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Conformational Equilibria in Formic Acid and the Adduct of Formic Acid and Hexafluoroacetone, $HCO_2C(CF_3)_2OH$

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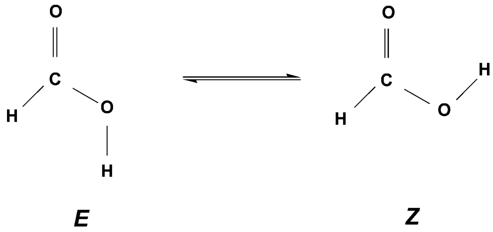
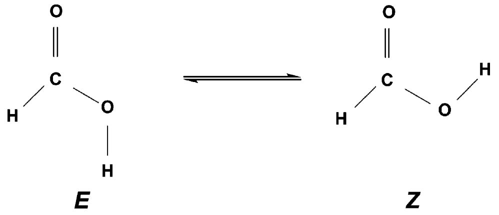


Low-temperature ^{1}H and ^{13}C NMR spectra of formic acid (**1**) showed separate signals for the *E* and *Z* conformations in solvents containing a hydrogen bond acceptor, dimethyl ether. The population of *E*-**1** **(**6.2% in 3:1:1 $CHClF_2/CHCl_2F/(CH_3)_2O$) was larger than that for ^{13}C-labeled methyl formate in the same solvent (0.2%), which indicated that the relative populations are not determined by steric effects. The free-energy difference between the *E* and *Z* conformations of **1** was 0.9 kcal/mol. In a 1:3 $CD_2Cl_2/(CH_3)_2O$ solvent mixture, peaks for *E* and *Z* conformations were found at low temperatures by ^{1}H and ^{13}C NMR for both formic acid and an adduct with hexafluoroacetone, $HCO_2C(CF_3)_2OH$ (**2**). The population of *E*-**1** in this solvent mixture was 4.3% by ^{13}C NMR. The carbon spectrum showed two peaks in the carbonyl carbon region of nearly equal intensities at −151.6 °C, with *E*-**2** (48%) absorbing downfield of the major *Z*-**2** (52%). The large population of *E*-**2** confirms that electron-withdrawing groups R′ in RCO_2R' enhance the populations of the *E*-isomers. The free-energy barriers for **2** of 6.24 (*E*-to-*Z*) and 6.26 kcal/mol (*Z*-to-*E*) were determined from rate constants obtained by line shape analysis at −143.2 °C.

Introduction

Dynamic NMR spectroscopy is often the most useful experimental method for studying conformational equilibria in solution. Rates and barriers for interconversion of conformations, in addition to the populations and free-energy differences, can generally be accurately determined if this method is applicable. Esters, thiolesters, and amides have been studied by dynamic NMR,[1] but carboxylic acids are an important class of compounds for which *E* and *Z* conformations have not been reported to be observed by this method. This is due to rapid interconversion of *E* and *Z* conformations, shown for formic acid (**1**), by intermolecular exchange of the acidic proton. Separate NMR signals for *E*- and *Z*-isomers of thioacetic acid in a ratio of 1:3 were found[2] at −150 °C, and nearly equal amounts of these conformations were later observed for thioformic acid[3] at −113 °C, but OH exchange in a carboxylic acid is generally a faster process than SH exchange in a thioacid.



Formic acid in the gas phase includes monomer and the cyclic dimer below, and the amount of cyclic dimer increases in the liquid phase.[4] The enthalpy change for dissociation of the dimer into two molecules of monomer is about 14 kcal/mol.[5] In the solid phase, the compound exists as long chains of monomer,

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[1] For example, see: Pawar, D. M.; Khalil, A. A.; Hooks, D. R.; Collins, K.; Elliott, T.; Stafford, J.; Smith, L.; Noe, E. A. *J. Am. Chem. Soc.* **1998**, *120*, 2108 and references cited therein.

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[3] Kalinowski, H. O.; Hocking, W. H.; Winnewisser, B. P. *J. Chem. Res.* **1978**, *7*, 260.

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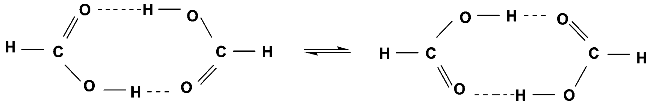

with individual molecules of the chain held together by CH···O and OH···O hydrogen bonds.[6] Most carboxylic acids exist in the solid state as cyclic hydrogen-bonded dimers, with structures analogous to the one shown above for formic acid. A solid-state T_1 NMR spin−lattice relaxation study[7] of *p*-toluic acid-d_7, completely deuterated except for the acidic proton, found an apparent activation energy of only 1.15 kcal/mol for the double proton transfer in this acid. Tunneling contributes significantly to this process, particularly at low temperatures.

For observation of the *E*-isomer of a carboxylic acid, the cyclic dimer needs to be avoided or minimized, as the conformation is necessarily *Z* in the dimer, and intermolecular exchange of the acidic proton is rapid in the dimer. Addition of weak bases can disrupt the cyclic dimer by hydrogen bonding to the OH proton, and ^{1}H NMR spectra of **1** in $CHClF_2$ with concentrations of 0.02−0.05 M and a (5−8)-fold excess of THF or HMPA showed doublets ($J = 11.6$ Hz) for each of the protons of the acid at temperatures from −163 to −123 °C.[8] The coupling constant observed is consistent with the trans relationship between hydrogens of the *Z* conformation. Cis and trans three-bond H−H coupling constants of ~0.7 and 10.0 Hz were found[9] for the *E*,*Z* conformation of diformamide, $(HCO)_2NH$. In the absence of a hydrogen-bonding solvent, a triplet was found[8] for the OH proton of **1** at low temperatures, and rapid double proton exchange within the dimer was assumed to account for the averaged coupling ($J_{H-H} = 5.9$ Hz, average of 11.8 and 0.0 Hz).

Signals for the *E*-isomer of **1** were observed in the gas phase by microwave spectroscopy,[10] and this conformation was found to be 3.9 kcal/mol higher in energy than *Z*-**1**. A barrier of 13.8 kcal/mol was estimated[10] for conversion of the *Z* conformation to the *E*. Ab initio calculations at the MP3/6-311+G**//6-31G* level[11] predict *E*−*Z* energy differences of 4.61 and 5.59 kcal/mol for formic acid and methyl formate, respectively, and the *Z*-to-*E* barrier for formic acid was calculated to be 12.4 kcal/mol. The dipole moments[10] of *E* and *Z* formic acid are 3.79 and 1.42 D, and the energy difference between these conformations is expected to decrease in solution. A free-energy difference of 2.15 kcal/mol was reported[12] for methyl formate in 1:1 acetone-d_6/DMF, and the *E*-*Z* free-energy difference for this ester was predicted[13] by ab initio calculations at the MP2/6-31+G*//6-31G* level to decrease from 5.16 kcal/mol in the gas phase to 1.66 kcal/mol for a solution in acetonitrile. Evidence for observable amounts of *E*-**1** in solution has been obtained[14] from the vibrational spectra of formic acid and HMPA in several solvents.

The *E*−*Z* energy differences for formic acid esters decrease in the order R′ = methyl > vinyl > ethynyl.[1,15] The hybridization of carbon in the corresponding hydrocarbons R′H changes from sp^3 to sp^2 to sp in the series, suggesting that the electron-withdrawing abilities of the groups may be important in enhancing the populations of the *E*-isomers. However, even with very highly electronegative R′ groups such as trifluoromethyl,[16] the *Z* conformations of esters are still generally preferred, although by smaller amounts. The calculated dipole moments for *E*- and *Z*-trifluoromethyl formate were 2.17 and 2.47 D at the MP2/6-311G(df,pd) level, and the *E*-isomer was calculated to have a free energy of 1.14 kcal per mol, relative to the *Z*. Although the difference in dipole moments was calculated to be close to zero, with a slightly more favorable[17] (lower) value for the *E*-isomer, the *Z*-isomer was predicted to predominate.[16]

In the present work, ^{1}H and ^{13}C NMR spectra of **1** were taken for solutions containing dimethyl ether for hydrogen bonding to the acid. Hexafluoroacetone was added to some samples to react with the water and form the hydrate. Formic acid also forms an adduct with hexafluoroacetone. *E* and *Z* conformations of **1** were observed without the hexafluoride, but a lower temperature was needed. In addition to lowering the amount of water, formation of the adduct will lower the concentration of the acid, which will tend to raise the coalescence temperature. Decoalescence was also observed for the signals of the adduct.

Results and Discussion

Low-temperature ^{1}H NMR spectra of a solution containing 2% formic acid and ca. 3% hexafluoroacetone in 1:3 CD_2Cl_2/dimethyl ether are shown in Figure 1, and larger spectra are shown in the Supporting Information. The proton NMR spectrum at −90.0 °C shows the expected four peaks for formic acid and adduct in the region of δ 11 to 7, as shown in Table 1. Both signals for formic acid decoalesce at lower temperatures into separate peaks for *E*- and *Z*-isomers, and the proton chemical shifts at −118.3 °C are summarized in Table 1. As expected, the signals for OH protons moved to lower field with decreasing temperature. For **1**, assignments are based on intensities, with the *Z*-isomer expected to predominate, based on the results of gas-phase calculations,[11] the microwave study,[10] and the effect of solvent on the *E*−*Z* free-energy difference for methyl formate.[13] The formyl protons of *E*-**1** and *Z*-**1** have the expected relative positions, but they are reversed for the carbonyl carbon peaks of **1**, although the *Z*−*E* shift difference is small. At still lower temperatures, both the OH and the CH signals of the adduct broadened, and separate signals for *E* and *Z* conformations were observed by −153.8 °C. The chemical shifts are listed in Table 1. Assignments to *E* and *Z* conformations are based on the assumption that the formyl hydrogen and carbonyl carbon peaks (see below) of *E*-**2** will be downfield of the corresponding peaks for *Z*-**2**, as is often observed for esters and related compounds.[1] The chemical shift for the OH protons

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[17] Dipole moments are often assumed to be a measure of dipole−dipole interactions, but Perrin and Young[18] have shown that this is not always valid, and have described two examples for which this assumption leads to the wrong conclusion. However, the relationship was described as applicable to esters.

TABLE 1. Chemical Shifts (in ppm) Obtained from Low-Temperature ^{1}H and ^{13}C NMR Spectra of a Solution Containing 2% Formic Acid and Ca. 3% Hexafluoroacetone in 1:3 CD_2Cl_2, $(CH_3)_2O$ (Internal Reference TMS)

	chemical shifts (ppm)											
	proton								carbon			
	formic acid				adduct				formic acid			
	OH		CH		OH		CH		C=O		adduct C=O	
temp (°C)	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
−90	10.87		7.93		9.18		8.42					
−118.2	11.75	11.45	8.46	7.98	9.77		8.58					
−120.0									163.34	163.76	158.52	
−151.6											159.33	158.70
−153.8					9.85	9.90	9.02	8.20				

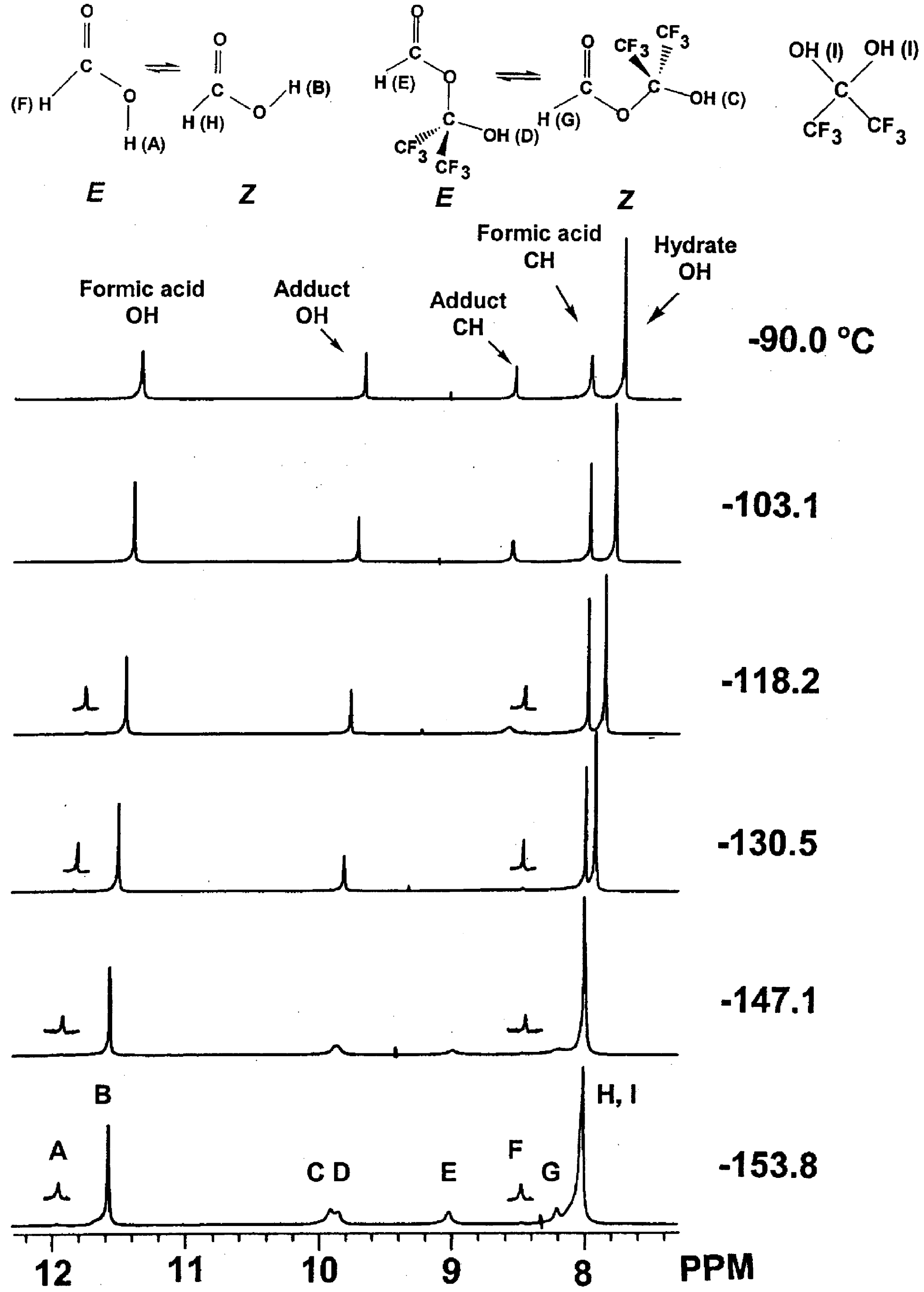

FIGURE 1. Low-temperature ^{1}H NMR spectra of a mixture of 2% formic acid and 3% hexafluoroacetone in 1:3 CD_2Cl_2/dimethyl ether.

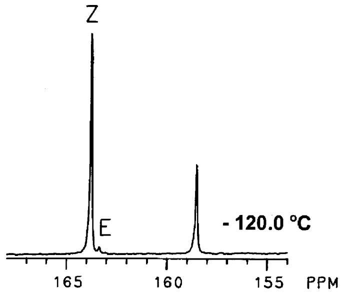

FIGURE 2. Low-temperature ^{13}C NMR spectrum for the carbonyl region of a mixture of formic acid and hexafluoroacetone in 1:3 CD_2Cl_2/dimethyl ether.

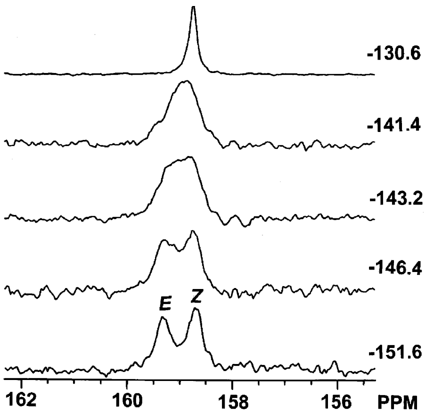

FIGURE 3. Low-temperature ^{13}C NMR spectrum for the carbonyl region of the adduct, $HCO_2C(CF_3)_2OH$, for a solution of 2% formic acid and 3% hexafluoroacetone dissolved in 1:3 $CD_2Cl_2/(CH_3)_2O$.

of the hydrate, $(CF_3)_2C(OH)_2$, was δ 7.23 and 7.85 at −90 and −118.2 °C, respectively.

The carbon spectrum for the carbonyl region at −120 °C is shown in Figure 2. The peaks for the *Z*-**1** and *E*-**1** isomers appear at δ 163.76 and 163.34, respectively. The peak at δ 158.52 is assigned to the adduct. At −120.0 °C, the population of *E*-**1** from the ^{13}C signals was 4.3%, and at −118.2 °C, the populations of this conformation from the ^1H spectrum were 4.5% (OH) and 4.2% (CH). Decoalescence of the carbonyl carbon peak of **2** at lower temperatures is shown in Figure 3. The chemical shifts at −151.6 °C were δ 159.33 (*E*) and 158.70 (*Z*).

Assignments of peaks in Figure 3 to conformations were based on the assumption that *E* absorbs downfield of *Z*, as found previously for formate esters,[1] but the chemical-shift difference is small, and the assignments could be reversed. Electronic integration of the ^{13}C spectrum at −151.6 °C gave populations of 48% and 52% for the *E* and *Z* conformations, respectively. The finding of a large population for *E*-**2** indicates that the electron-withdrawing groups tend to favor the *E*-isomer. A first-order rate constant of 84.6 s^{-1} was obtained by line shape matching program[19] for the *E* to *Z* conversion at the coalescence temperature of −143.2 °C (Figure 3), corresponding to a free-energy barrier of 6.24 kcal/mol. The rate constant for the reverse process was $84.6 \times (48/52) = 78.1\ s^{-1}$, and the *Z*-to-*E* free-energy barrier at this temperature was 6.26 kcal/mol.

For a solution containing 2% formic acid and 3% hexafluoroacetone in 3:1:1 $CHClF_2/CHCl_2F/(CH_3)_2O$, coalescence was observed at −90.3 °C, and the OH proton signals absorbed at δ 11.77 and 12.22 at −107 °C for the *Z*- and *E*-isomers, respectively. Integration of the spectrum gave populations of 0.938 and 0.062. These values are somewhat larger than those observed for 1:3 $CD_2Cl_2/(CH_3)_2O$ as solvent, as noted above. The higher population for this solution can be attributed to a higher dielectric constant due to the smaller amount of dimethyl ether and/or the higher temperature. The free-energy barriers for methyl formate at −70.8 °C in 1:1 acetone-d_6/DMF are 9.85 and 11.91 kcal/mol,[20] and the population for the *E*-isomer of this ester at −82.5 °C in 3:1:1 $CHClF_2/CHCl_2F$/dimethyl ether is 0.002. On the basis of the barriers for methyl formate, a coalescence temperature of ≥−90.3 °C is reasonable for intramolecular exchange in **1**. As long as exchange of the OH proton between the *E* and *Z* conformations of **1** is slow, it is not necessary for the corresponding *E*−*E* and *Z*−*Z* exchanges to also be slow to see separate signals for the *E* and *Z* conformations, although we expect *E*−*E* exchange to also be slow (see below). The absence of splitting at −107 °C for the OH signal of *Z*-**1** at δ 11.77 indicates that exchange between *Z* conformations is still rapid at this temperature, but the absence of splitting for the *E*-isomer does not provide any information about the rate of *E*−*E* exchange because the coupling constant is expected to be close to zero.[8,9] We believe that *Z*−*Z* exchange occurs by way of the cyclic hydrogen-bonded dimer after loss of the solvating dimethyl ether. This pathway is not available for *E*−*E* and *E*−*Z* exchange, and the barriers for interconversion of the *E* and *Z* conformations by rotation about the C−OH bond are then responsible for the slower *E*−*E* and *E*−*Z* exchanges.

To obtain further information about the rate of proton exchange between *Z*-isomers, a 0.5% solution of a mixture of formic acid and acetic acid in a ratio of 1:1 by volume was studied at low temperatures in a 3:1:1 mixture of $CHClF_2/CHCl_2F/(CH_3)_2O$ containing a small amount of acetic anhydride. No hexafluoroacetone was present. By approximately −144 °C,[21] a small peak for *E*-**1** and a large averaged OH signal for *Z*-**1** and acetic acid were observed at δ 13.5 and 12.0, respectively, and the latter peak split into two broad peaks at δ 12.2 and 11.5 by about −173 °C, as exchange between *Z*-**1** and acetic acid becomes slow. This experiment provides information about the temperature required for the slow exchange between molecules of *Z*-formic acid under these conditions. Slowing *Z*−*Z* exchange probably requires slow dissociation of the hydrogen bonds between the acids and dimethyl ether, and this requires a lower temperature than for *E*−*Z* exchange, which requires rotation about the C−OH bond of the acid for conversion of *E* to *Z*, followed by rapid proton exchange by way of the dimer. With the large ratio of dimethyl ether to carboxylic acids used, nearly all of the acids are expected to be monomeric and hydrogen bonded to the dimethyl ether.

A 2% formic acid solution in 3:1:1 $CHClF_2/CHCl_2F/(CH_3)_2O$, but without hexafluoroacetone, also showed peaks for the *E* and *Z* conformations in the OH region at about −144 °C. The presence of hexafluoroacetone does not markedly change the

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(21) The temperatures for this experiment were not calibrated promptly after the spectra were taken, and were estimated from many other calibrations. The error limits (ca. ±5 °C) are larger than those for the other spectra.

populations of the *E* and *Z* conformations for **1**, but does raise the coalescence temperature, probably by removal of water and also by decreasing the concentration of the acid by formation of the adduct. *E*−Z free-energy differences of 2.15, 1.67, 1.36, and 0.48 kcal/mol were reported[12] for solutions of methyl, ethyl, isopropyl, and *tert*-butyl formate, and the trend is expected, based on the sizes of groups attached to oxygen. The finding of a larger population for the *E*-isomer of formic acid than for methyl formate indicates that the relative populations are not determined by steric effects.

Conclusions

Low-temperature ^{1}H and ^{13}C NMR spectra of solutions of formic acid (**1**) showed separate signals for the *E* and *Z* conformations. Dimethyl ether was used to hydrogen bond with the acid and break up the cyclic dimer. A 2% solution of **1** in 1:3 $CD_2Cl_2/(CH_3)_2O$, which also contained 3% hexafluoroacetone, gave populations of 4.3%, 4.5%, and 4.2% *E*-**1** from integration of the signals from the carbonyl carbons, hydroxyl protons, and formyl protons of **1** at −120 °C (carbon) or −118 °C (proton). The population of *E*-**1** in 3:1:1 $CHClF_2/CHCl_2F/(CH_3)_2O$ was larger (6.2%) than that for ^{13}C-labeled methyl formate (0.2%), which indicated that the relative populations are not determined entirely by steric effects. The presence of electron-withdrawing groups on the ether oxygen of ester **2**, $HCO_2C(CF_3)_2OH$, markedly increased the population of the *E*-isomer (48%).

Experimental Section

According to the label, the formic acid contained about 2% or less water, which was not removed before use. Three solvent systems were used: (1) 2% formic acid + 3% hexafluoroacetone in 3:1:1 $CHClF_2/CHCl_2F/(CH_3)_2O$; (2) 2% formic acid in 3:1:1 $CHClF_2/CHCl_2F/(CH_3)_2O$; and (3) 2% formic acid + 3% hexafluoroacetone in 1:3 $CD_2Cl_2/(CH_3)_2O$. Dimethyl ether was used as a hydrogen-bonding solvent. The NMR samples were prepared in 5-mm thin-walled screw-capped NMR tubes, and a small amount of TMS was added for an internal reference. **Caution**: High pressure. The sample tubes were stored and handled below 0 °C most of the time. Spectra were recorded on a wide-bore NMR spectrometer operating at 300.52 MHz for proton and 75.57 MHz for carbon. The ^{1}H and ^{13}C spectra were obtained with a 5-mm dual probe. For proton spectra, a pulse width of 8.2 μs, corresponding to a tip angle of 83°, and a pulse repetition period of 3 s were used. A sweep width of ±3200 Hz, data size of 64 K, and 800 pulses were used. Carbon spectra were recorded with a line broadening of 3.0 Hz. Spinning was discontinued below about −140 °C.

Because of the difficulty in ejecting the samples at lower temperatures, the temperature calibrations were performed separately, using a copper−constantan thermocouple immersed in the same solvents contained in a nonspinning sample tube and under conditions as nearly identical as possible. The emf's were measured with a potentiometer. The uncertainty in temperatures was estimated to be ±2 °C.

Acknowledgment. We thank the National Institutes of Health for financial support (NIH-SCORE grant no. S06GM-0084047).

Supporting Information Available: The NMR spectra for (1) a mixture of formic acid and acetic acid in a ratio of 1:1 by volume in a 3:1:1 mixture of $CHClF_2/CHCl_2F/(CH_3)_2O$ containing a small amount of acetic anhydride, (2) low-temperature ^{1}H NMR spectra of 2% formic acid + 3% hexafluoroacetone in 3:1 dimethyl ether/dichloromethane solvent mixture, for eight temperatures, (3) low-temperature ^{13}C NMR spectra of 2% formic acid + 3% hexafluoroacetone in 3:1 dimethyl ether/dichloromethane solvent mixture. This material is available free of charge via the Internet at http://pubs.acs.org.

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