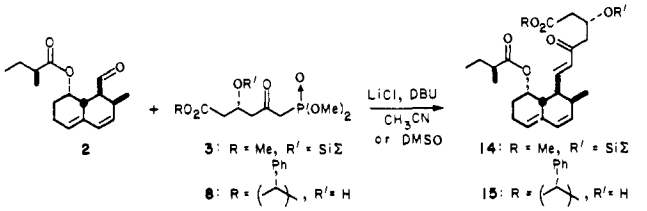
phenethyl ester and esterification of the resulting acid affords keto phosphonate **3** in 79% yield for the three-step sequence.

The enantiomerically homogeneous aldehyde **2** is obtained by Swern oxidation[21] of the corresponding alcohol (90–100% yield).[1] Reaction of aldehyde **2** with phosphonate **3** in the presence of lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[22] affords enone **14**. The reaction is quite clean; the only materials isolated are coupled product (35–60%) and recovered aldehyde (35–50%). Condensation of **2** and hydroxy keto phosphonate **8** also occurs under these mild conditions to give coupled β-hydroxy ketone **15** in 42% yield. It should be noted that the coupling procedure is sufficiently mild that the (*S*)-2-methylbutyryl moiety may be present, thus obviating the need to employ a protecting group for the C-8 hydroxyl. Condensation of **2** and hydroxy keto

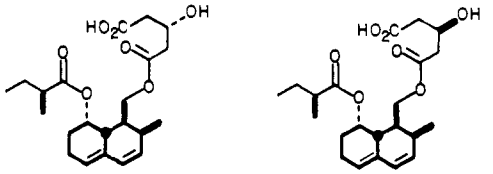


2 3: R = Me, R' = SiΣ 8: R = Ph, R' = H 14: R = Me, R' = SiΣ 15: R = Ph, R' = H

phosphonate **8** also occurs under these mild conditions to give coupled β-hydroxy ketone **15** in 42% yield.

Conversion of **14** to the natural product is summarized in Scheme II. Selective 1,4-reduction of the enone functionality is accomplished smoothly with triethylsilane and tris(triphenylphosphine)rhodium(I) chloride;[23] concentration of the reaction mixture and treatment of the residue with aqueous HF in acetonitrile furnishes hydroxy ketone **16** in 87% yield. Sodium borohydride reduction of **16** gives diastereomers **17** and **18** in a ratio of about 2:1. The diols are separated easily by HPLC, and the major product is lactonized with *p*-toluenesulfonic acid in benzene to give (+)-compactin (**1**) (70% yield).[9a]

Silyloxy diester **5** should have general utility. The three differentiated functional groups provide potential access to numerous optically active synthons from this readily available precursor. The enantiomer of **5** may easily be obtained by employing (*S*)-phenethyl alcohol for the anhydride opening. This technology has allowed us to prepare several enantiomerically homogeneous compactin analogues, including **19** and **20**. The interesting



19 20

biological activity of these substances, as well as that of the hydroxy acids derived from **14** and **16** and of 5-epicompactin (derived from lactonization of dihydroxy ester **18**), will be reported elsewhere.

Acknowledgment. This work was supported by a grant from the United States Public Health Service (GM 29815). T. R. acknowledges the U. C. Regents for a fellowship. We also thank Dr. A. G. Brown, of Beecham Pharmaceuticals, for a sample of compactin.

Supplementary Material Available: ^{1}H NMR spectral data for compounds **2**, **3**, **5–10**, and **14–18** (3 pages). Ordering information is given on any current masthead page.

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High-Resolution Nuclear Magnetic Resonance Spectroscopy of Quadrupolar Nuclei: Nitrogen-14 and Oxygen-17 Examples†

Jan M. Robert and Ronald F. Evilia*

Department of Chemistry, Unive, sity of New Orleans New Orleans, Louisiana 70148

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Approximately three-fourths of the more than 100 magnetically active isotopes have spin quantum numbers greater than $^1/_2$.[1] These nuclei have been unsuitable for high-resolution nuclear magnetic resonance examination because of severe line broadening caused by efficient spin relaxation via the interaction of their nuclear quadrupoles with fluctuating electric field gradients.[2] Because of the large number of quadrupolar nuclei that are difficult to study there is great interest in the minimization of quadrupolar relaxation.[3] The efficiency of quadrupolar relaxation, in the extreme narrowing limit, is directly proportional to the correlation time, τ_c, which is, in turn, directly proportional to the solution viscosity.[4,5] In this paper we report on the utilization of supercritical and near critical fluids to reduce the efficiency of quadrupolar relaxation such that high-resolution spectra are observed for quadrupolar nuclei.

Supercritical fluids are solvents whose viscosities can be up to 2 orders of magnitude less than typical liquids.[6] Hence, their use as solvents for NMR studies of quadrupolar nuclei can result in substantial resolution enhancements. Supercritical solvents have been shown to dissolve a wide variety of solutes of varying polarity and molecular weight such as benzoic acid, naphthalene, cobalt chloride, MW 400 000 biomolecules, nicotine, and many other solutes.[6,7] However, it is not presently possible to predict a priori the solubility of a particular solute in a particular solvent. In general, however, the solubility increases as the density of the supercritical phase increases.[6-8] In this work our goal was to evaluate the suitability of standard thick-walled tubes for use at the high pressures required (>50 atm) and to demonstrate that significant resolution enhancements are obtained. A systematic study of the dissolving power and resolution enhancements of various solvents for a variety of nuclei and molecular types and sizes is in progress. Those results will be reported in the future.

In this report we show the spectra and enhancements observed for ^{14}N and ^{17}O as well as ^{14}N–^{14}N, ^{1}H–^{14}N, and ^{14}N–^{17}O coupling. All samples were prepared as described in the figure legend and were pressure tested by heating to 60 °C prior to insertion in the NMR probe. The pressures developed are believed to be in considerable excess of the maximum value recommended by the manufacturer.[9] Spectra were acquired on a JEOL FX90Q

† Presented in part at 36th Pittsburgh Conference and Exposition, New Orleans, Feb, 1985.
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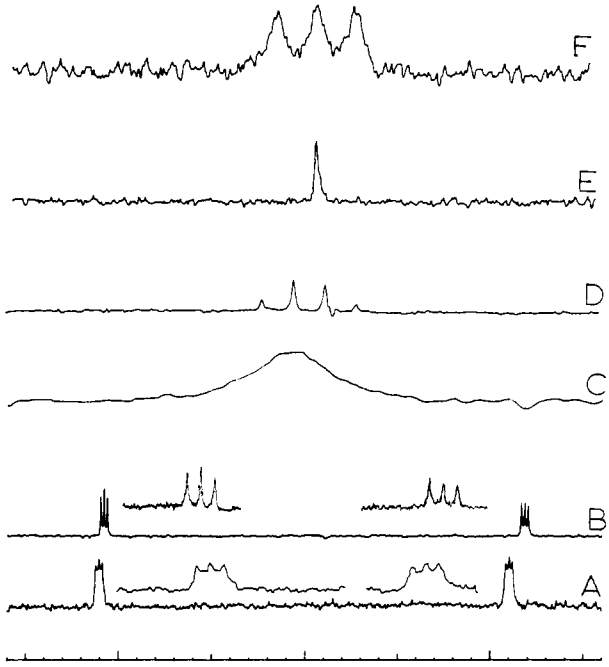

Figure 1. Natural abundance Fourier-transform NMR spectra in super and subcritical phases. All spectra are 800-Hz scans. Each division is 25 Hz. Samples prepared in sealed, 5-mm, thick-walled, glass NMR tubes (Wilmad 522 pp) by condensation of the desired quantity of solute from a vacuum rack and warming to the desired temperature. All tubes were pressurized while cold with helium to 1 atm to eliminate the inward pressure from the atmosphere during the sealing process and, thereby, produce a stronger seal. (A) ^{14}N spectrum of hexane saturated with nitrous oxide at 1 atm, 28 °C; (B) ^{14}N spectrum of supercritical nitrous oxide at 40 °C; (C) ^{14}N spectrum of 7 M aqueous NH_3; (D) ^{14}N spectrum of 0.5 M NH_3 in supercritical ethylene at 28 °C; (E) ^{17}O spectrum of subcritical carbon dioxide at 28 °C; (F) ^{17}O spectrum of subcritical nitrous oxide at 28 °C.

spectrometer at a field strength of 2.1 T.

The results of these preliminary experiments are shown in Figure 1. Spectrum B shows the ^{14}N spectrum of neat supercritical nitrous oxide at 40 °C ($T_c \sim 36.5$ °C). The ^{14}N–^{14}N coupling of 4.5 Hz is easily observable as the multiplets are resolved to the base line. The downfield line width varies slightly within the multiplets from a minimum of 0.6 Hz for the central line to 0.7 Hz for the outside lines of that multiplet. The line widths of the terminal nitrogen multiplet are 1.0 Hz. These differences are reproducible. Since these spectra were acquired without spinning and with an external lock, some instrumental line broadening is expected. The instrumental line width is estimated to be approximately 0.5 Hz from the line width of the ^{13}C proton-decoupled spectrum of acetaldehyde taken under similar conditions and corrected for the magnetogyric ratio difference. The T_1 relaxation times were measured by the inversion recovery method as 2.9 s for the downfield peaks (central nitrogen)[12,13] and approximately 0.35 s for the upfield peaks (terminal nitrogen).[12,13] Figure 1A shows the ^{14}N spectrum of nitrous oxide in hexane at 28 °C. Hexane is one of the least viscous solvents available (~0.29 cP at 28 °C) and, hence, yields one of the highest resolution spectra possible in liquids. It is not possible to accurately measure the line widths in the hexane spectrum because of severe overlap within the multiplets. A reasonable estimate appears to be about 6 Hz. A previous observation of the ^{14}N spectrum of N_2O in hexane saw no ^{14}N–^{14}N splitting.[14] Thus the resolution enhancement is a factor of about 10 assuming that no instrumental broadening is affecting spectrum B. If the expected instrumental line broadening is substracted, an even larger enhancement of a factor greater than 30 is estimated. Thus, the true T_2 is unknown. The central nitrogen multiplet, however, shows evidence of T_2 scalar relaxation of the second kind as manifested by the line width of the central peak[16] which indicates that $T_2 < T_1$ in this case.

Figure 1C,D shows a comparison of the proton-coupled ^{14}N spectrum of ammonia in water and supercritical ethylene at 28 °C (the critical temperature of ethylene is ~9 °C). The full width at half-height in ethylene of 6 Hz agrees fairly well with the measured T_1 of 58 ms, indicating that $T_2 \sim T_1$. The enhancement is a factor of 25. The enhancement predicted from the relative viscosities, however, is a factor of about 60.[15] This discrepancy may be explained by a specific interaction of water with NH_3 increasing the symmetry and resulting in a less efficient net relaxation. The concentration of ammonia in the ethylene sample is approximately 0.5 M. More concentrated solutions show rapid proton exchange and collapse of the quartet. No attempt was made to quantitatively study the exchange reaction kinetics.

Spectrum E shows the ^{17}O spectrum of carbon dioxide at a slightly subcritical temperature of 28 °C ($T_c = 31$ °C). The full width at half-height of this peak is 1.9 Hz. This line width is consistent with the 150-ms T_1 measured for this oxygen, indicating that $T_1 \sim T_2$. This appears to be equal to the longest previously measured ^{17}O T_1 and at least an order of magnitude longer than most ^{17}O T_1's.[17]

Figure 1F shows the ^{17}O spectrum of subcritical nitrous oxide (28 °C) obtained in an overnight run. The ^{14}N–^{17}O splitting of 37 Hz is clearly visible. It is assumed that this coupling corresponds to the ^1J coupling. The observed line width of 11 Hz is approximately 5 Hz wider than the broadening expected from drift of the external lock over the time period of the acquisition (19 h). Because of the long time required to acquire this spectrum, no attempt to measure the T_1 was made. If one assumes that $T_2 = T_1$ and that the true line width is approximately 5 H_z, T_1 is estimated to be approximately 60 ms.

Inspection of Figure 1F indicates that an additional splitting of ~5 Hz or greater should be visible at the resolution of this spectrum. Because no indication of the ^2J ^{14}N–^{17}O coupling is observed in this spectrum, we conclude that this coupling constant is less than 5 Hz. We observed approximately a 20% improvement in the ^{14}N line width when the nitrous oxide was heated above the critical point (40 °C). Unfortunately, the sample exploded when we attempted to acquire a ^{17}O spectrum at this temperature.[18] We were unable to obtain an ^{17}O spectrum of nitrous oxide or carbon dioxide in other solvents because of sensitivity limitations of our instrument.

Relatively few experimental measurements of supercritical phase viscosities have been reported. Those that have been measured primarily fall in the range of about 0.01 to 0.1 cP[15] while normal liquids fall in the range of about 0.2 to 2 cP.[19] Thus enhancements of from 2 to 200 can be expected in future studies. The correlation time of the nitrous oxide sample is estimated from the known quadrupole coupling constants[20] to be approximately 0.3 ps, as-

(9) The pressure developed in these samples are difficult to estimate accurately. Assuming that the density is linearly proportional to the pressure in the vicinity of the critical point we estimate that the maximum pressures developed is approximately 70 atm. The manufacturer of these tubes, Wilmad Glass Co., will not specify a pressure limit for which they will guarantee tube integrity because of variation in sealing-induced stress and surface scratches. However, if one assumes that the pressure limit is equal to a constant times the ratio of wall thickness to tube diameter[10] and a value of 133 atm for the constant,[11] 38 atm is calculated as the failure limit of the tubes.

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(18) All tubes were tested at 60 °C for several hours before inserting them in the probe. In spite of these precautions the nitrous oxide sample (P_c – 72 atm) exploded during an overnight run at 40 °C. The resulting explosion destroyed the probe insert and internal Dewar of the probe body. Great precautions and extensive testing of all tubes should be undertaken before placing a sample in the probe as there is a significant possibility for extensive damage. We are currently investigating quartz, fuzed alumina and other materials as potential high-resolution, high-pressure tube materials.

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suming that the asymmetry parameter is 0. By use of the known viscosity of CO_2, the oxygen quadrupole coupling constant of CO_2 is estimated to be about 3.4 MHz. While we could not find a literature value for CO_2 to which this can be compared, the value compares reasonably well to the 4.4 MHz reported for the ^{17}O quadrupole coupling constant of CO.[17]

In conclusion, we believe that these results demonstrate the potential of supercritical fluid solvents for the acquisition of high-resolution NMR spectra of quadrupolar nuclei. We are examining other nuclei and nonvolatile compounds and will report those results in future publications.

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N-Alkylporphyrin Formation during the Reactions of Cytochrome P-450 Model Systems†

Toshio Mashiko and David Dolphin*

Department of Chemistry
University of British Columbia
Vancouver, British Columbia, Canada V6T 1Y6

Taku Nakano and T. G. Traylor*

Department of Chemistry
University of California, San Diego
La Jolla, California 92093

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We have recently found that the electronegatively substituted hemin [5,10,15,20-tetrakis(2,6-dichlorophenyl)porphinato]iron(III) chloride (**1**) is an effective catalyst for the rapid oxidation of organic compounds with the oxidant iodosopentafluorobenzene (**2**).[1] Unlike all other hemin catalysts so far described, compound **1** is especially robust. We have, for instance, measured 10000 turnovers, at room temperature, for the epoxidation of norbornene! During our studies we noticed that the reaction solution was at first green. However, at the end of the reaction, the hemin was either destroyed (no or very resistant substrate), returned to its original spectrum (reactive substrate), or changed to a new species having a different spectrum. The latter observation occurred mostly with terminal olefins.

Recently, isolations of *N*-alkylporphyrins from the livers of animals treated with cytochrome P-450 inhibitors such as terminal olefins and acetylenes, monoalkylhydrazines, 4-alkyl-3,5-bis-(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridines, and 1-aminobenzotriazoles have been reported.[2] The *N*-alkyl hemes, derived from such suicide inhibitors, have been shown to result in hepatic porphyrias accompanied by the formation of the so-called "green pigment".

Since the hemin **1** can catalyze numerous turnovers, it might be used to explore the less frequent P-450 chemistry wherein suicide labeling of liver microsomes occurs approximately 1 in 200 turnovers. In this paper we report a reaction that closely mimics the self-catalyzed inactivation of P-450 enzymes.

In a typical experiment the oxidant **2** (1 g) was added in five portions, every 15 min, to a mixture of the hemin **1** (50 mg) and 4,4-dimethyl-1-pentene (**3**, 3 g) in dichloromethane (50 mL) and the mixture stirred at room temperature for 15 min.[3] The solution

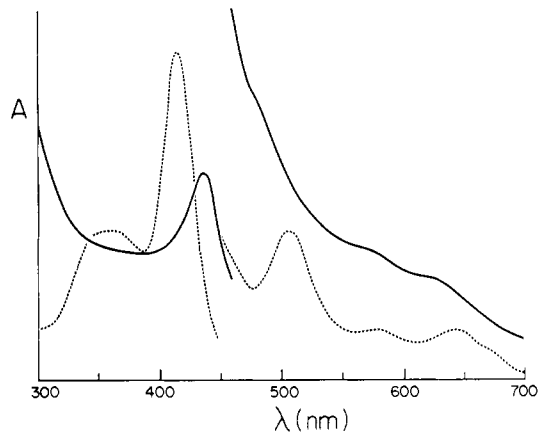

Figure 1. Visible absorption spectra, in CH_2Cl_2, of the reaction mixtures of hemin **1** and 4,4-dimethyl-1-pentene (**3**) before (---) and after (—) the addition of iodosopentafluorobenzene (**2**).

changed from brown to green-brown and the reaction was monitored by the disappearance of the Soret band of **1** (417 nm) coupled with the development of a new band at 435 nm (Figure 1). The remaining oxidant was destroyed with 10% aqueous sodium metabisulfite (10 mL), and the green product was demetalated in a mixture of concentrated HCl (1 mL) and acetic acid (20 mL). After chromatography the *N*-alkylporphyrin **4**[4] was isolated in 53% yield.

Metalation of **4** with $FeCl_2$ in refluxing THF[5] followed by workup in dichloromethane using 1% aqueous HCl and then H_2O gave the aquoiron(III) complex **5**.[6] Addition of the oxidant **2** to **5**, in dichloromethane, gave virtually the same optical spectrum (λ_{max} 435, 570, and 620 nm) as that of the initial green-brown reaction mixture. The analogous spectrum was obtained when a solution of **5**, in dichloromethane, which had been previously treated with 1% aqueous HCl[7] or saturated aqueous $NaHCO_3$[8]

† Presented in part at the 36th Southeastern Regional Meeting of the American Chemical Society, Raleigh, NC, Oct 24-26, 1984.

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(3) The principal product from the reaction is the epoxide. Thus during a catalytic experiment a solution of the hemin **1** (10^{-4} mmol) in 20 μL of dichloromethane was added to **2** (2 mg, 6.5×10^{-3} mmol) and **3** (0.2 mmol) in 80 μL of dichloromethane. The suspension was shaken until the oxidant dissolved. This required about 3 min. Analysis of the reaction mixture on GLC with Carbowax-20M showed that the yield of epoxide was close to 100% based upon **2**. A diluted sample of the reaction mixture had a Soret absorption at 435 nm. The same results were obtained when the reaction was run under argon in the absence of air.

(4) 21-(4,4-Dimethyl-2-hydroxypentyl)-5,10,15,20-tetrakis(2,6-dichlorophenyl)porphine (**4**): mp 285-286 °C (CH_2Cl_2-hexane). Anal. Calcd for $C_{51}H_{36}N_4OCl_8(CH_2Cl_2)_{0.45}$: C, 59.27; H, 3.57; N, 5.37. Found: C, 59.54; H, 3.66; N, 5.07. Calcd *m/e* for $^{12}C_{51}{}^1H_{36}{}^{14}N_4{}^{16}O^{35}Cl_8$: 1000.0397. Found: 1000.0355. UV λ_{max} (CH_2Cl_2, log ε) 428 (5.41), 521 (4.57), 555 (4.36), 608 (4.16), 665 (v weak) nm. This optical spectrum is comparable to that of the *N*-alkylporphyrin derived from protoporphyrin after the liver microsomal metabolism of allylisopropylacetamide: Ortiz de Montellano, P. R.; Mico, B. A.; Yost, G. S. *Biochem. Biophys. Res. Commun.* **1978**, *83*, 132-137. IR ν_{max} (KBr pellet) 3300 (NH), 3580 (OH) cm^{-1}. ^1H NMR (CD_2Cl_2) δ -4.48 (d of d, J_{AB} = 14.5, J_{AX} = 2.2 Hz, NCH_AH_B), -4.21 (d of d, J_{AB} = 14.5, J_{BX} = 11.1 Hz, NCH_AH_B), -2.28 (d of d, J_{AB} = 14.2, J_{AX} = 4.2 Hz, $CH_AH_BC(CH_3)_3$), -2.18 (br s, NH), -0.92 (d of d, J_{AB} = 14.2, J_{BX} = 6.1 Hz, $CH_AH_BC(CH_3)_3$), -0.68 (s, $C(CH_3)_3$), -0.54 (d, J = 5.6 Hz, OH), 0.64-0.72 (m, CHOH), 7.63-7.98 (m, phenyl H × 12), 8.32-8.43 (m, pyrrole H × 8).

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(6) [21-(4,4-Dimethyl-2-oxidopentyl)-5,10,15,20-tetrakis(2,6-dichlorophenyl)porphinato]aquoiron(III) chloride **5**: Anal. Calcd for $C_{51}H_{36}N_4O_2Cl_9Fe$: C, 55.10; H, 3.26; N, 5.04. Found: C, 55.23; H, 3.52; N, 4.84. UV λ_{max} (CH_2Cl_2, log ε) 425 (sh), 444 (4.70), 455 (sh), 556 (3.93), 599 (3.88), 640 (sh), 670 (sh). IR ν_{max} (KBr pellet) 1750, 3420 (H_2O) cm^{-1}. An example of the five-membered chelate ring formation of the N-substituent in an iron (*N*-alkylporphyrin) complex was shown by: Mansuy, D.; Battioni, J.-P.; Akhrem, I.; Dupré, D.; Fischer, J.; Weiss, R.; Morgenstern-Badarau, I. *J. Am. Chem. Soc.* **1984**, *106*, 6112.

(7) Chemical and spectroscopic properties of the species generated by this treatment suggest it is the chloride **6** (Scheme I): UV λ_{max} (CH_2Cl_2) 425, 442, 510, 580 nm; MS, *m/e* 1054 (M^+ - Cl).

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