¹⁷ Their data for ¹*J*(CN) and ²*J*(CN) are identical with ours measured at natural abundance. ²*J*(CN) is again fairly large, larger than in (*Z*)-6 or (*Z*)-11. The *Z*/*E* ratio is lower than in 6, demonstrating a slight interaction between the amide moieties in the case of the larger acyl substituent.

Amides 9-11

The NMR parameters of the amides 9–11 have been intensively studied.^{18–30} The ¹H and ¹⁵N NMR parameters of formamide (9) were given by Sørensen *et al.*¹⁴ and our measurements do not differ significantly from theirs. Dorman and Bovey¹⁸ and Barboiu and Petrescu,¹⁹ however, reported a conformational dependence of the two ²J(CH) couplings (2.4 and *ca.* 5.5 Hz,¹⁸ and +2.9 and -5.2 Hz,¹⁹ respectively, also cited in Hansen's review²⁰), which we were unable to reproduce. We found ²J = 2.8 Hz for both protons in a solution of 400 mg of 9 in 3 ml of dry DMSO-*d*₆ and in neat 9 containing traces of acetone-*d*₆. Our result is in good agreement with ²J(CNH) in acetamide (both ²J = 2.5 Hz).²¹ The ¹³C and ¹⁵N chemical shifts^{18,22-25} and

¹J(NH) values^{14,22} of *N*-methylformamide have been reported. The ¹H and ¹⁵N parameters were given by Sørensen *et al.*,¹⁴ and all *J* values of (*Z*)-10 were listed by Khetrapal and Kunwar.²⁶ Since Dorman and Bovey¹⁸ listed only the *J*(CH) values of (*Z*)-10, we present here the *J*(CH) values of (*E*)-10 together with those of (*Z*)-10. ³*J*(C-4,H-2) is smaller in (*E*)-10 than in (*Z*)-10, but larger than expected from a comparison with the analogous ³*J*(HH) values (12.9 and 1.8 Hz).¹⁴

For N-methylacetamide (11), the ¹³C, ¹⁵N, ¹J(NH) and J(CH) data of the Z rotamer have already been reported.^{18,23,24,27-29} Therefore, we report here only the ¹J(CC) and J(NC) values of (Z)-11 and all the available data for (E)-11, observed here for the first time.

EXPERIMENTAL

The NMR spectra were measured on a Bruker WM 400 NMR spectrometer in the Fourier transform mode at 298 K in dry DMSO- d_6 . The ¹H and ¹³C NMR spectra were recorded in 5 mm o.d. tubes at concentrations of 50–100 mg ml⁻¹ and referenced to the solvent peak (¹H, 2.50 ppm; ¹³C, 39.5 ppm). The ¹⁵N NMR spectra were recorded in 10 mm o.d. tubes at concentrations of 100–200 mg ml⁻¹, referenced to external CH₃NO₂ and

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converted to the liquid anhydrous ammonia scale. The flip angles employed were 50° (¹H), 70° (¹³C) and 90° (¹⁵N). The acquisition time was chosen such that the accuracy of the chemical shifts was ± 0.01 ppm (¹⁵N, 0.02 ppm) and that of the coupling constants was ± 0.2 Hz.

Preparation of 1

To 71 g (0.5 mol) of ethyl trifluoroacetate in 200 ml of absolute ethanol, 23.8 g (0.475 mol) of hydrazine hydrate were added with stirring. The temperature rose to about 50 °C and the colourless solution was stirred for an additional 2 h. After evaporation, the resulting oil was distilled (b.p. 76 °C/12 Torr) to give 56 g (92%) trifluoroacethydrazide (1). The distillate crystallized on seeding in form of needles, m.p. 39–40 °C. Analysis: calculated for $C_2H_3F_3N_2O$, C 18.76, H 2.36, N 21.88, F 44.51; found, C 18.4, H 2.4, N 21.5, F 44.1%.

On standing for several days, 1 was transformed into 2, which can be recrystallized from isobutanol, m.p. 132-134 °C. Analysis: found, C 18.5, H 2.3, N 21.8, F 44.0%.

The remaining compounds are commercially available (5, 7, 9–11) or are known compounds $(1, {}^{3-6}, 4, {}^{6}, 6, {}^{32}, 8^{33})$.

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