MAGNETIC RESONANCE IN CHEMISTRY, VOL. 35, 571–576 (1997)

Synthesis of Propiolamide and ^{1}H, ^{13}C and ^{15}N NMR Spectra of Formamide, Acetamide and Propiolamide

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A high-yield synthesis and purification of propiolamide is described. The structure and purity of the compound were confirmed by ^{1}H, ^{13}C and ^{15}N NMR studies. Natural abundance ^{13}C and ^{15}N chemical shift measurements in 3.0 M acetonitrile solutions are reported along with ^{1}H–^{1}H, ^{1}H–^{15}N and ^{1}H–^{13}C spin coupling constants. Polarization transfer techniques were used for the ^{15}N and ^{13}C measurements. The propiolamide NMR parameters were compared with those for 3.0 M solutions of formamide and acetamide in acetonitrile solution. Measurements at 298 and 278 K indicated that for all three compounds there is still significant rotation about the carbon–nitrogen bond at room temperature. © **1997 by John Wiley & Sons, Ltd.**

Magn. Reson. Chem. **35**, 571–576 (1997) No. of Figures: 6 No. of Tables: 2 No. of References: 18

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; ^{15}N NMR; formamide; acetamide; propiolamide

Received 30 December 1996; revised 28 March 1997; accepted 9 April 1997

INTRODUCTION

Amide compounds have been the subject of many spectroscopic and theoretical investigations for several decades. Because of its small size and its role as a model compound for hydrogen bonding in peptides and proteins, formamide has been extensively studied.[1–3] Until recently, however, little was known about the structures or dynamics of formamide and related compounds in the liquid state. Recent advances in NMR relaxation methods and the ability to carry out accurate calculations of NMR parameters such as the chemical shift tensor and the quadrupole coupling tensor have made it possible to obtain detailed insight into the structure of simple liquids.[4,5] The work reported here is part of an ongoing effort to learn more about how electronic structure, steric effects and intermolecular interactions between solvent and solute affect the liquid structure.

Since formamide and its derivatives serve as building blocks for peptides and proteins, an understanding of these apparently simple systems gives insight into protein and peptide structure and the roles played by steric, hydrophobic and hydrogen bonding interactions in influencing their structure. Recent theoretical and experimental work with *N*-methylformamide[6] and *N*-methylacetamide[7] show clearly that the presence of the methyl groups significantly alters the liquid structure. Propiolamide is an important model compound since it presents a large blocking group on the carbonyl carbon. In addition, it is the immediate precursor in the synthesis of cyanoacetylene, a compound of significant importance as a model compound for the study of hydrogen bonding, solution structure and molecular dynamics.

Recent single-crystal x-ray studies have shown that propiolamide is a planar molecule consisting of non-symmetric dimers with the two monomer units slightly non-planar.[8] Owing to the high degree of conjugation caused by the carbonyl and acetylenic bonds and the lone pair on the nitrogen, one might expect that the electronic structure of formamide and propiolamide would be different and lead to significant differences in the barrier to rotation about the C—N bond and to substantial differences in the NMR chemical shifts and spin coupling constants. To test this supposition, we carried out NMR measurements on formamide, acetamide and propiolamide (Fig. 1) in 3.0 M solutions of acetonitrile-d_3. Measurements were made at both 298 and 278 K. Spectra are shown only for the lower temperature where the spectral resolution is much better owing to the slower rotation about the C—N bond.

EXPERIMENTAL

Materials

Formamide (99+%), acetamide, acetonitrile and acetonitrile-d_3 were obtained from Aldrich Chemical.

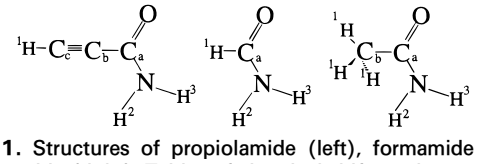

Figure 1. Structures of propiolamide (left), formamide (center) and acetamide (right). Tables of chemical shifts and coupling constants follow the labeling shown here.

* *Correspondence to*: T. C. Farrar.
Contract grant sponsor: National Science Foundation; *Contract grant number*: CHE-9500735.

CCC 0749–1581/97/090571–06 $17.50

The acetonitrile and deuterated acetonitrile were dried over molecular sieve material before use. The formamide and acetamide were used as received.

Synthesis of propiolamide

Propiolamide was synthesized by the addition of ethyl propiolate (99%, Aldrich) to liquid ammonia (99.99+%, Aldrich) through a modified procedure of Murahashi *et al.*[9] A 50 ml volume of liquid ammonia was collected in a dry, three-necked reaction flask that was submerged in a dry-ice–acetonitrile eutectic bath at −55 °C. Previous methods involved a dry-ice–ethanol bath, but the synthesis is simplified by using a warmer eutectic bath such as acetonitrile because the ethanol formed in the reaction becomes very viscous at lower temperatures and interferes with stirring as the reaction proceeds. A dry-ice–ethanol bath could be used if it was maintained at −55 °C. Using a syringe, 20 ml (0.197 mol) of ethyl propiolate, injected through a septum, was added dropwise to the liquid ammonia.

The resulting mixture was stirred at −55 °C for 9 h. At this point the dry-ice–acetonitrile bath was replaced with a 30 °C water-bath and dry nitrogen was cycled through the system to remove the remaining ammonia; the removal took about 20 min. Quick removal of the ammonia at the higher temperature is a necessary condition for a high yield.[10] Flushing with dry nitrogen was continued until the ethanol was completely removed. This procedure left a yellow solid material. The solid was dissolved in cold anhydrous diethyl either, leaving behind a yellow–orange oil as an impurity. The ether solution was decanted and the ether evaporated in a dry nitrogen atmosphere. This procedure removed most, but not all, of the impurities.

The final step in purification was accomplished by placing the solid propiolamide in a round-bottomed flask connected to a water-cooled condensing column, which was in turn attached to a vacuum line. The water condenser was cooled to 15 °C by cold tap water and the propiolamide was slowly heated to the boiling point under reduced pressure (approximately 80 °C at 0.1 Torr). Using this procedure, white crystals formed on the inside of the condensing column. Caution should be used with this procedure since propiolamide sublimes under vacuum, even at room temperature.

Final recrystallization was accomplished by dissolving the solid in an excess of anhydrous diethyl ether, adding hexane until the solution started to cloud, and finally slowly evaporating the ether to produce white needles which precipitated out in the remaining hexane. The needles were dried under partial vacuum. The final product had a melting point of 61.2–62 °C; this compares well with the literature value of 61–62 °C.[11] The overall yield was 83%. At higher temperature (around 80 °C) in an open container, propiolamide polymerizes to a brown viscous oil. Propiolamide is very soluble in diethyl ether, water and acetone. It is slightly soluble in chloroform (7 g l^{-1}) and insoluble in hexane and carbon tetrachloride.

Warning. Propiolamide is a vesicant. Contact (especially in the ether solution) causes irritation lasting for several days. Propiolamide is also hygroscopic and slowly sublimes in air. In a dry nitrogen atmosphere, it is stable indefinitely. In aqueous solutions, it is known that propiolamide undergoes slow proton exchange;[12] however, it does not otherwise react at any appreciable rate.

NMR measurements

The natural abundance ^{15}N NMR measurements were made on a Bruker AM500 spectrometer operating at 50.68 MHz and 298 K. The spectrometer digital resolution was 0.0625 Hz. RINEPT + pulse sequences[13] were used to obtain both chemical shift and coupling information. Acetonitrile was used as a reference for the nitrogen chemical shift.[14] ^{13}C and ^{1}H measurements were made at 298 K on a Bruker AC300 spectrometer operating at 74.51 and 299.87 MHz, respectively. Carbon chemical shift data were obtained using standard WALTZ decoupling and RINEPT + pulse sequences were used to collect coupling information. Both proton and carbon chemical shifts were referenced to internal TMS. The times required to record the nitrogen spectra were about 15 min and those for the carbon spectra were about 20 min. Solutions of approximately 3.0 M concentration in acetonitrile were used in 5.0 mm o.d. NMR tubes to obtain spectra of all three compounds. The digital resolution values for ^{13}C, ^{1}H and ^{15}N spectra were 0.898, 0.179 and 0.061 Hz per point, respectively.

RESULTS AND DISCUSSION

Nitrogen spectra

The natural abundance ^{15}N NMR spectra for propiolamide, formamide and acetamide are shown in Fig. 2(A), (B) and (C), respectively. The spectrum of propiolamide is a doublet of doublets arising from the spin coupling with the two non-equivalent amide protons which are *cis* and *trans* to the carbonyl R group (where R = H, CH_3 or C≡CH). The spin coupling constants are $J_{NH}^{trans} = 91.2$ Hz and $J_{NH}^{cis} = 89.2$ Hz. Spin coupling of the ^{15}N with the acetylenic proton is so small that it is not resolved.

The ^{15}N spectrum of formamide is a doublet of doublets of doublets. The long-range proton–nitrogen coupling from the carbonyl proton to the nitrogen is 15.3 Hz. The *cis* and *trans* NH coupling constant are 87.9 and 90.3 Hz, respectively. As can be seen, there is a substantial (about 2 ppm) change to lower field in the nitrogen chemical shift of propiolamide relative to formamide. The spectrum of acetamide is a doublet of doublets of quartets. The long-range coupling to the methyl protons is 1.2 Hz. Here the nitrogen chemical shift is to higher field (lower frequency) relative to formamide.

Owing to the partial double bond character of the C—N bond, formamide is a planar, essentially rigid molecule at room temperature, as evidenced by the fact that one clearly observes two well defined peaks for the two amide protons. However, the linewidths can be narrowed substantially by working at lower temperature. For this reason, the spectra were obtained at 278 K. At room temperature (298 K), the linewidths in the ^{15}N spectrum of formamide are 1.6 Hz; at 278 K the linewidths are 0.5 Hz. The chemical shift data are summarized in Table 1 and the coupling constant data in Table 2.

Carbon spectra

The ^{13}C chemical shifts of the three compounds (Table 1) were measured using composite pulse (WALTZ) decoupling. With no attached protons, the two interior carbons of propiolamide, (C_a and C_b in Fig. 1) have very long relaxation times, but with appropriate changes in the delay times of the RINEPT + sequence, good quality spectra can still be obtained in about 10 min.

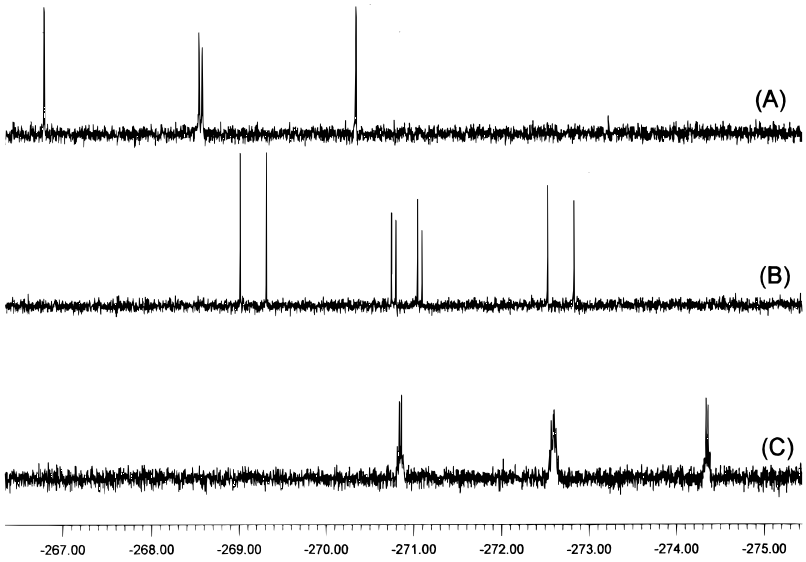

Figure 2. ^{15}N RINEPT + spectra of propiolamide (A), formamide (B) and acetamide (C) in 3.0 M acetonitrile. Chemical shifts are referenced to external acetonitrile; 64 scans were taken with a relaxation delay of 5 s.

The difference in shifts between the carbonyl carbons in the three samples (Table 1) is substantial and is attributed to increased electron density from the delocalization of the acetylenic π_{CC} bond perpendicular to the plane of the molecule into the π^*_{CO} antibond in propiolamide.

The ^{13}C proton-coupled spectra for propiolamide, formamide and acetamide are shown in Fig. 3(A), (B) and (C), respectively. The doublet and the doublet of doublets at about 75 ppm in the propiolamide spectrum are due to the acetylenic carbon nuclei. The doublet ($J_{HC_c} \approx 256$ Hz) is due to the terminal carbon (C_c, Fig. 1) and the doublet of doublets is due to C_b, which is coupled to H^1 and to H^3. The peak at about 150 ppm is due to the carbonyl carbon, C_a. The proton–carbon spin coupling constants (Table 2) were determined by use of RINEPT + pulse sequences. The assignment of the H^3–C_b coupling was determined by decoupling the H^3 proton resonance during the coupled RINEPT + sequence. The result of this experiment was a collapse of a doublet of doublets into a single doublet with an H^1–C_b coupling constant of 49.6 Hz. Decoupling the other amide proton, H^2, had no observable effect on the ^{13}C spectrum.

Table 1. Chemical shifts (ppm) of various nuclei for amide systems at room temperature (298 K) in acetonitrile solution (3 M)[a]

	Propiolamide	Acetamide	Formamide
N	−269.1	−273.3	−271.5
C_a	154.9	174.3	164.8
C_b	77.8	22.6	—
C_c	75.4	—	—
H^3	6.6	6.4	6.5
H^2	6.9	6.7	6.6_5
H^1	3.3	1.9	8.1

[a] ^{15}N chemical shifts are referenced to external acetonitrile. ^{13}C and ^1H shifts are referenced to internal TMS. Numerical subscripts refer to protons (3 = *trans*; 2 = *cis*; 1 = terminal/methyl) and letters refer to carbon (a = carbonyl, etc.).

Table 2. Coupling constants (Hz) at 298 K for amide systems in 3.0 M acetonitrile solution[a]

	Propiolamide	Acetamide	Formamide
J_{H^3N}	91.2	89.5	90.3
J_{H^2N}	89.2	87.9	87.9
J_{H^1N}	—	1.2	15.1
$J_{H^1C_c}$	256.0	—	—
$J_{H^1C_b}$	49.2	128.0	—
$J_{H^3C_b}$	10.2	7.0	—
$J_{H^1C_a}$	5.6	—	189.9
$J_{H^1H^2}$	—	—	1.6
$J_{H^1H^3}$	—	0.7	13.5
$J_{H^2H^3}$	2.2	2.9	2.7

[a] Data were obtained using RINEPT + pulse sequences. Numerals refer to protons (3 = *trans*; 2 = *cis*; 1 = terminal/methyl) and letters refer to carbons (a = carbonyl, etc.).

Proton spectra

The proton spectra for all three compounds (Figs 4–6) show very broad peaks for the amide protons due to spin coupling to the nitrogen-14; the nitrogen-14 has a very short relaxation time owing to quadrupole relaxation. This results in short T_2 values for the protons (due to scalar relaxation[13]) and broad lines, since $1/(\pi T_2) = \Delta\nu_{1/2}$, where $\Delta\nu_{1/2}$ is the proton linewidth at its half maximum height. The fact that the broad proton linewidths are due to interaction with the rapidly relaxing nitrogen nucleus, rather than rotation about the C—N bond, is clearly demonstrated by the fact that the proton lines are narrow (about 1 Hz) in the nitrogen-15-containing molecules. The chemical shifts (Table 1) for the amide protons are similar for all three compounds and in the same general range as for most substituted amides. The acetylenic proton chemical shift is typical of other acetylenic compounds.

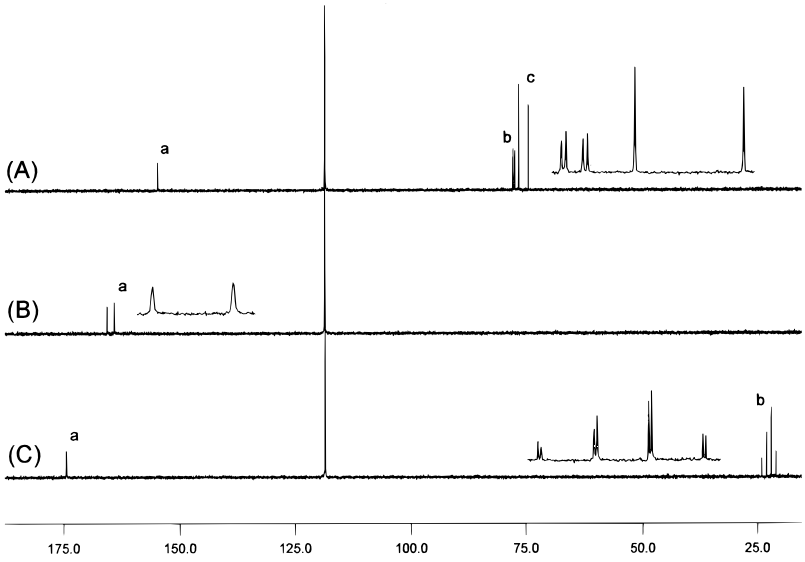

Figure 3. Coupled ^{13}C NMR spectra of propiolamide (A), formamide (B) and acetamide (C) in 3.0 M acetonitrile. Carbon chemical shifts are referenced to internal TMS; 128 scans were taken with a relaxation delay of 15 s.

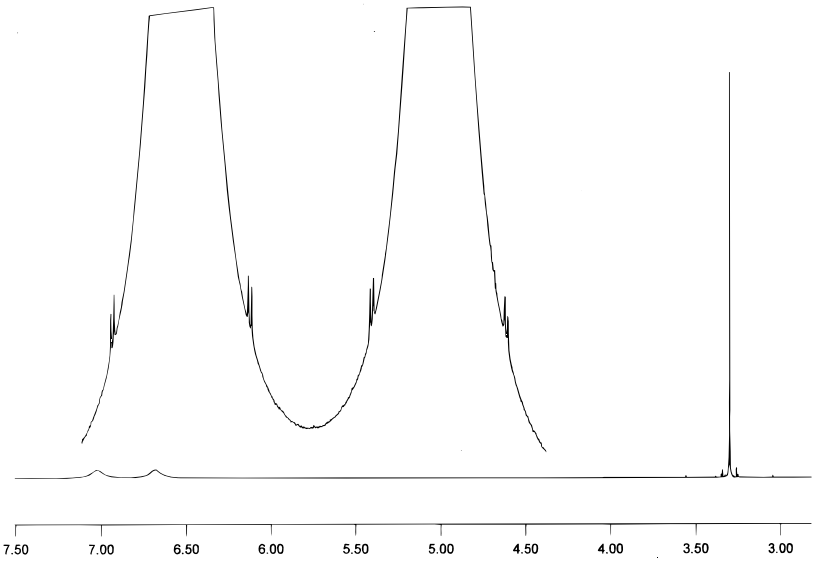

Figure 4. Proton NMR spectra of propiolamide in 3.0 M acetoni- trile. Expanded sections show the satellite lines arising from the ^{1}H–^{1}H, ^{1}H–^{13}C and ^{1}H–^{15}N spin coupling interaction. Chemical shifts are referenced to internal TMS; 32 scans were taken with a relaxation delay of 5 s.

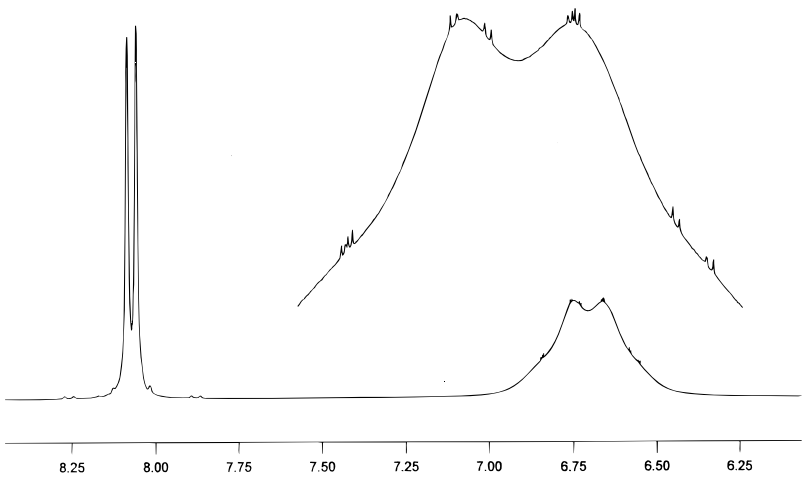

Figure 5. Proton NMR spectra of acetamide in 3.0 M acetonitrile. Expanded sections show the satellite lines arising from the ^{1}H–^{1}H, ^{1}H–^{13}C and ^{1}H–^{15}N spin coupling interaction; 32 scans were taken with a relaxation delay of 5 s.

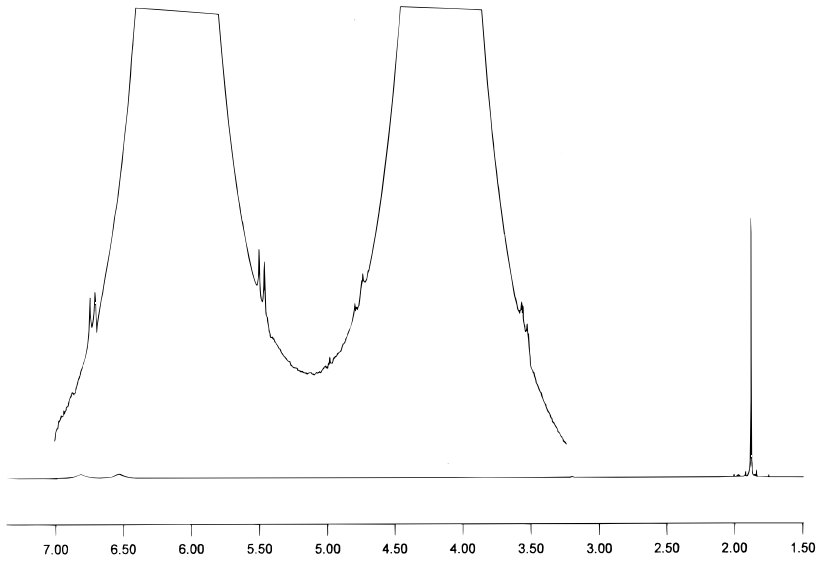

Figure 6. Proton NMR spectra of formamide in 3.0 M acetonitrile. Expanded sections show the satellite lines arising from the ^{1}H–^{1}H, ^{1}H–^{13}C and ^{1}H–^{15}N spin coupling interaction; 32 scans were taken with a relaxation delay of 5 s.

Figure 4 shows the proton spectrum for propiolamide with expanded sections for the amide protons and for the terminal acetylene proton. Superimposed on the sides of the broad amide proton peaks are doublets of doublets which arise from the 0.37% of the molecules containing nitrogen-15. The doublet of doublets on the broad low-frequency peak (the *cis*-amide proton) arises from the interaction with the nitrogen-15 ($J_{NH^2} = J_{NH}^{cis} = 89.2$ Hz) and with the *trans*-amide proton ($J_{H^2H^3} = 2.2$ Hz). A similar doublet of doublets is seen on the high-frequency proton (the *trans*-amide proton) peak from which we obtain $J_{NH^3} = J_{NH}^{trans} = 91.2$ Hz. The fine structure on the acetylenic proton gives information about the various carbon–hydrogen coupling constants with $J_{CH} = 256.0$, $J_{CCH} = 49.2$ and $J_{CCCH} = 5.6$ Hz.

Figure 5 shows the proton spectrum of acetamide. Here, in a similar fashion, the fine structure on the low-frequency amide peak is a doublet of quartets with $J_{NH^2} = J_{NH}^{cis} = 87.9$, $J_{NH^3} = J_{NH}^{trans} = 89.5$, $J_{HH} = 2.9$ and $J_{H^1CNH^3} = 0.7$ Hz. The fine structure on the high-frequency (the *cis*-amide) proton peak is a doublet of doublets, since the coupling of the *cis*-amide proton to the methyl protons is too small to be resolved.

Figure 6 shows the spectrum of formamide. For both amide protons, the fine structure is a doublet of doublets with $J_{NH^3} = 90.3$, $J_{NH^2} = 87.9$, $J_{H^2H^3} = 2.7$, $J_{H^1H^2} = 1.6$ and $J_{H^1H^3} = 13.5$ Hz. These results are summarized in Table 2.

CONCLUSION

The data for the scalar couplings and the chemical shifts which we obtained here are in amazingly good agreement with the earlier results for the spin coupling constants in *N*-methylacetamide reported by DeMarco and Llinás,[15] especially considering the fact that DeMarco and Llinás's spectra were obtained as 0.6 M solutions in dimethyl sulfoxide (DMSO) and the spectra reported here were for 3.0 M solutions in acetonitrile. Acetonitrile is a very weak and DMSO is a very strong hydrogen bonding solvent. One might therefore have expected to see substantial solvent-dependent changes in the chemical shifts and/or spin coupling constants of the amide protons. There is almost no solvent change in the amide proton of acetamide which is *cis* to the oxygen. There is a shift of about 0.7 ppm for the proton which is *trans* to the oxygen. This is what is to be expected on the basis of recent experimental and theoretical work on chemical shifts in amides.[4]

There is a substantial change (0.5–0.7 Hz) in the geminal proton–proton coupling of the propiolamide compared with formamide and acetamide. The other spin coupling constants change relatively little. Similarly, there are substantial changes in the carbonyl carbon chemical shifts of propiolamide, acetamide and formamide, but relatively little change for the other nuclei. A theoretical natural bond order analysis (NBO) is being carried out for these three molecules and will be reported later.

Propiolamide is easily synthesized in high yield and purified by the method described here. All of the NMR spectra indicate that the product is of high purity. The carbon chemical shift data indicate that the extended conjugation in propiolamide leads to a significant shielding of the carbonyl carbon. The high-resolution satellite fine structure of the proton spectra of all three compounds is well resolved and provides accurate data for proton spin coupling to all of the NMR-active nuclei.

Acknowledgements

We thank the National Science Foundation, Grant No. CHE-9500735, for support of this research. The 500 and 300 MHz NMR spectrometers used for part of this research were purchased with the aid of NSF Grant No. CHE-8306121 and NIH Grant No. NIH 1 S10 RR-2388-01. We thank Mr Mark Wendt for a number of helpful discussions and comments.

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