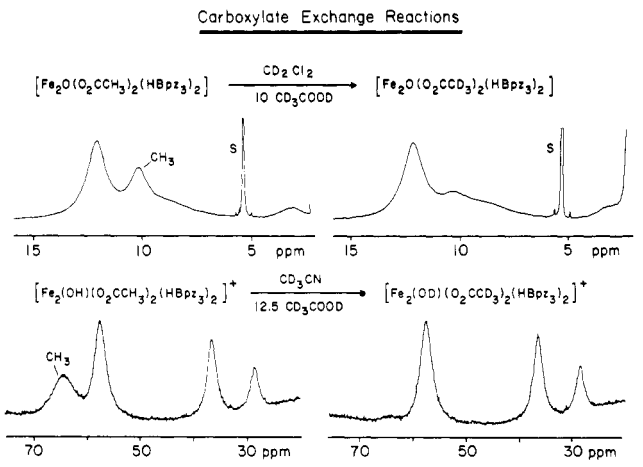

Figure 1. Carboxylate exchange reactions of **1** (top) and **2** (bottom) as monitored by ^1H NMR spectroscopy at 270 MHz. Assignments of the methyl (CH_3) resonances of the bridging acetate groups and the solvent (S) peaks in the top spectra are indicated.

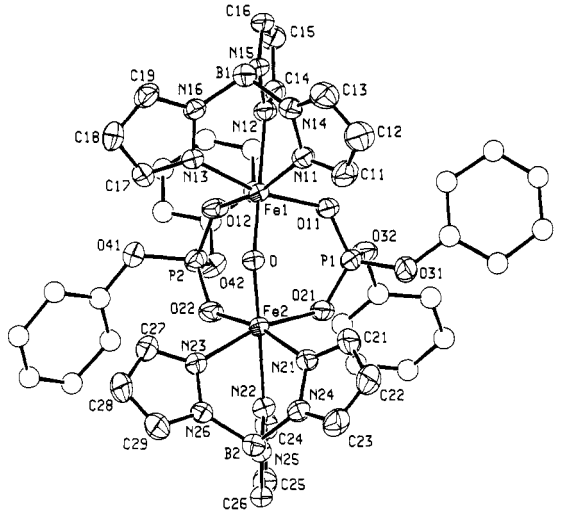

Figure 2. Structure of (μ-oxo)bis(μ-diphenylphosphato)bis{hydrotris(1-pyrazolyl)borato}diiron(III) (**3**) showing the 40% probability thermal ellipsoids and atom-labeling scheme. The phenyl ring carbon atoms are depicted as spheres with an arbitrary B value of 3.0 Å^2. For clarity, hydrogen atoms are omitted and the phenyl ring carbon atoms are not labeled. Selected interatomic distances (Å) and angles (deg) are as follows: Fe1-O 1.812 (5), Fe2-O 1.804 (5), Fe1-O11 2.059 (5), Fe1-O12 2.041 (5), Fe2-O21 2.045 (5), Fe2-O22 2.035 (5), Fe1-N11 2.137 (7), Fe1-N13 2.121 (6), Fe1-N12 2.213 (6), Fe2-N21 2.121 (6), Fe2-N23 2.142 (6), Fe2-N22 2.210 (7), Fe1···Fe2 3.337 (1), Fe1···P1 3.217 (2), Fe1···P2 3.210 (2), Fe2···P1 3.213 (2), Fe2···P2 3.205 (2), O11···O21 2.566 (7), O12···O22 2.576 (7), Fe1-O-Fe2 134.7 (3), O-Fe1-N12 179.8 (3), O-Fe2-N22 178.6 (2), N-Fe-N 81.0 (2)-85.3 (2).

observed in the structure of **1**.[1] The Fe···Fe distance of 3.337 Å and the Fe···P separations in the range 3.205-3.217 Å in **3** compare favorably with the corresponding distances of 3.36 and 3.27 Å determined by EXAFS measurements of a polynuclear Fe^{III}-ATP complex.[9]

Magnetic susceptibility measurements for a powdered sample of **3**[14] were made by using a SQUID-type susceptometer in the range 5-300 K. The data were well fit by the expression[15] for χ_M vs. T derived from the spin-exchange Hamiltonian, $H' = -2J\vec{S}_1\cdot\vec{S}_2$, with $S_1 = S_2 = {}^5/_2$ and $g = 2.0$, $J = -98$ cm^{-1}.[16] This value for the antiferromagnetic exchange interaction constant is somewhat less negative than found for **1** ($J = -121$ cm^{-1}),[1] perhaps owing to the slightly increased Fe-O_{oxo} distances in **3** and/or the lesser contribution to the exchange coupling of phosphate compared to acetate. The effective magnetic moment of 1.87 μ_B per iron at 295 K in the solid state agrees well with the value of 1.91 μ_B measured for **3** in CD_2Cl_2 solution with use of an NMR method.[16] The electronic spectrum of **3**[16] bears a marked resemblance to that of **1** with the principal differences being a shift of the band at 699 nm in **1** (in CH_2Cl_2) to 624 nm in **3** and a sharp decrease for **3** in the intensity of the band at 492 nm in **1**. Resonances in the ^1H NMR spectrum of **3**[16] in CD_2Cl_2 solution fall in three regions. The pyrazolyl ring proton resonances occur between -10.9 and -13.8 ppm whereas the phenyl ring proton resonances fall in the range -7.15 to -7.9 ppm. The B-H signal is found at approximately -2.5 ppm. These magnetic and spectroscopic results establish the structural integrity of **3** in solution.

In conclusion, we have observed facile exchange of the bridging carboxylate ligands in **1** and demonstrated the synthetic utility of such a reaction by preparing the novel diphenylphosphate-bridged analogue **3**. This latter complex may be relevant to several naturally occurring Fe^{III}-phosphate systems. The ability to exchange ligands into the bridging positions of the $\{Fe_2O(bridge)_2\}^{2+}$ core is a significant discovery, affording a route to the synthesis of a variety of new compounds of chemical and biological interest.

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Supplementary Material Available: Atomic positional and thermal parameters for compound **3**·$CHCl_3$ (7 pages). Ordering information is given on any current masthead page.

(14) The sample used for susceptibility measurements was powdered and dried under vacuum, and it analyzes well for **3**·0.80 $CHCl_3$. Anal. Calcd for $Fe_2C_{42.8}H_{40.8}B_2Cl_{2.4}N_{12}O_9P_2$: C, 44.79; H, 3.58; Cl, 7.41; N, 14.65. Found: C, 44.38; H, 3.62; Cl, 7.42; N, 14.72.

(15) O'Connor, C. J. *Prog. Inorg. Chem.* **1982**, *29*, 204-283 and references cited therein.

(16) Magnetic and spectroscopic data: IR (KBr cm^{-1}) 2500 (BH), 1594, 1491, 1088, 948; magnetic susceptibility, solid state [(T, K) μ_{eff}/Fe atom] (300) 1.89, (200) 1.46, (100) 0.79, (70) 0.46, (25) 0.03; solution (295 K, CD_2Cl_2) 1.91 μ_B per iron; UV-vis spectrum (CH_2Cl_2) λ 320 nm (ϵ_{Fe} 5830 cm^{-1} M^{-1}), 365 (5200), 478 sh (258), 624 (67); proton NMR spectrum (250 MHz, 295 K, CD_2Cl_2) δ 13.8, ~12.7 sh, ~10.9 sh, 7.9 sh, 7.37, 7.27, 7.15, ~2.5 (positive shifts are downfield of Me_4Si).

Total Synthesis of (+)-Compactin[1]

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Atherosclerosis is a condition in which abnormal amounts of lipids are deposited in certain arteries, resulting in intimal thickening. It manifests itself in circulatory occlusion, principally in the coronary, cerebral, and peripheral arteries. The ensuing complications lead to coronary heart disease, cerebrovascular disease, and some forms of peripheral vascular disease. These conditions are the major causes of death in the United States. In fact, the National Heart and Lung Institute Task Force on Arteriosclerosis reported in 1971 that approximately one-half of the deaths that occur in the United States each year are attributed to atherosclerosis.[2] It has long been known that there is a relationship between atherosclerosis and lipid metabolism. Since the condition results from abnormal deposition of lipids, there is

(1) Part 4 in the series "Synthetic and Biological Studies of Compactin and Related Compounds". For part 3, see: Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190.

(2) "Arteriosclerosis: A report by the National Heart and Lung Institute Task Force on Arteriosclerosis"; 2, Govt. Printing Office: Washington, DC, 1971; DHEW Publication [NIH] 72-219 Vol. 2.

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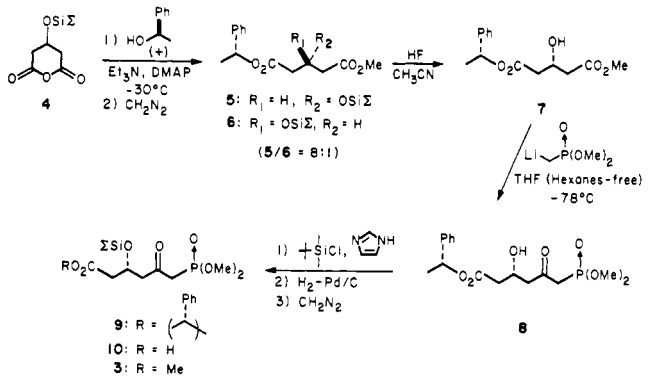
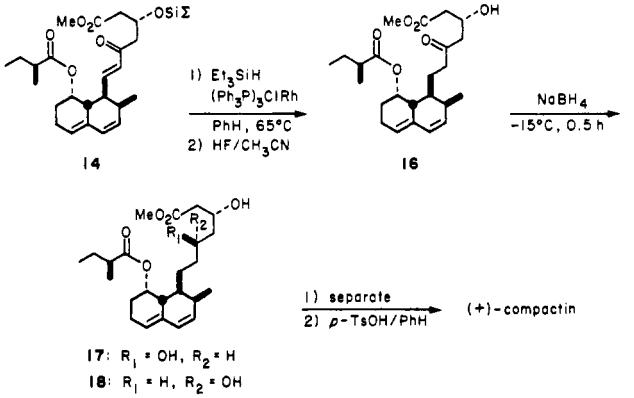
Scheme I

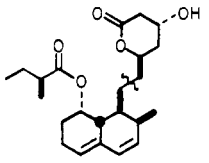


Scheme II



reason to suspect that the probability of contracting atherosclerosis is related to high levels of plasma lipids, particularly cholesterol in its various bound forms (VLD, LD, and HD lipoproteins). Indeed, hypercholesterolemia is known to be a primary risk factor for coronary artery disease.[3,4] In humans, more than one-half of total body cholesterol is derived from de novo synthesis.[5] The rate-limiting step in the mammalian biosynthesis of cholesterol, reduction of (hydroxymethyl)glutarylcoenzyme A (HMG CoA) to mevalonate, is regulated by the membrane-bound enzyme HMG CoA reductase.[6]

It is not surprising then that the isolation of the HMG CoA reductase inhibitor compactin in 1976[7,8] resulted in a flurry of

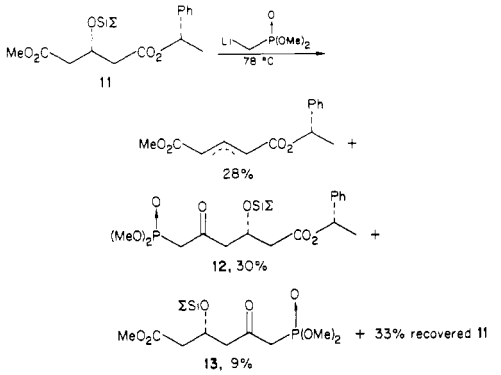


1

research directed at its synthesis and the synthesis of related compounds.[1,9-12] Numerous approaches and model studies have appeared that dissect **1** into a hexalin portion and a lactone synthon which would be coupled at a late synthetic stage.[1,10a,b,d-f,h,k-n,11,12] Such a convergent approach is particularly attractive in light of the hypocholesterolemic properties of **1**,[13] as it is conducive to the expedient preparation of simpler analogues for biological study. However, in spite of the appeal of this strategy, it has proven to be a difficult one to reduce to practice. The only successful syntheses employing this approach are syntheses of dihydrocompactin[11,12] and dihydromevinolin,[11] both of which utilize alkylation of a sulfone dianion for formation of the crucial bond. In this paper, we report a highly convergent synthesis of (+)-compactin in which the key reaction is the Wadsworth–Emmons coupling of aldehyde **2** and phosphonate **3**. The synthesis reported is a highly versatile one for the preparation of compactin stereoisomers and other structural analogues.

The synthesis of **3** is summarized in Scheme I. Treatment of anhydride **4**[14] with (*R*)-phenethyl alcohol and subsequent esterification with diazomethane furnishes optically active diesters **5** and **6** (65–75% yield). The anhydride opening proceeds with a surprisingly high degree of asymmetric induction; **5** and **6** are obtained in a ratio of 8:1.[15,16] After chromatographic separation, **5** is desilylated with HF to give hydroxy diester **7**. Condensation of **7** with lithium dimethyl methylphosphonate (650 mol%, 10 min, −78 °C) affords keto phosphonate **8** (43% yield),[17,18] attack occurring exclusively at the methyl ester. Silylation of **8** with *tert*-butylchlorodimethylsilane[20] followed by hydrogenolysis of the

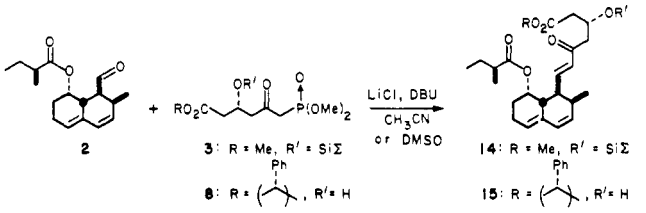
(3) Kannel, W. B.; Castelli, W. P.; Gordon, T.; McNamara, P. M. *Ann. Intern. Med.* **1971**, *74*, 1.
(4) Stamler, I. *Arch. Surg. (Chicago)* **1978**, *113*, 21.
(5) Grundy, S. M. *West. J. Med.* **1978**, *128*, 13.
(6) (a) Slakey, L. L.; Craig, M. C.; Beytia, E.; Briedis, A. V.; Feldbrugge, D. H.; Dugan, R. E.; Qureshi, A. A.; Subbarayan, C.; Porter, J. W. *J. Biol. Chem.* **1972**, *247*, 3014. (b) White, L. W.; Rudney, H. *Biochemistry* **1970**, *9*, 2725.
(7) (a) Endo, A.; Kuroda M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (c) Endo, A.; Tsujita, Y.; Kuroda M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31.
(8) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp. R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, *1165*.
(9) Total syntheses. Compactin: (a) Wang, N. Y.; Hsu C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538. (b) Hirama, M.; Uei, M. *Ibid.* **1982**, *104*, 4251. (c) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *Ibid.* **1983**, *105*, 1403. (d) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501. (e) Girotra N. N.; Wendler, N. L. *Ibid.* **1983**, *24*, 3687. Mevinolin: (f) Hirama M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811.
(10) Synthetic studies: (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Funk R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (c) Deutsch, E. A.; Snider, B. B. *Ibid.* **1982**, *47*, 2682. (d) Prugh; J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, *23*, 281. (e) Yang, Y.-L.; Falck, J. R. *Ibid.* **1982**, *23*, 4305. (f) Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popják, G. *Ibid.* **1982**, *23*, 4747. (g) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750. (h) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* **1983**, *24*, 1373. (i) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991. (j) Deutsch, E. A.; Snider, B. B. *Tetrahedron Lett.* **1983**, *24*, 3701. (k) Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Ibid.* **1984**, *25*, 1655. (l) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Ibid.* **1984**, *25*, 2101. (m) Prasad, K.; Repic, O. *Ibid.* **1984**, *25*, 2435. (n) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3994.
(11) (a) Yang, Y.-L.; Manna S.; Falck, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 3811. (b) Falck J. R.; Yang, Y.-L. *Tetrahedron Lett.* **1984**, *25*, 3563.
(12) Funk, R. L.; Zeller, W. E. *J. Am. Chem. Soc.*, submitted for publication.
(13) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi J.; Takeda, R. *N. Engl. J. Med.* **1981**, *305*, 478.
(14) Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657.
(15) The absolute configurations of **5** and **6** were established by conversion to the corresponding phenethylamides.[14]
(16) For a recent report on the opening of related prochiral anhydrides with chiral amines, see: Kawakami, Y.; Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1984**, *779*.
(17) The modest yield is due to competing retro-aldol reaction of the alkoxide of **7**.
(18) If the phosphonate condensation is performed with the silyl ether **11**,[19] a substantial quantity of elimination products is produced:



Furthermore, the reaction proceeds with only modest regioselectivity; **12** and **13** are isolated in a ratio of less than 3:1.

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

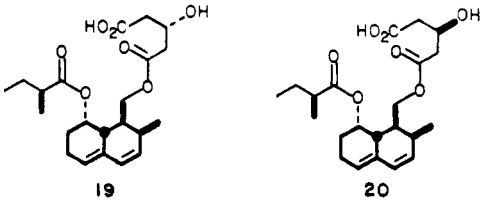
The enantiomerically homogeneous aldehyde **2** is obtained by Swern oxidation[21] of the corresponding alcohol (90–100% yield).[1] Reaction of aldehyde **2** with phosphonate **3** in the presence of lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[22] affords enone **14**. The reaction 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



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



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.

(19) Compound **11** is obtained analogously to its enantiomer **5** by using (*S*)-phenethyl alcohol to open anhydride **4**.
(20) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(21) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1977**, *42*, 2480.
(22) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(23) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, 5035.

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

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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.
(1) Wehrli, F. W. *Annu. Rep. NMR Spectrosc.* **1979**, *9*, 125–214.
(2) (a) Abragam, A. "The Principles of Nuclear Magnetism"; Clarendon Press: Oxford, 1961; p 269. (b) Day, R. S.; Reilley, C. N. *Anal. Chem.* **1966**, *38*, 1323–1330.
(3) (a) Wehrli, F. W. *Annu. Rep. NMR Spectrosc.* **1979**, *9*, 126–220. (b) Siddall, T. H.; Flurry, R. L. *J. Magn. Reson.* **1980**, *39*, 487–497. (c) Siddall, T. H.; Flurry, R. L. *J. Magn. Reson.* **1981**, *43*, 357–372. (d) Siddall, T. H. *J. Phys. Chem.* **1982**, *86*, 91–96.
(4) In ref 2a, p 314.
(5) Anderson, J. A.; Astheimer, R. J.; Odom, J. D.; Sneddon, L. G. *J. Am. Chem. Soc.* **1984**, *106*, 2275–2283.
(6) (a) Randall, L. G. *Sep. Sci. Technol.* **1982**, *17*, 1–118 and references therein. (b) Smith, R. D.; Udseth, H. R. *Anal. Chem.* **1983**, *55*, 2266–2272.
(7) (a) Hannay, J. B.; Hagarth, J. *Proc. R. Soc. London* **1879**, *29*, 324–326. (b) Stahl, E.; Schilz, W.; Schultz, E.; Willing, E. "Extraction with Supercritical Gases"; Schneider, G. M., Stahl, E., Wilke, G., Eds.; Verlag Chemie: Berlin, 1980; pp 93–114. (c) McLoren, L.; Myers, M. N.; Giddings, J. C. *Science (Washington, D. C.)* **1968**, *159*, 197–199. (d) Albaugh, E. W.; Borst, D.; Talorico, P. C. Abstr. *Pap—Am. Chem. Soc.* **1983**, *185th*, ORPL 135.
(8) (a) Giddings, J. C.; Meyers, M. N.; McLoren, L.; Kelley, R. A. *Science (Washington, D.C.)* **1968**, *162*, 67–73. (b) Peters, S.; Brunner, G. "Extraction with Supercritical Gases"; Schneider, G. M, Stahl, E., Wilke, G., Eds.; Verlag Chemie: Berlin, 1980; pp 141–154.

0002-7863/85/1507-3733$01.50/0