Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Differential Rates of N–H Proton-Transfer Reactions in Phenylhydrazine[1]

Issa Yavari and John D. Roberts*

Contribution No. 5710 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125. Received December 12, 1977

Abstract: High-resolution proton-coupled ^{15}N NMR spectra of neat phenylhydrazine (**1**) have been studied at the natural-abundance level over the temperature range of 20–70 °C. Proton transfer from the –NH₂ group was found to be about two orders of magnitude faster than that from the –NH– group. The ^{15}N chemical shifts of **1** in a variety of basic, neutral, and acidic solvents show that influences of the medium are different for the two types of nitrogens in **1**. Proton-coupled ^{15}N spectra of **1** in various solvents confirm the results of the variable-temperature studies. The differential rates of the proton-transfer reactions of **1** can be ascribed to two different bimolecular exchange mechanisms.

Introduction

Proton transfers catalyzed by Brønsted acids and bases are perhaps the most fundamental and widely studied chemical reactions.[2-5] In the past 3 decades, with development of relaxation spectroscopy[3,4] and dynamic NMR spectroscopy,[5-15] it has been possible to study fast (and "ultrafast"[9]) proton-transfer reactions, in particular those involving oxygen,[10] sulfur,[11] and nitrogen[4,12-15] acids and bases.

Although ^{15}N NMR spectroscopy has become very important in the last few years for structural study of organic compounds,[16] few dynamic processes have been investigated as yet by this technique.[14,15] Part of the problem is that the broadened resonances, which are characteristic of dynamic NMR effects, make the observation of ^{15}N NMR spectra with adequate signal-to-noise ratios very difficult. Nonetheless, ^{15}N NMR spectroscopy can be confidently expected to be outstanding for monitoring rates of fast N–H proton-transfer reactions. An important factor in this is the relatively large ^{15}N–^1H spin-spin coupling constant (50–100 Hz), which provides a sensitive probe for N–H exchange processes. This paper discusses the use of dynamic ^{15}N NMR spectroscopy to study the proton-transfer reactions of phenylhydrazine (**1**), which has two nonequivalent nitrogens, of which the –NH₂ is known to be the more basic (pK = 5.20).[17]

$$C_6H_5NHNH_2$$

1

When intermolecular proton transfers are slow relative to the ^{15}N NMR time scale and neglecting all two-bond ^{15}N–proton couplings, the proton-coupled ^{15}N NMR spectrum of **1** should exhibit a 1:1 doublet and a 1:2:1 triplet. When intermolecular N–H proton transfers are fast, the spin-spin splittings should vanish, yielding two single lines.

Experimental Section

Phenylhydrazine (Aldrich) was stored over basic alumina for a few days, then distilled at reduced pressure under argon and transferred to the ^{15}N NMR tube (under argon). Reagent-grade triethylamine, dimethyl sulfoxide, chloroform, ethanol, 2,2,2-trifluoroethanol, and trifluoroacetic acid were employed as solvents. Dimethyl sulfoxide and chloroform were stored over Linde molecular sieves (Union Carbide Corp.) for a few days before use.

The natural-abundance ^{15}N NMR spectra were obtained at a frequency of 18.25 MHz with a Bruker WH-180 pulse spectrometer, which has been described in detail elsewhere.[18] A 25-mm o.d. spinning sample tube containing about 25 mL of sample was used. The reported gated-proton noise-decoupled ^{15}N spectra are the Fourier transforms of the sum of 50–400 free induction decays obtained with a 70° pulse

angle, 8K data points, 3000-Hz spectrum width, and a pulse interval of 6 s. A 5-mm concentric tube containing a 1.0 M solution of 98% ^{15}N-enriched nitric acid in D₂O provided both the external reference standard and the field-frequency lock. To obtain the ^{15}N chemical shifts, the protons were noise decoupled at a power of 4 W. The spectral width was 7000 Hz. Chemical shifts are reported in parts per million upfield from H^{15}NO₃ with a precision of about ±0.1 ppm.

At each temperature, the sample was allowed to equilibrate for about 1 h. The sample temperatures were measured by direct insertion of a thermometer into the solution before and after taking each spectrum.

Results and Discussion

Natural-abundance ^{15}N NMR spectra of neat phenylhydrazine (**1**) at various temperatures are displayed in Figure 1. The ^1H noise-decoupled spectrum at 30 °C exhibits two equal-intensity resonances at +288.6 (–^{15}NH–) and at +313.8 ppm (–^{15}NH₂) upfield from the external nitric acid standard.[19,20] The gated ^1H noise-decoupled spectrum at 30 °C shows a fairly sharp doublet ($^1J_{^{15}N-^1H}$ = 88 Hz) for the –^{15}NH– signal and a broad, structureless resonance for the –^{15}NH₂ signal. When the temperature is lowered to about 20 °C, a broad but distinct triplet was found for the –^{15}NH₂ resonance, while the –^{15}NH– doublet remained unchanged. On raising temperature to about 60 °C, the –^{15}NH₂ triplet coalesces into a single broad band with only slight broadening of the components of the –^{15}NH doublet. This behavior was reproducible in three different samples of **1** and was essentially unchanged when 10 g of basic alumina was added directly to the NMR sample tube. On the other hand, spin-spin splittings of the ^{15}N resonances were wholly wiped out when a few percent of trifluoroacetic acid was added to the sample.

Line-shape calculations for the ^{15}N spectrum, using a natural line width of 3 Hz and ^{15}N–^1H spin-spin coupling constant of 88 Hz (the long-range spin-spin coupling constants involving ^{15}N were ignored), showed that the spectrum of **1** at 60 °C could be well simulated with rate constants of 2 and 600 s^{-1} for the –NH– and –NH₂ resonances, respectively.[21] From absolute rate theory, these rates correspond to free energies of activation ($\Delta G^{\ddagger}$) of 15.3 ± 0.5 and 19.2 ± 0.5 kcal/mol for proton transfers from the –NH₂ and –NH– groups, respectively.[22]

The ^{15}N chemical shifts of **1** in a variety of basic, neutral, and acidic solvents are given in Table I. The solvent effects on the ^{15}N chemical shifts of the two kinds of nitrogens are clearly different. In polar aprotic solvents, such as dimethyl sulfoxide, the –^{15}NH– resonance moves to lower field by 0.3 ppm, whereas the –^{15}NH₂ signal moves to higher field (0.6 ppm)
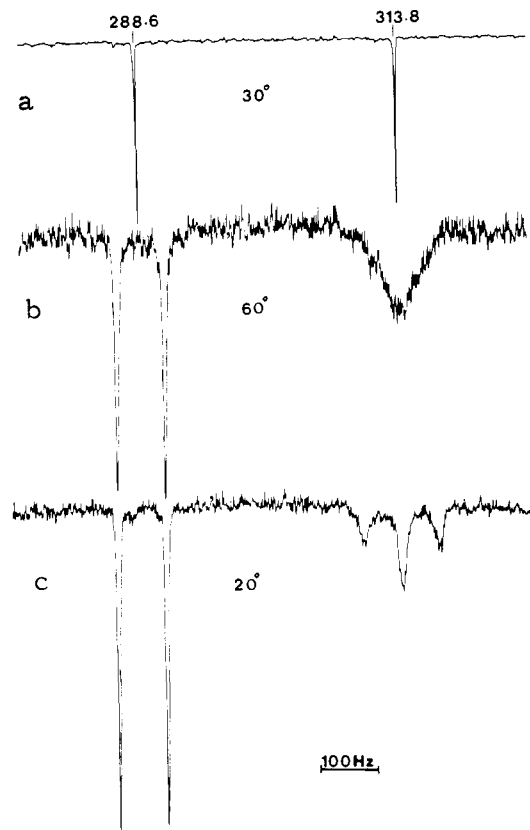
Figure 1. Natural-abundance ^{15}N NMR spectra of neat phenylhydrazine: (a) with ^{1}H noise decoupling, one transient; (b) with gated ^{1}H noise decoupling, 50 transients; (c) as (b) but at lower temperature.

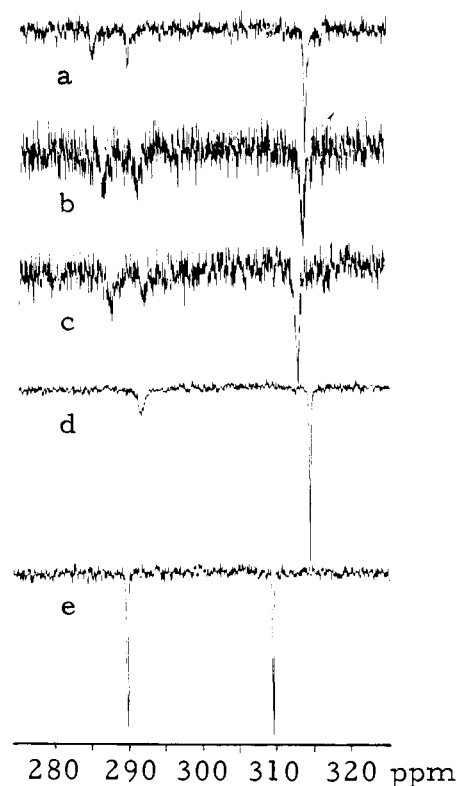**Figure 2.** Natural-abundance ^{15}N NMR spectra (parts per million upfield from H^{15}NO$_3$) of phenylhydrazine in various solvents (20% v/v) at 30 °C with gated ^{1}H noise decoupling: (a) in dimethyl sulfoxide, 220 transients; (b) in absolute ethanol, 300 transients; (c) in ethanol-water (1:1), 300 transients; (d) in 2,2,2-trifluoroethanol, 150 transients; (e) in trifluoroacetic acid, 100 transients.

Table I. Nitrogen-15 Resonances[a] in Phenylhydrazine at 30 °C

solvent	concn[b]	–^{15}NH–	–^{15}NH$_2$
none	100	288.6	313.8
triethylamine	20	288.6	314.2
dimethyl sulfoxide	20	288.3	314.4
chloroform	20	289.0	313.8
ethanol (absolute)	20	289.1	314.1
50% ethanol	20	290.3	312.8
2,2,2-trifluoroethanol	20	291.5	314.0
trifluoroacetic acid	20	289.4	309.2

[a] In parts per million *upfield* from external nitric acid (1.0 M 98% ^{15}N-enriched nitric acid in D$_2$O). [b] % v:v.

compared to neat phenylhydrazine. Successive upfield shifts of the –NH– resonance occur in the change from neat liquid to solutions in polar protic solvents capable of increasingly strong hydrogen-bond formation (but not protonation). The overall sequence chloroform to ethanol to 2,2,2-trifluoroethanol produced an overall upfield shift from the neat liquid of 2.9 ppm. The –^{15}NH$_2$ resonance position is much less sensitive to these changes in protic solvents.[23] Phenylhydrazine is expected to be extensively protonated at the –NH$_2$ group in trifluoroacetic acid (pK_a = −2.51[24]). The resulting downfield shift of 4.6 ppm for the –^{15}NH$_2$ compared to the small upfield shift of 0.8 ppm for the –NH– resonance is in accord with this conclusion.

Qualitative effects of solvents on the rates of proton-transfer reactions of **1** could be determined from the proton-coupled ^{15}N spectra (Figure 2). In trimethylamine, dimethyl sulfoxide, and absolute or 50% ethanol, the –NH$_2$ protons exchange faster than the –NH– protons because only a single broad resonance is observed for the –^{15}NH$_2$ group, whereas the –^{15}NH– resonance appears as a broad doublet. It is interesting that the line shapes are little changed when 50% ethanol is used

as solvent. More dramatic effects are seen for 2,2,2-trifluoroethanol and in trifluoroacetic acid. In both these solvents only two resonances are observed in the proton-coupled ^{15}N spectrum. The –^{15}NH– signal in the trifluoroethanol is very broad while the –^{15}NH$_2$ signal is sharp. Both lines are sharp in trifluoroacetic acid. In all solvents studied, except trifluoroacetic acid (where it cannot be determined), the rates of proton transfer for the −NH$_2$ are clearly much faster than for the –NH– group.

Why are the rates of proton transfer for the two types of nitrogens in phenylhydrazine so different? One reason is surely that the –NH$_2$ nitrogen is more basic than the –NH– nitrogen, and we have seen how acidic solvents accentuate exchange. The different rates of exchange in the absence of acids clearly rule out the *exclusive* operation of any kind of a bimolecular exchange mechanism giving two proton transfers, as suggested by Titov and co-workers,[21] eq 1. An alternate bimolecular mechanism (eq 2) involves only the –NH$_2$ group and has a
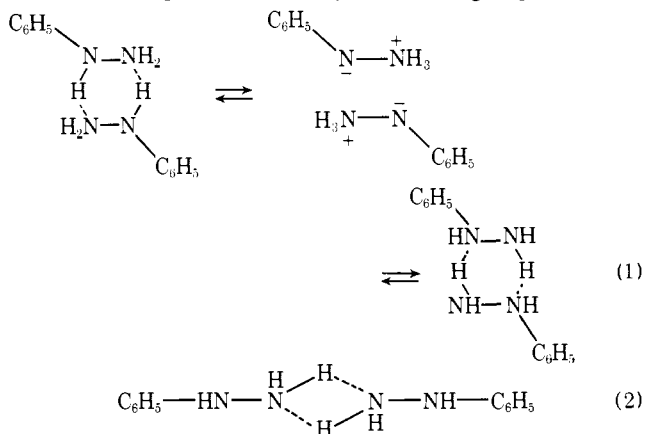
four-membered transition state similar to that proposed[25] to account for bimolecular proton exchange in ketimines. It is also possible that some exchange might occur as the result of autoprotolysis of 1. This seems unlikely to be important from the fact that the exchange is about equally fast in ethanol as in 50% ethanol.

References and Notes

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(21) E. V. Titov, L. M. Kapkan, and A. Yu. Chervinskii [*Theor. Eksp. Khim.*, **8**, 202–209 (1972)] have examined the 40-MHz ^{1}H NMR spectrum of 1 in dimethyl sulfoxide at room temperature and report that the –NH– signal had a line width at half-peak height twice that of the –NH$_2$ signal. The difference in line width was attributed to the fact that the –NH$_2$ group has two exchangeable protons and thus the probability of proton transfer from this group is twice that from the –NH– group. However, the difference we observe between the two rates of proton transfer is much too large to be explained by statistical considerations used by Titov and co-workers.

(22) The present experimental data are not suitable for obtaining meaningful values of $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$, even though the errors in $\Delta G^{\ddagger}$ are not large [F. A. L. Anet and R. Anet in "Determination of Organic Structures by Physical Methods", Vol. 3, F. C. Nachod and J. J. Zuckermann, Ed., Academic Press, New York, N.Y., 1971, pp 343–420; L. Lunazzi, A. Dondoni, G. Barbaro, and D. Macciantelli, *Tetrahedron Lett.*, 1079–1080 (1977)].

(23) The pK_a of 2,2,2-trifluoroethanol is 12.8 [B. L. Dyatkin, E. P. Mochalina, and I. L. Knunants, *Tetrahedron*, **21**, 2991–2995 (1965)], while that of 1 is 5.20.[17] Therefore, we do not expect that 1 will be very extensively protonated. On the other hand, there is every reason to expect 1 to be considerably hydrogen bonded in this solvent. Because hydrogen bonding with the solvent is not per se expected to increase the rate of exchange by either of the mechanisms shown in eq 1 and 2, it seems likely that, in trifluoroethanol, the predominant exchange mechanism is the result of acid catalysis.

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Characterization of Anisotropic Motion in Fatty Acid Micelles by Analysis of Transverse Relaxation in an AX$_2$ Nuclear Spin System

James H. Prestegard[*1a] and **David M. Grant**[1b]

Contribution from the Departments of Chemistry, Yale University, New Haven, Connecticut 06520, and the University of Utah, Salt Lake City, Utah 84112. Received November 28, 1977

Abstract: An attempt is made to characterize the motion of a methylene group analogue in a fatty acid micelle using line shapes from a spin coupled ^{13}C NMR spectrum. The analogue used is the fluorinated methylene of 6,6-difluorosodium myristate which under conditions of proton decoupling can be viewed as an AX$_2$ spin system with carbon-13 being the A spin. Expressions for line shapes in an AX$_2$ spin system in a non-extreme-narrowing limit are derived. It is observed that differences in widths of outer and inner lines of the ^{13}C multiplet are simply related to the cross-correlation spectral density for the two carbon–fluorine dipolar interactions. The observed sign and magnitude of the cross-correlation density is compared to predictions based on models having isotropic, anisotropic, or restricted internal motions.

Introduction

Motional processes can in principle be characterized at a molecular level through the measurement of longitudinal and transverse relaxation phenomena in magnetic resonance. These measurements sample spectral density functions associated with temporal fluctuations in the interactions responsible for relaxation. The discrete frequencies which are sampled depend in part on the magnetic field strength chosen for the experiment.

In simple cases, such as two isolated spins at fixed internuclear distance undergoing isotropic reorientation by a Brownian process, a single sampling such as a T_1 measurement is often sufficient to characterize the time scale of motion. In more complex cases, for example, reorientation of a methylene of a hydrocarbon chain in the semiordered array of a micelle or biological membrane, analysis is less straightforward. In these instances the assumption of isolated spin groupings may be invalid, and an adequate rotational model could require full consideration of both restricted and anisotropic molecular motion. Complete characterization of time parameters for such