

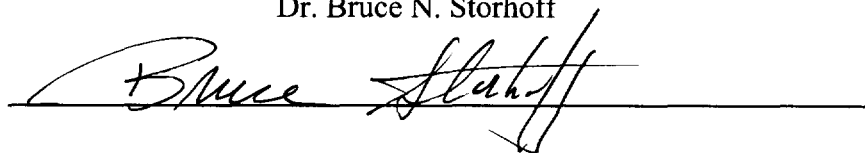
**THE SYNTHESIS AND STUDY OF PHOSPHINE FUNCTIONALIZED CROWN
ETHERS WITH FLUORINE IN POSITIONS TO ASSIST WITH ION BINDING.**

An Honors Thesis

By

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Thesis Advisor
Dr. Bruce N. Storhoff

A handwritten signature in black ink, reading "Bruce Storhoff", is written over a solid horizontal line. The signature is cursive and stylized.

Ball State University

Muncie, Indiana

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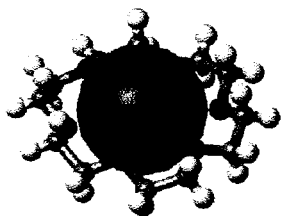
In addition, I would also like to thank the Ball State University chemistry department for all of the extra work that is put into the summer research program. I've gained a wealth of knowledge from the experience, and I am truly grateful. I would also like to thank the American Petrochemical Research Fund for providing the financial backing for this research.

Abstract

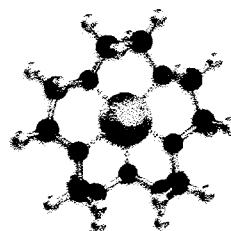
Phosphine-crown ethers based on 1,3-xylyl-18-crown-5 units with fluorine atoms in the 2-positions and P(III) donors in the 5-positions have been synthesized and characterized. The starting materials for the crown ether portions of the molecules were 4-bromo-2,6-dimethylaniline, NaBF₄, NBS and tetraethylene glycol. The P(III) moieties have been introduced by generating the carbanions at the 5-positions by way of Br-Li exchange reactions. The procedures used during the synthesis along with the spectroscopic characteristics of the intermediates and final products will be discussed.

Introduction

In 1967, the American chemist Charles John Pedersen synthesized the first crown ethers¹, defined as uncharged macroheterocyclics with several ether linkages containing the repeating unit $(-O-CH_2-CH_2-)_n$. Being cyclic compounds, every crown has a center cavity into which the oxygen atoms are pointed towards, and the crown binds to metal ions or organic molecules that match the size of that cavity^{2,3}. Crown ethers are named [X]-crown-[Y], where X is the total number of atoms in the ring, and Y is the number of oxygen atoms in the ring. Below are examples of an 18-crown-6 molecule with a potassium ion bound within the center cavity, and a 15-crown-5 molecule with a sodium ion in the center cavity.



18-crown-6 with Potassium Ion



15-crown-5 with Sodium Ion

The 18-crown-6 molecule binds potassium ions strongly because the inner diameter of the central cavity is very close to the ionic diameter of potassium. The 15-crown-5 molecule binds strongly to a sodium ion because the crown has an inner diameter of 1.7 to 2.2 angstroms, and a sodium ion has an ionic diameter of 1.8 angstroms³.

In this relationship, the crown ether is called the host and the species it binds is called the guest. The host and guest will not react because the ether linkages are chemically inert, but the crown is able to hold ions because of the interaction of the positively charged guest ion with the nonbonding electrons of the oxygens that point into the crown ether cavity³.

Another remarkable property of crown ethers is that they allow certain compounds that are not soluble in non-polar solvents to be dissolved in non-polar solvents. This allows reactions to occur in non-polar solvents that would otherwise only be able to occur in polar solvents. In this sense, crown ethers can be used as phase transfer catalysts, which are compounds that catalyze a reaction by transferring a reagent into a phase, organic or aqueous, in which it is needed⁴.

Phosphorous (III) ligands have the general formula PR_3 where R is a halide, hydrogen, phenyl ring, etc⁵. They are neutral, two electron donors that bind to transition metals through their lone pairs⁶. As a class of compounds, they interact with a variety of transition metals, forming complexes such as $Rh(Cl)(PR_3)_3$ which catalyze a range of reactions including the hydrogenation of olefins^{5,7,8}.

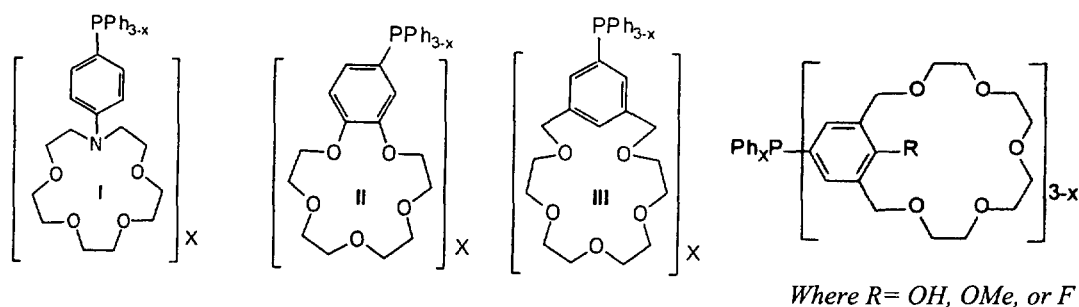
The binding abilities of phosphine ligands depend on both the steric and electronic attributes of the ligand, but since these ligands are easily synthesized, one can control both the bulk and electronic properties of the ligand, making those properties tunable^{5,9,10}. Furthermore, the electronic character of phosphines has two main features. The first is the sigma donation of the phosphine lone pair to an empty orbital on the metal. The

second is the backdonation of electrons from a filled metal orbital to an empty orbital (probably a d) on the phosphine ligand.

As electron withdrawing, or electronegative, groups are placed upon the phosphorous atom, the sigma donating effect of the phosphine ligand tends to decrease. Simultaneously, the energy of the sigma* electrons on phosphorous are lowered in energy, providing an increase in backbonding ability⁵. Therefore, the backbonding in a phosphine metal complex can also be tuned by binding compounds with various electro negativities.

Phosphines functionalized with crown ethers

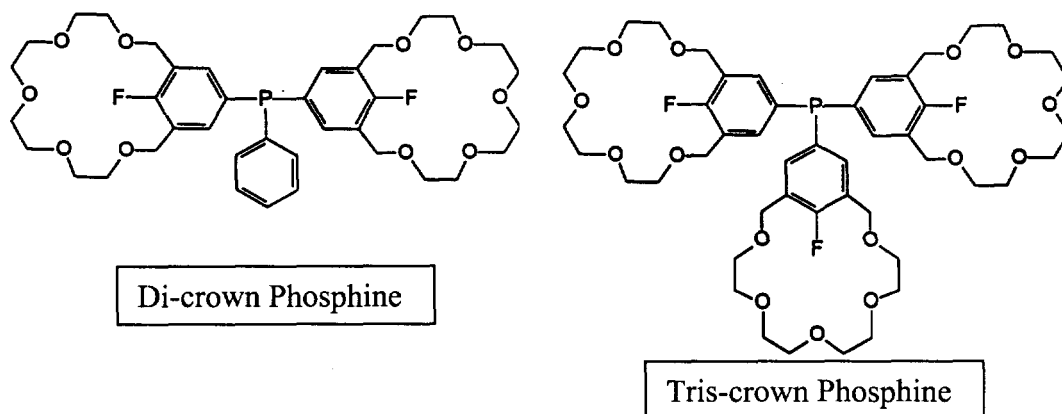
Objectives and Rationale of Study. My research is part of a program to synthesize and completely characterize the following compounds:



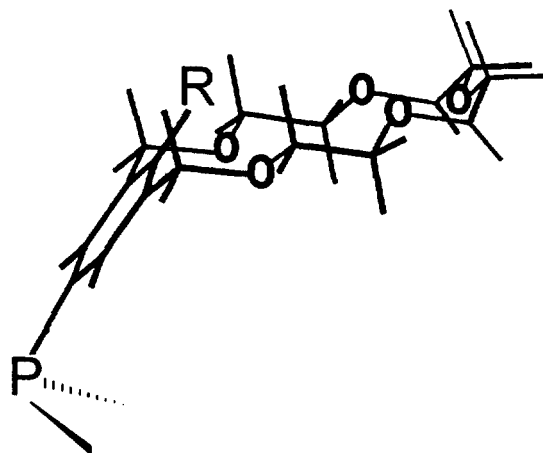
The common characteristic that these compounds share is a benzene ring and a crown ether. Since the donor and steric properties of the P(III) centers in phosphines depend upon the nature of the attached groups, it is proposed that crown ether groups attached to phosphines could be used to do any of the following:

- Increase the water solubility of the phosphines which might lead to novel donor catalysts that can function in aqueous and or non-aqueous solvents³.
- Bind alkali or alkaline earth metals which in turn could decrease the donor ability of the P(III) centers. This “tunability” has been demonstrated for related systems¹¹.
- Provide sites that could be used to recover phosphine-based catalysts from solutions. For example, polymers with ammonium ions could precipitate or immobilize such complexes.

The focus of this project was to synthesize the first examples of these molecules:

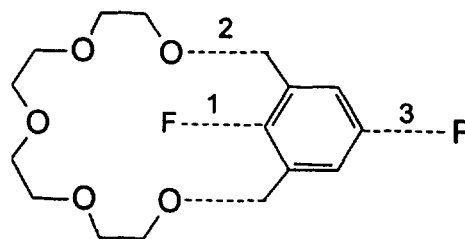


The reason for incorporating a fluorine in the 1 position of the benzene ring is that this atom can serve as an additional donor to hold alkali metals in the crown pocket. A representation of the orientation of the groups, $R=F$, is shown below^{12,13}.



The fluorine will also test the idea that the donor atoms positioned on the phenyl rings will increase the potential for information transfer to the P(III) center of systems where the crown ether binds to an ion. A common method for testing for this information transfer is to measure the nickel carbonyl stretches in $Ni(CO)_3PR_3$ complexes¹⁴.

Bonds to be Formed



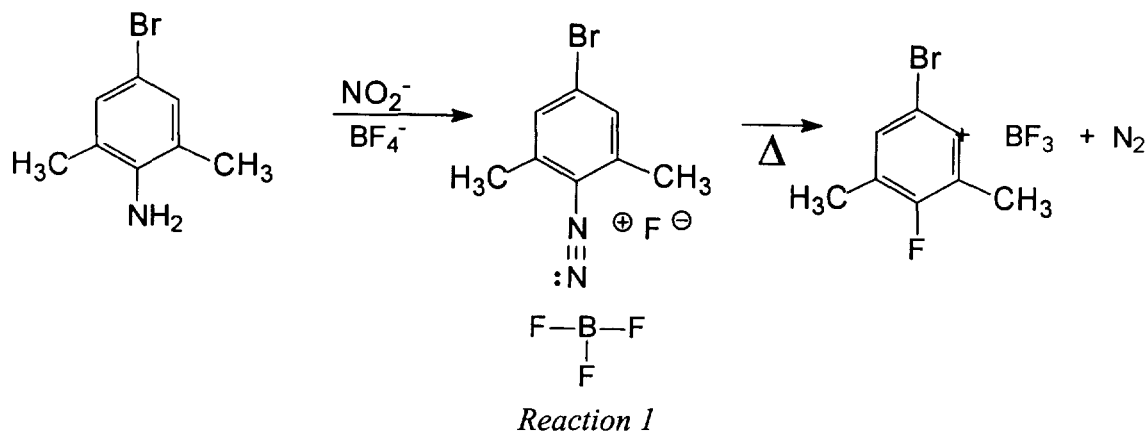
For the synthesis of these di and tris crowns, three major bonds need to be formed. The first involves bonding a fluorine atom in the #4 position of the 4-bromo-2,6-dimethylaniline. The second bond is attaching the ends of the tetraethylene glycol to the #2 and #6 positions on the benzene ring to form the crown ether portion of the target molecule. Finally, the third bond attaches the phosphorous atom to the #1 position on the benzene ring.

Experimental Methods

Reagents and Materials. 4-Bromo-2,6-dimethylaniline, triphenyl phosphite, n-bromosuccinimide, tetraethyleneglycol, sodium tetrafluoroborate, sodium nitrite, carbon tetrachloride, methylene chloride, and tetrahydrofuran (THF) were purchased from Aldrich Chemical Company.

To ensure that it was anhydrous, the THF was distilled over sodium metal and benzophenone prior to use. Carbon tetrachloride and triphenyl phosphite were also distilled over molecular sieves before use. N-bromosuccinimide (NBS) was purified through a recrystallization process which involved dissolving 100 g of stock NBS crystals into 1000 ml of boiling distilled water in a 4000 ml Erlenmeyer flask. Upon dissolving all of the NBS crystals, the flask was placed in an ice bath in a dark room for recrystallization due to the light sensitivity of NBS.

Formation of the Xylyl Group Precursor. 4-bromo-2,6-dimethylaniline (49.5 g, 0.247 mol) was dissolved in 60 ml of cooled, concentrated HCl, and allowed to stir for a few hours. Sodium nitrite (16.5 g, 0.239 mol) was dissolved in 150ml of distilled water, and placed into a separatory funnel. The NaNO₂ solution was added dropwise to the 4-bromo-2,6-dimethylaniline solution over the course of two hours while stirring. Sodium tetrafluoroborate (37.5 g, 0.25 mol) was dissolved in 100 ml of distilled water, and was added to the already stirring mixture to form the intermediate shown in the reaction scheme below.

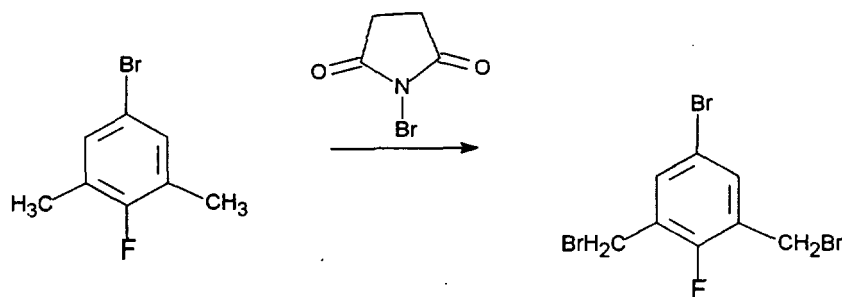


This product of this Scheimann reaction was washed with 100 ml of ether, placed under vacuum filtration, and further dried by storing in an evacuated desiccator overnight in a refrigerated environment.

Once dry, this solid was placed into a 250 ml round bottom flask fitted with a condenser. The flask was then momentarily heated with a flame in order to begin the decomposition reaction. Upon complete decomposition, the round bottom flask was

cooled and connected to a high vacuum system where distillation was resumed and carried out at around 60° Celsius. The average yields were around 40 %.

Formation of the Tribromide. Under an argon environment, the 4-Bromo-2,6-dimethyl-1-fluoroaniline (24.86 g, 0.122 mol) was added to NBS (47.9 g, 0.27 mol) and 350ml of freshly distilled carbon tetrachloride in a 500ml round bottom flask. With a heating pad and a magnetic stir bar, the flask was fitted with a condenser and allowed to reflux for overnight. Because of its light sensitivity, an external light source was used to aid the decomposition of NBS, making it more likely to lose a bromine free radical.

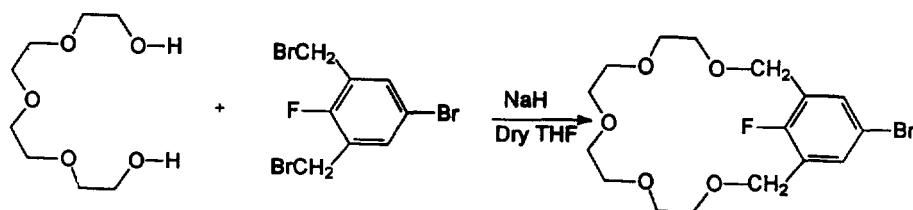


Reaction 2

The resulting mixture was filtered into another 500ml round bottom flask, washed with methylene chloride, and condensed. This reddish compound was then stirred and brought to a boil with 75 ml of cyclohexane to re-crystallize, then placed in a refrigerated environment overnight. The average yields for this reaction were around 40 percent.

Synthesis of Fluorobenzyl Crown Ether. Tribromofluorobenzene (12 g, 0.033 mol) was placed under high vacuum for 24 hours prior to the reaction and all glassware was oven dried. An argon environment was used throughout this step of the experiment. THF (500 ml) was placed in a three-neck, one-liter flask. Sodium hydride (2.80 g, 0.043 mol) was washed twice with distilled pentane and placed, by syringe, in the one liter, three-neck flask with the distilled THF. The tribromide was mixed with ~30 ml of THF and placed into a dropping funnel that was fitted to one of the three necks of the one liter flask. Tetraethyleneglycol was added to the THF-tribromide mixture in the dropping funnel. The remaining two necks of the one-liter flask were fitted with a glass stopper, and a reflux condenser with an argon fitting at the top.

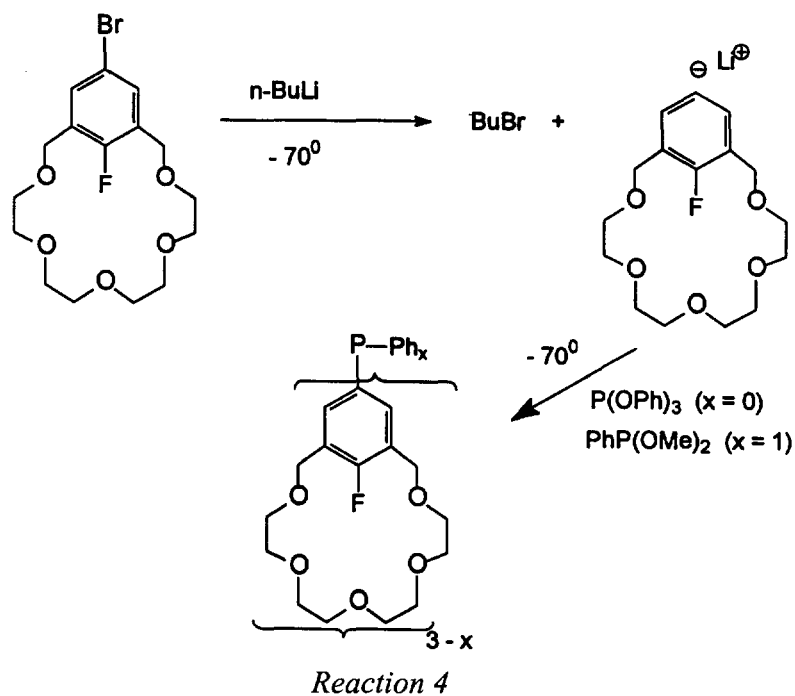
The tetraethyleneglycol-tribromide solution was added dropwise about every four to five seconds, a magnetic stirrer was used, and heat was applied to the system until a gentle reflux was achieved. After the reaction had refluxed for 24 hours, a couple of milliliters of water were added to ensure the sodium hydride had completely reacted. Below is a schematic diagram of the overall reaction.



Reaction 3

The mixture was filtered using a vacuum filtration apparatus, washed with dichloromethane, and condensed under vacuum. The resultant orange oil was then dissolved in a separatory funnel with ~150 ml of dichloromethane and washed with ~100 ml of distilled water. Allowing this mixture to separate overnight, the bottom layer was collected, and the top layer was washed an additional three times with 100 ml of dichloromethane. These dichloromethane layers were combined and condensed into an orange liquid. Four 100 ml portions of hot heptane were used to extract the crown from the by-products. The crown was further purified by dissolving 5.0 g of crown in 5.0 ml of methylene chloride, and this was placed on top of a 50 mm column packed with 90mm of active alumina. The crown was then eluted with a mixture of 80% ethyl acetate, 15% acetone, and 5% methylene chloride. The solvent was then removed under vacuum.

Preparation of the Fluorocrown Phosphine. All glassware was oven dried and the reaction takes place under argon. Fluorobenzyl crown ether (8.05g, 0.0205 mol) was added to ~250 ml of dry THF in a one liter, three neck flask. The flask was then placed in a cold bath of liquid nitrogen and ethyl acetate. An excess of n-butyl lithium was added via an oven-dried syringe over the course of about a half hour. The reaction was then allowed to stir for an additional half hour¹⁵. The triphenylphosphite (1.73 ml, 0.0205 mol) was also added via syringe over 15 minutes and the mixture was allowed to stir overnight. Upon completion, a few milliliters of distilled water were added to the mixture to ensure that there was no excess of butyl lithium. The solution was then condensed and yellow oil resulted. The overall reaction is as follows:



The yellow oil was washed with ~200 ml of methylene chloride and ~100 ml of distilled water. The bottom layer in the separatory funnel contained the phosphine crown, so it was drained and collected. Three additional methylene chloride washes were collected and all of these layers were combined and condensed. The product was purified by chromatography on a silica gel column using 95% ethyl acetate and 5% acetone.

Discussion

Throughout the preparation of each step in this synthesis, information was obtained on the purity of the compounds based upon the product yields of the subsequent reactions. While the purity of the products can be and was checked through the use of ^1H , ^{13}C and ^{31}P NMR spectroscopy, the relatively low yields of certain reactions suggested that an additional purification step was needed. As indicated above, this involved using an alumina column which removed the impurities, assumed to be OH containing compounds.

For the synthesis of the 4-bromo-2,6-dimethyl-1-fluoroaniline and tribromide, the percent yields were around 40 percent for each reaction run. The percent yield for the synthesis of the fluorobenzyl crown ether appeared to be high at first analysis, and ^1H NMR showed a reasonably acceptable spectrum. However, when the fluorobenzyl crown ether was used in the synthesis of the fluorocrown phosphine, an extremely low yield was obtained for that reaction.

In order to run a successful synthesis of the fluorocrown phosphine, the Li-Br substitution in reaction 4 is vital. Since yields were low, something was using up the butyl lithium. While analyzing the possible sources of error, we concluded that the fluorobenzyl crown ether was the cause of the low yield. We have not yet repeated the Li-Br step using the purified material, but an NMR analysis shows that the bromo-fluorocrown is much more pure after the additional step.

It should be noted, however, that small quantities of the tris-crown phosphine shown on p3 has been prepared and isolated as shown by proton and phosphorous spectra shown in the appendices.

REFERENCES

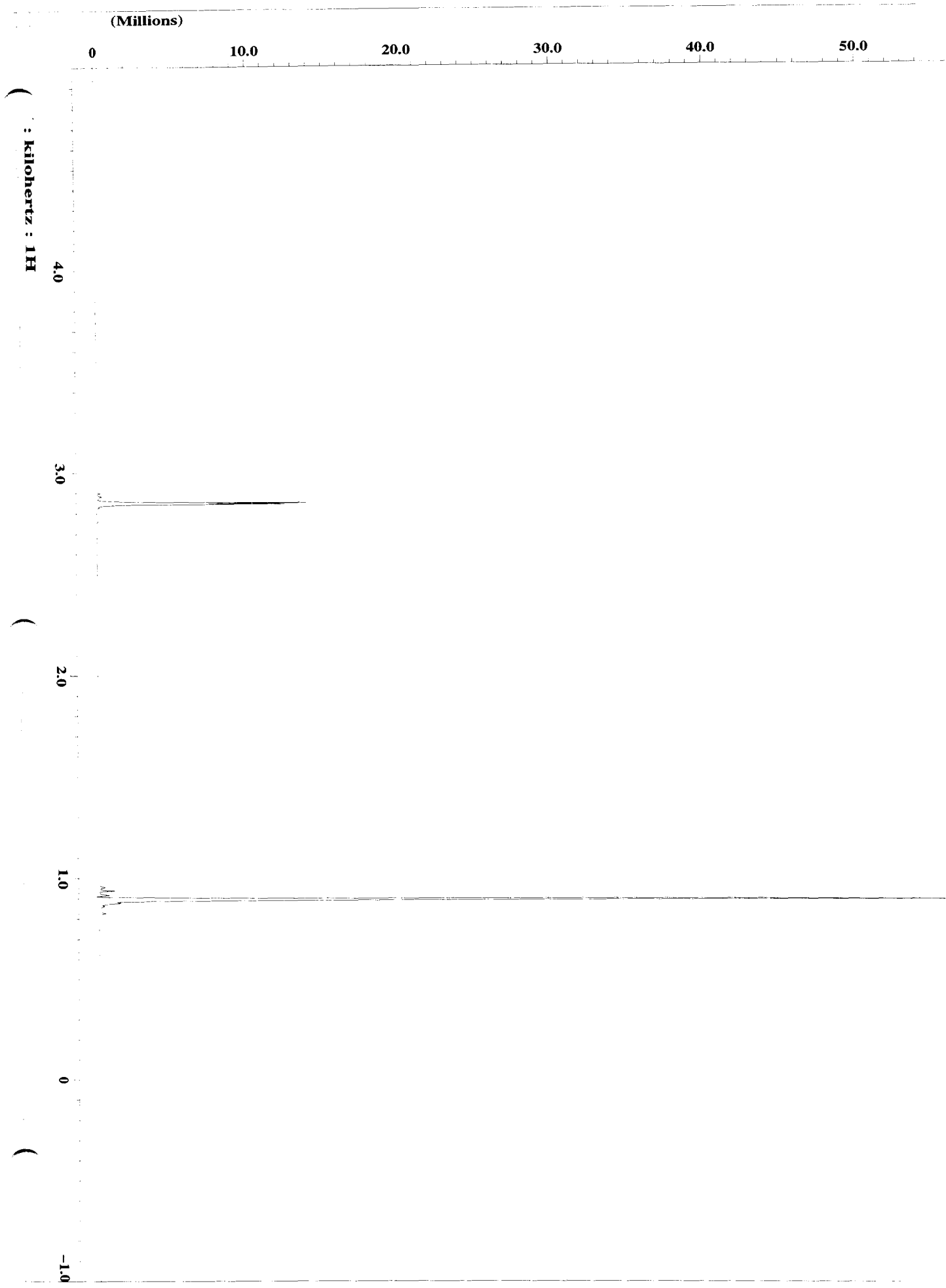
1. Pedersen, C. J. *Journal of the American Chemical Society* **1967**, *89*, 7017.
2. Pedersen, C. J. *Journal of the American Chemical Society* **1970**, *92*, 386.
3. Weber, E.; Toner, J. L.; Goldberg, I., Vogtle, F.; Laidler, D.; Stoddard, J. F.; Bartsch, R. A.; Liotta, C. L. *Crown Ethers and Analogs*; John Wiley and Sons: New York, 1989.
4. Pederson, C. J.; Frensdorff, H. K. *Angewante. Chemie, International. Edition* **1972**, *11*, 16.
5. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books: Mill Valley, CA, 1987.
6. McAuliffe, C. A. In *Comprehensive Coordination Chemistry* Wilkinson, G., Gillard, R. D., McCleverty, J. A, Ed.; Pergamon Press: New York, 1987, Vol. 2; pp 989- 1066.
7. Hayashi, T. *Accounts of Chemical Research* **2000**, *33*, 354-362.
8. Burk, M.. *Accounts of Chemical Research* **2000**, *33*, 363-372.
9. Tolman, C. A. *Journal of the American Chemical Society* **1970**, *92*, 2953.
10. Tolman, C. A. *Chemical Reviews* **1977**, *77*, 313.
11. Barg, L. A.; Byrn, R. W., Carr, M. D., Nolan, D. H.; Storhoff, B. N.; Huffman, J. C. *Organometallics* **1998**, *17*, 1340-46.
12. Goddard, R. I.; Niemeyer, C. M.; Reetz, M. T. *Acta Crystallographica, Section C* **1993**, *49*, 402- 404.
13. McKervey, M.A.; Mulholland, D.L. *Journal of the Chemical Society, Chemical Communications* **1977**, 438.

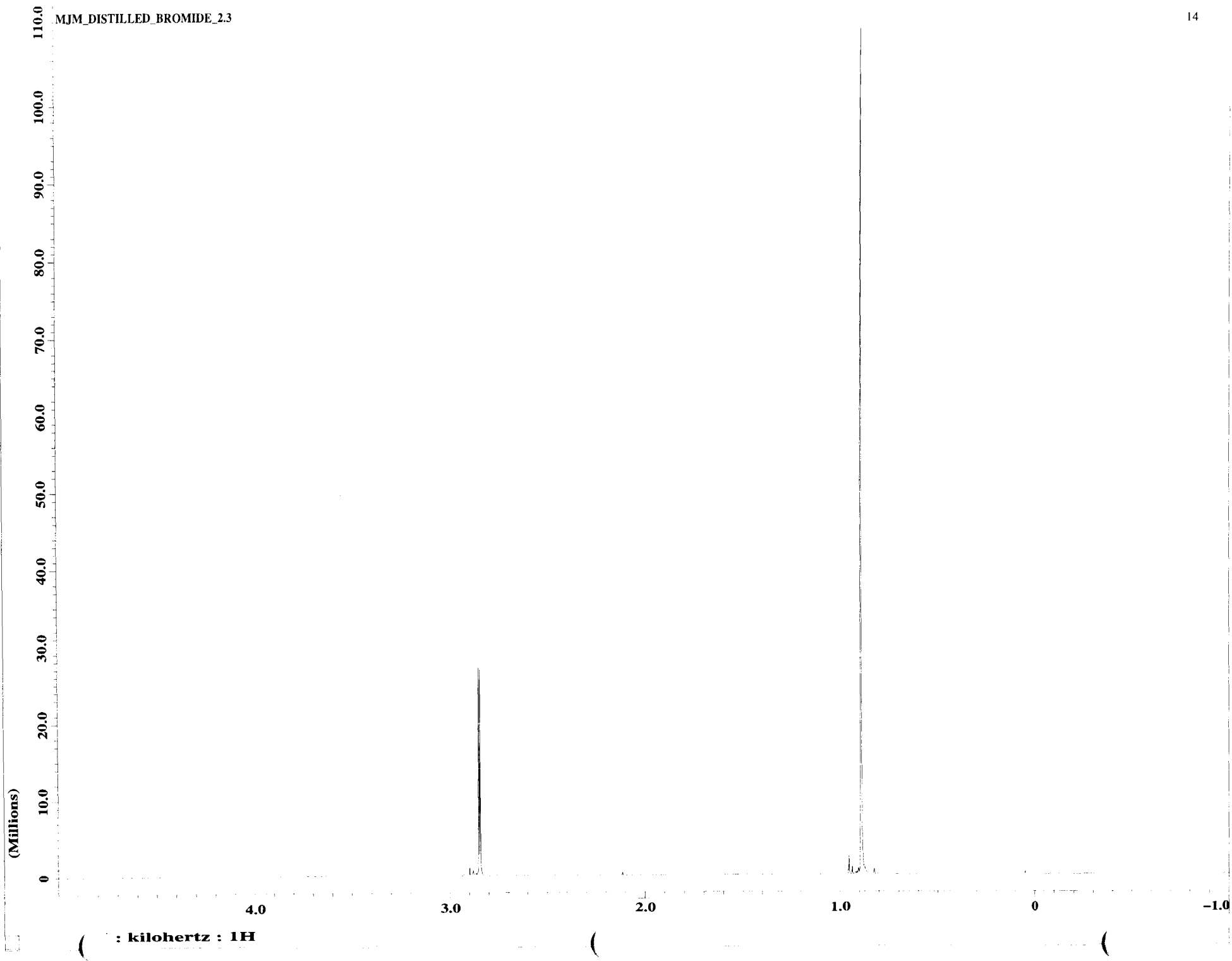
14. Drago, R. S. *Organometallics* **1995**, *14*, 3408.
15. Wakefield, B.J. *Organo Lithium Methods*, Academic Press: New York, 1988.

Appendix 1

¹H NMR of fluorinated starting materials

These are three separate spectra of the fluorinated starting materials. All three were consistent in their purity.





(Millions)

0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0

: Kilohertz : IH

4.0

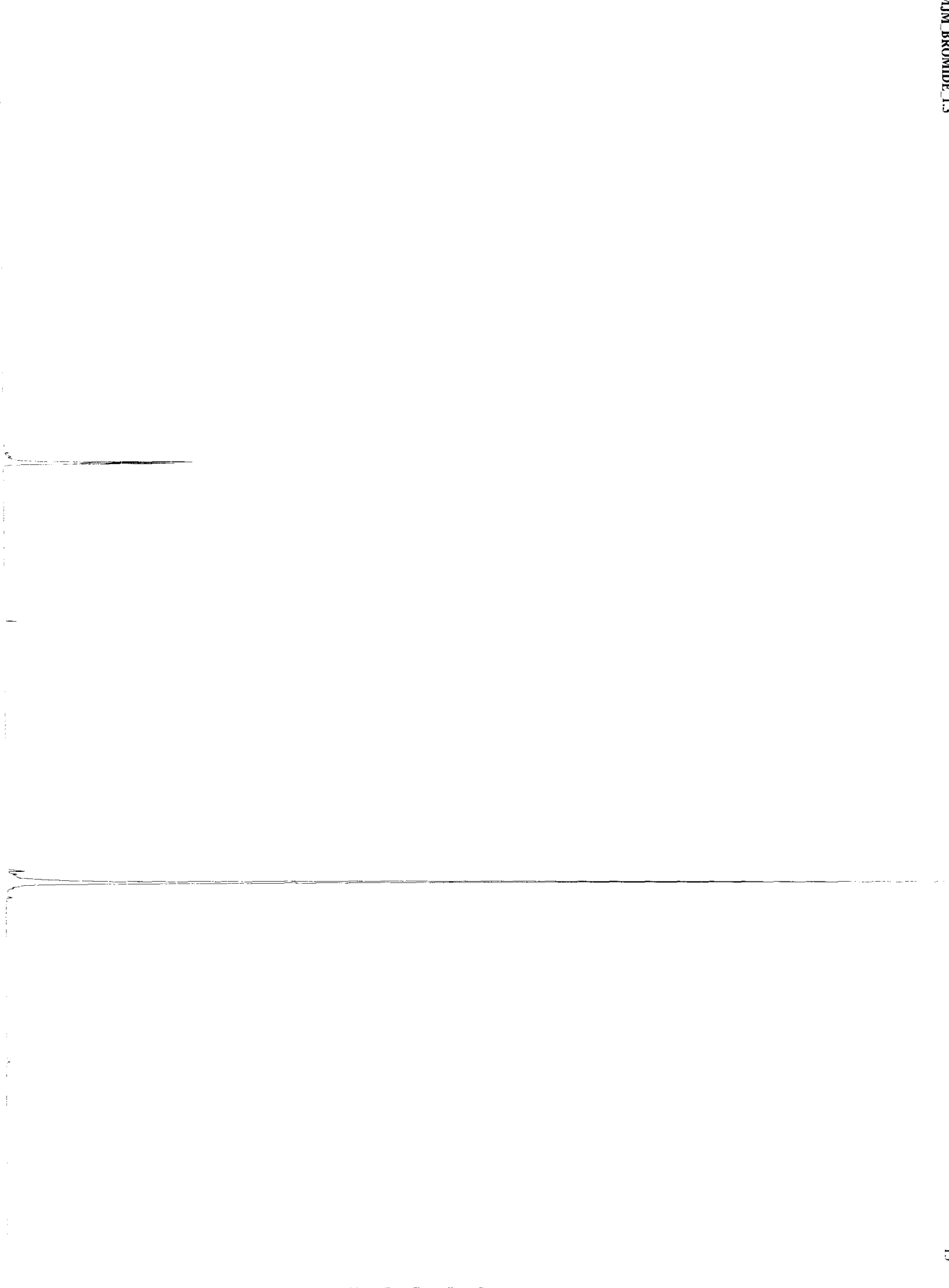
3.0

2.0

1.0

0

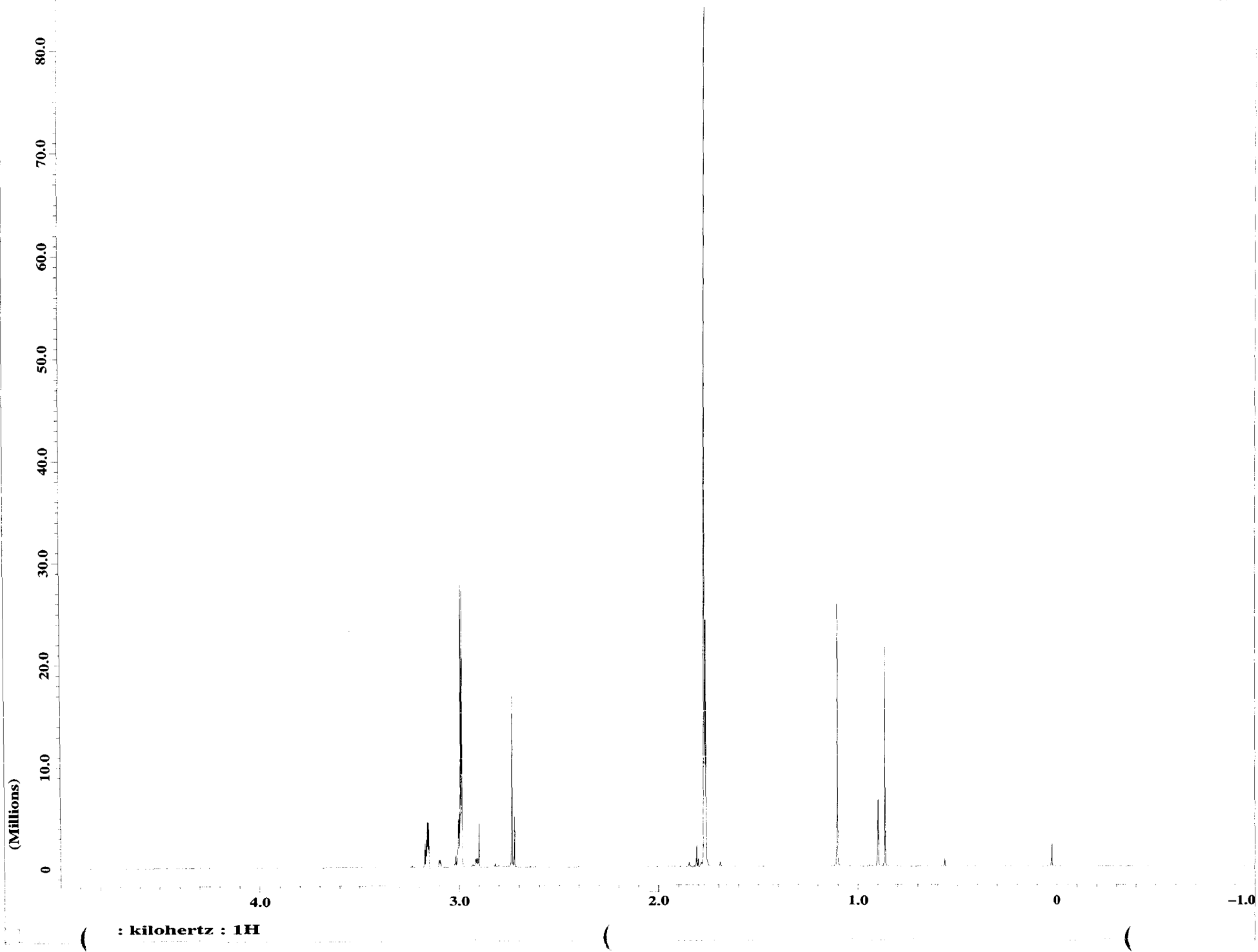
-1.0

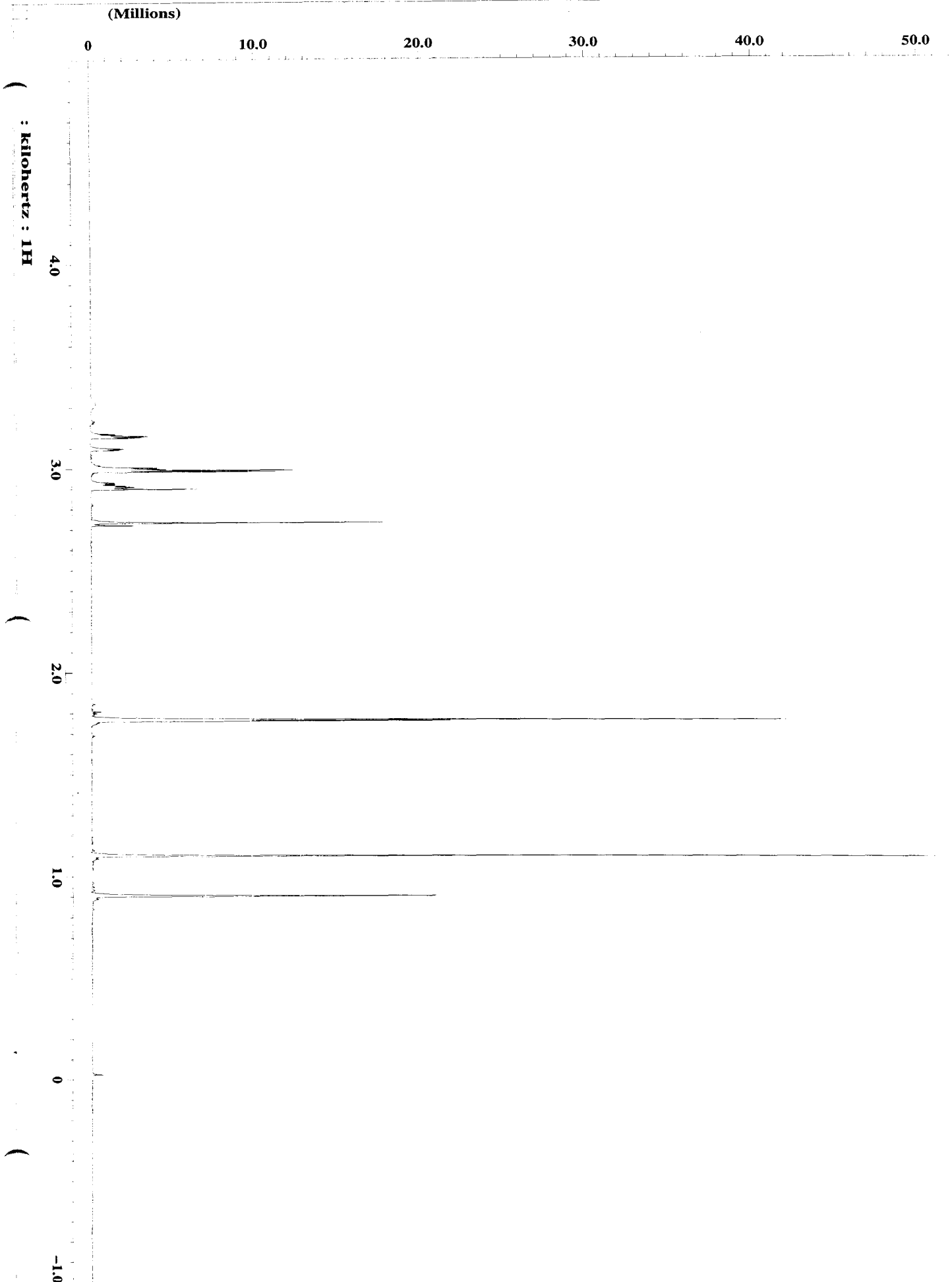


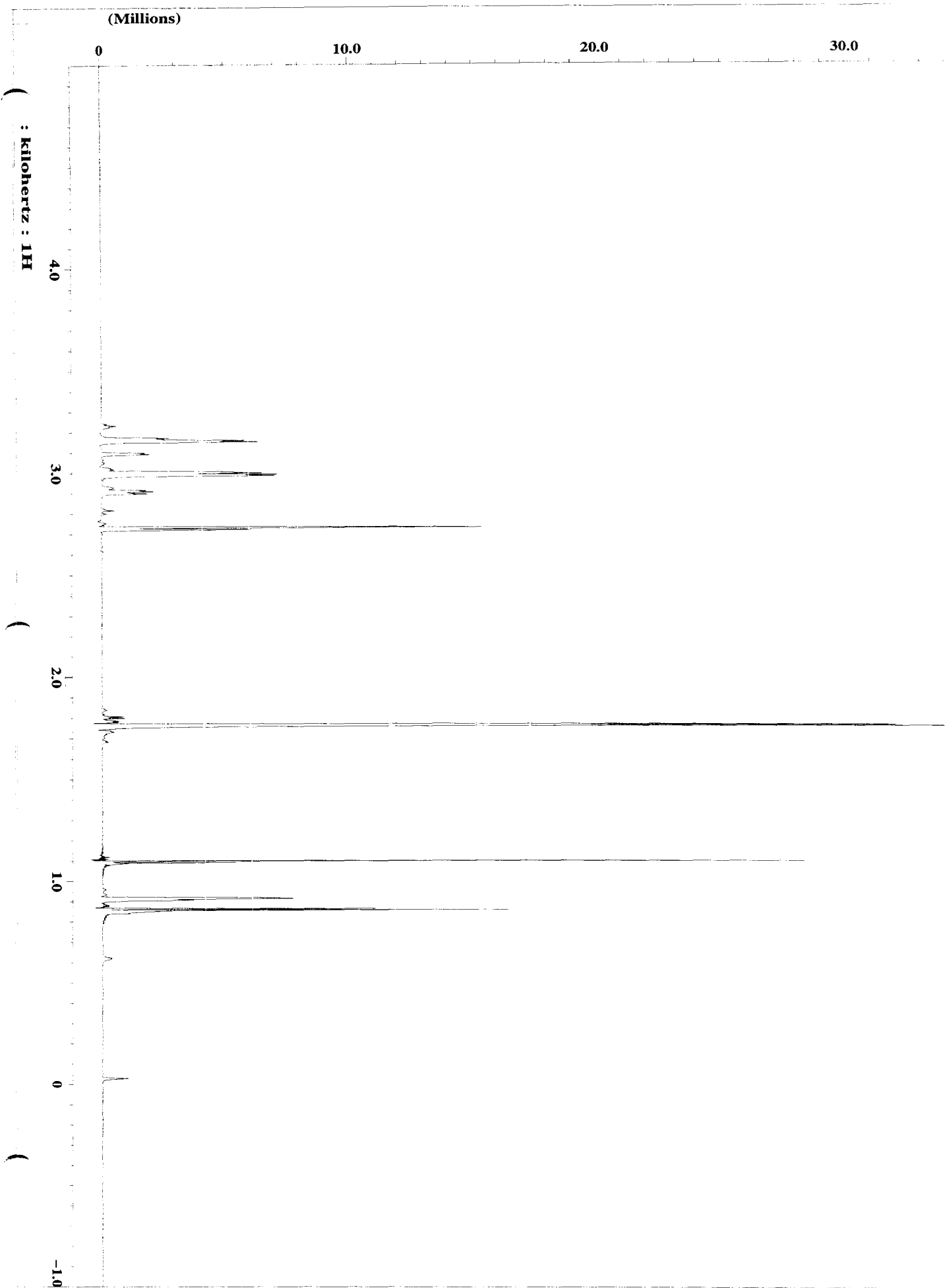
Appendix 2

¹H NMR of Tribromides

The TRIBROMOFLUOROBENZENE is the cleanest of these spectra, but the others were included to show how the progress of this free radical bromination can be monitored based upon the area of the product peaks as compared to the area of the reactant peaks.







Appendix 3

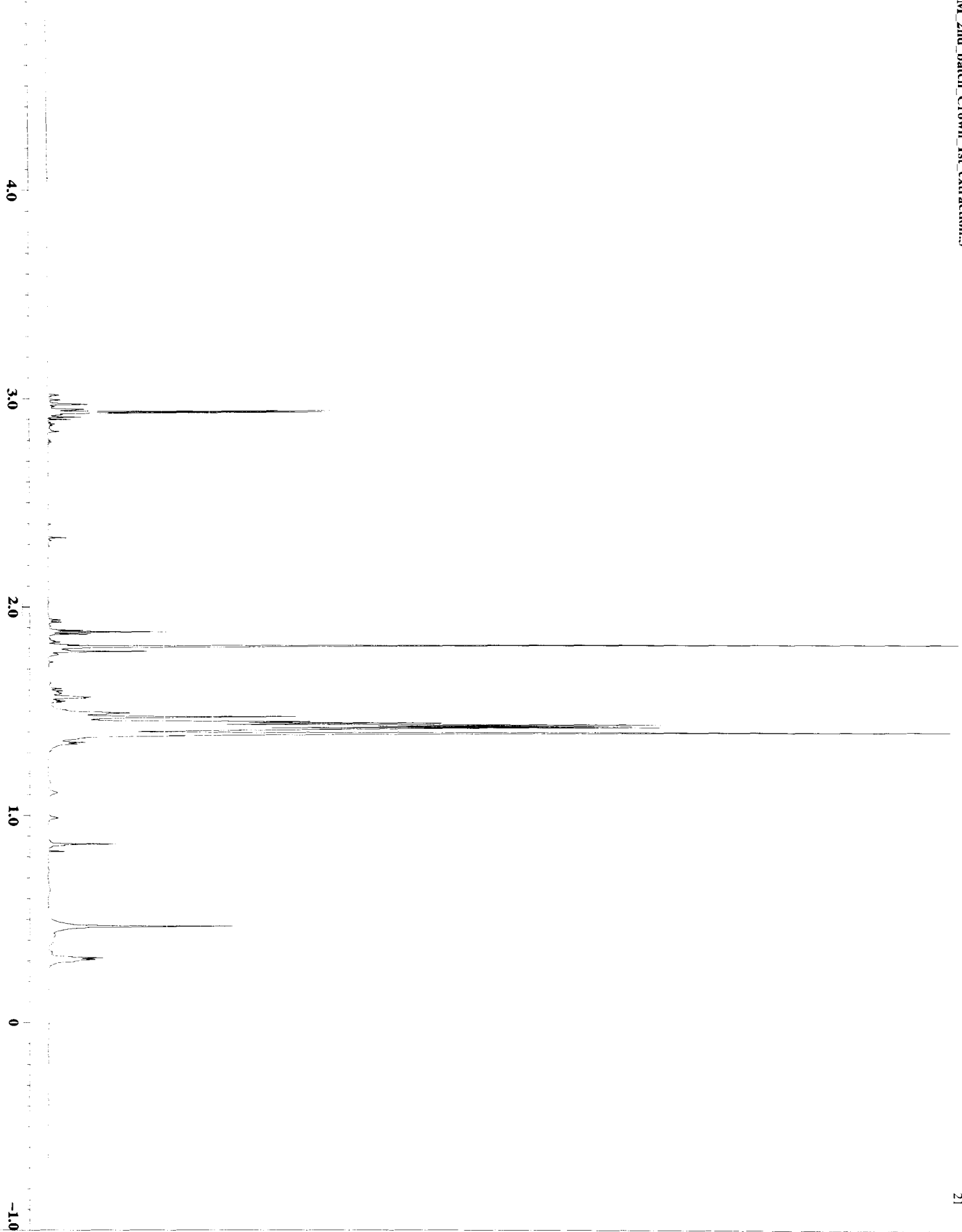
¹H NMR of Crude and Purified Fluorobenzyl Crown

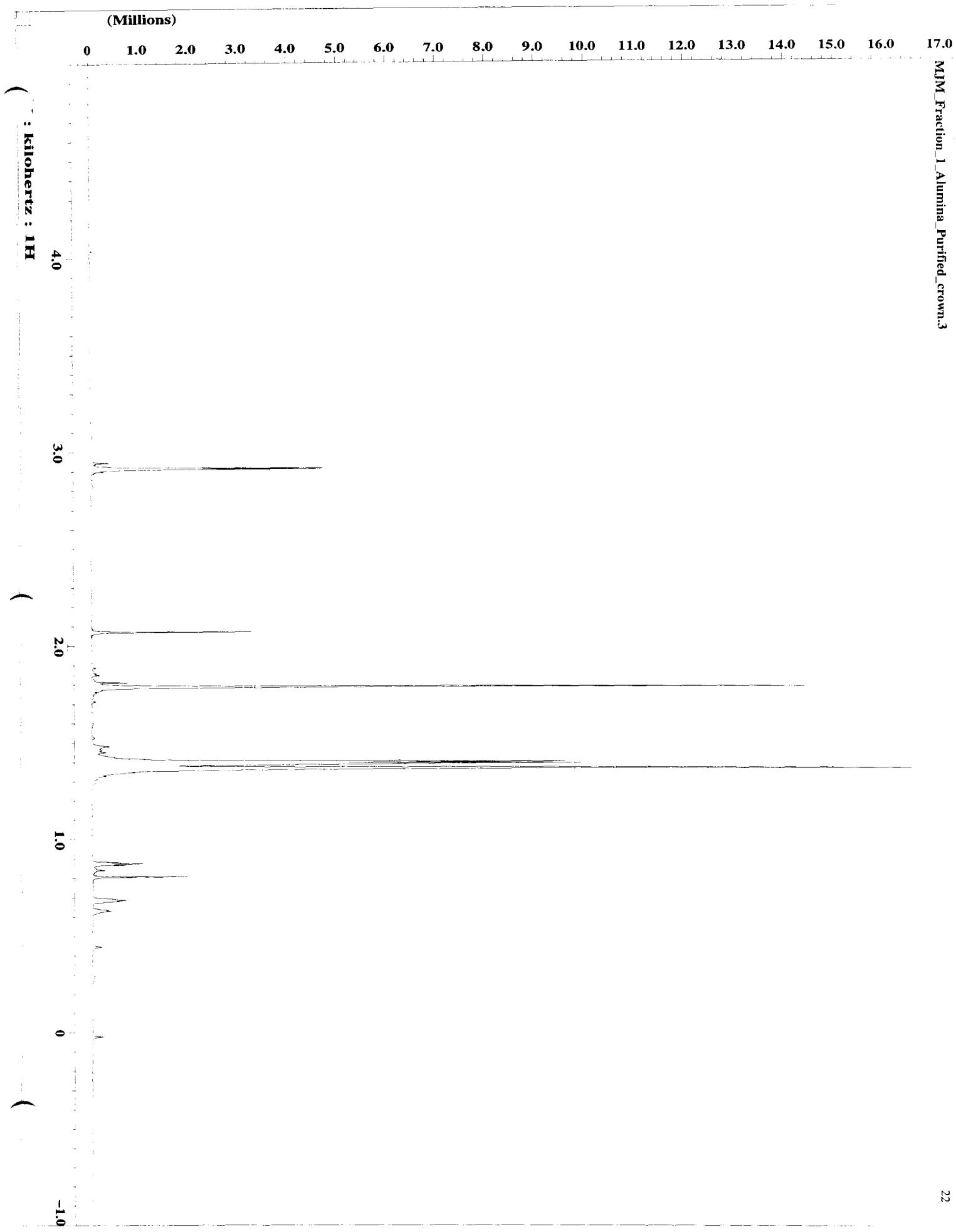
The spectrum labeled 1st extraction is a scan of the crude sample after the hot heptane extraction. Although it does not appear to be impure, a large difference can be seen between this spectrum and the spectra of the crown after purification by the alumina column.

(Millions)

0 1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0 17.0 18.0

4.0
3.0
2.0
1.0
0
-1.0
: Kilohertz : 1H

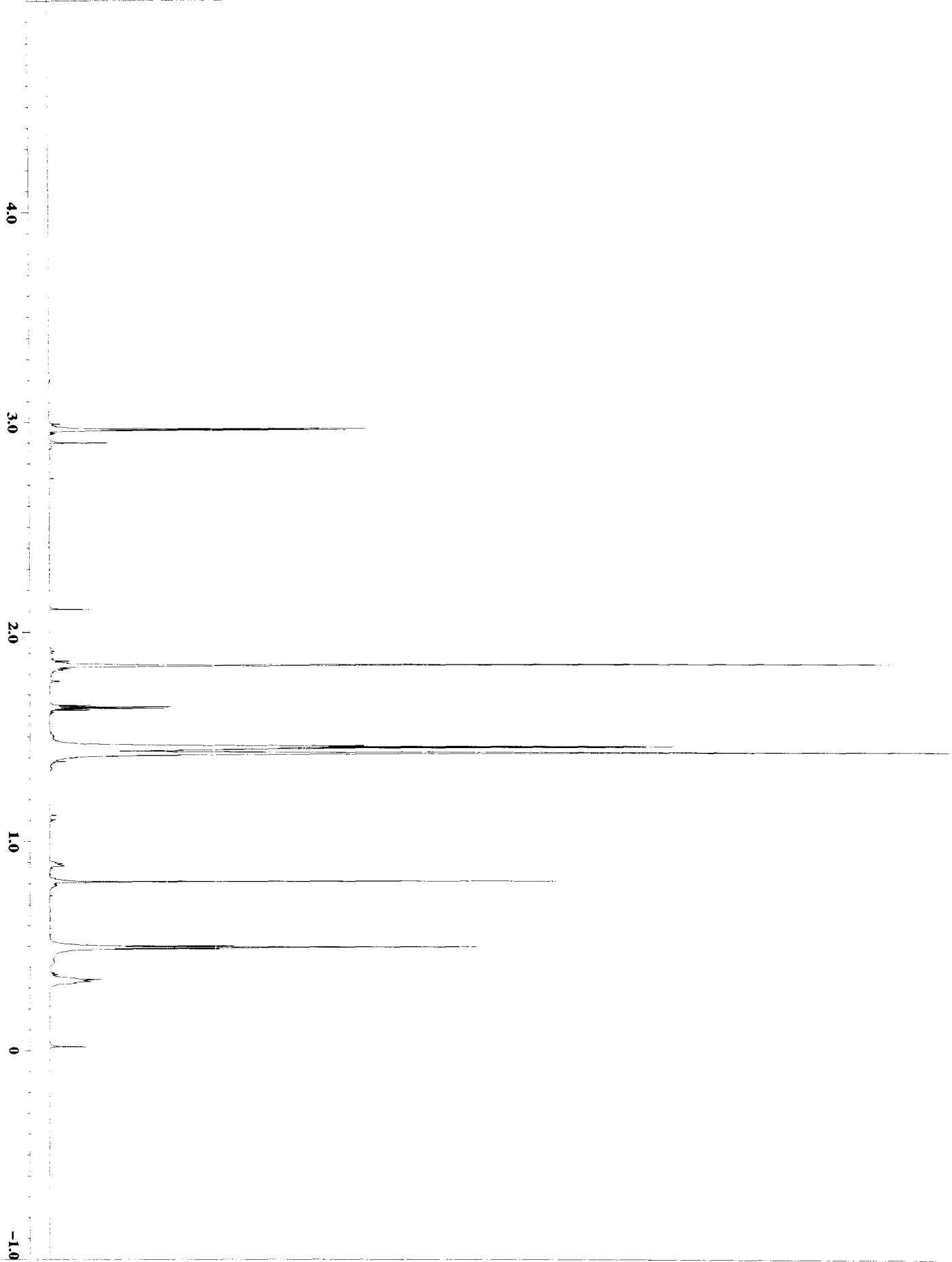




(Millions)

0 1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0 17.0 18.0 19.0

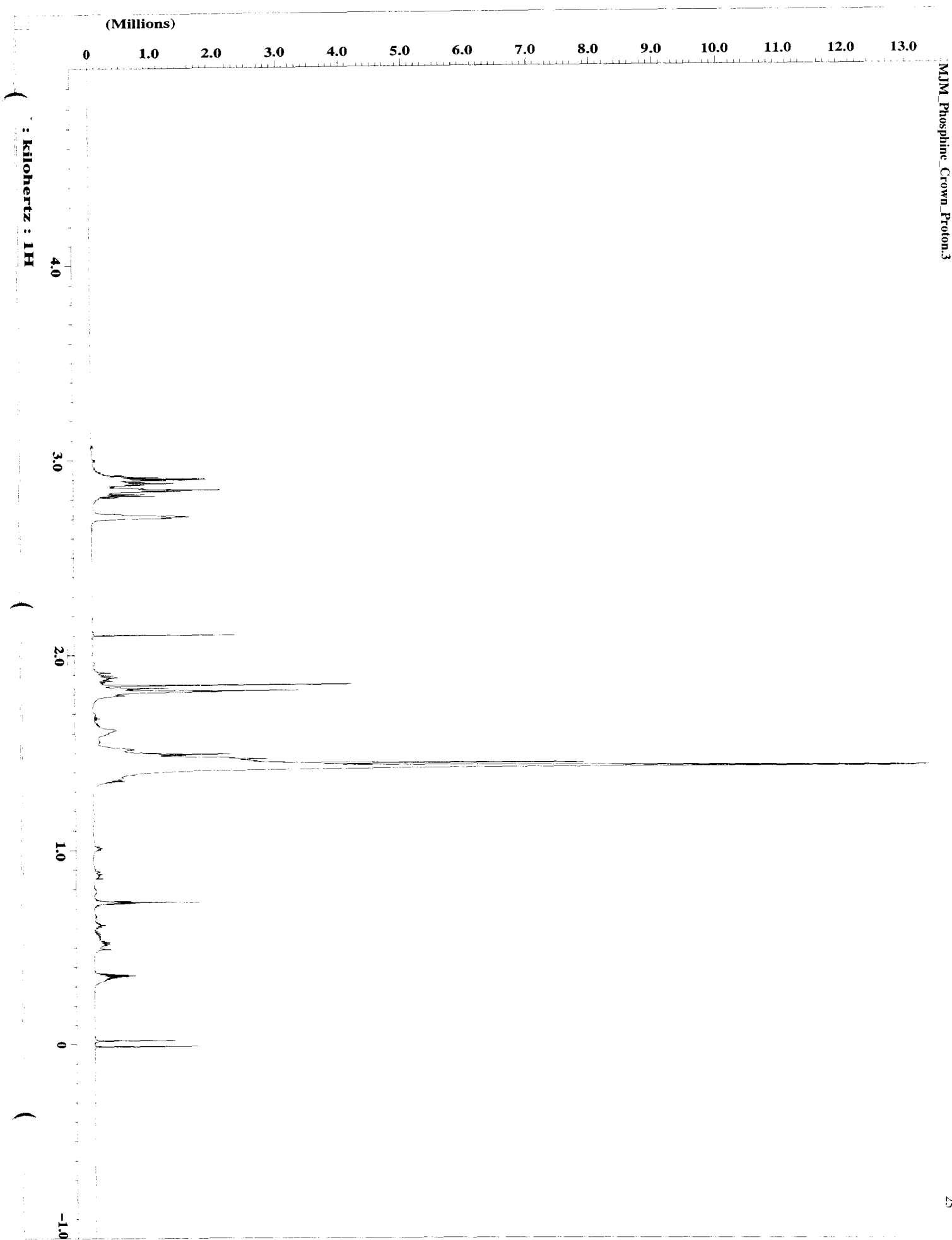
: Kilohertz : 1H



Appendix 4

¹H NMR of Fluorocrown Phosphine

The PHOSPHINE CROWN PROTON spectrum is a scan of a somewhat pure sample of the products of the phosphine addition reaction. The spectrum labeled PHOSPHINE TRICROWN is a much cleaner sample that probably resulted from a more purified fluorobenzyl crown reactant.



(Millions)

0 1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0 17.0 18.0 19.0 20.0 21.0 22.0 23.0 24.0 25.0 26.0 27.0 28.0 29.0

(: Kilohertz : 1H

4.0

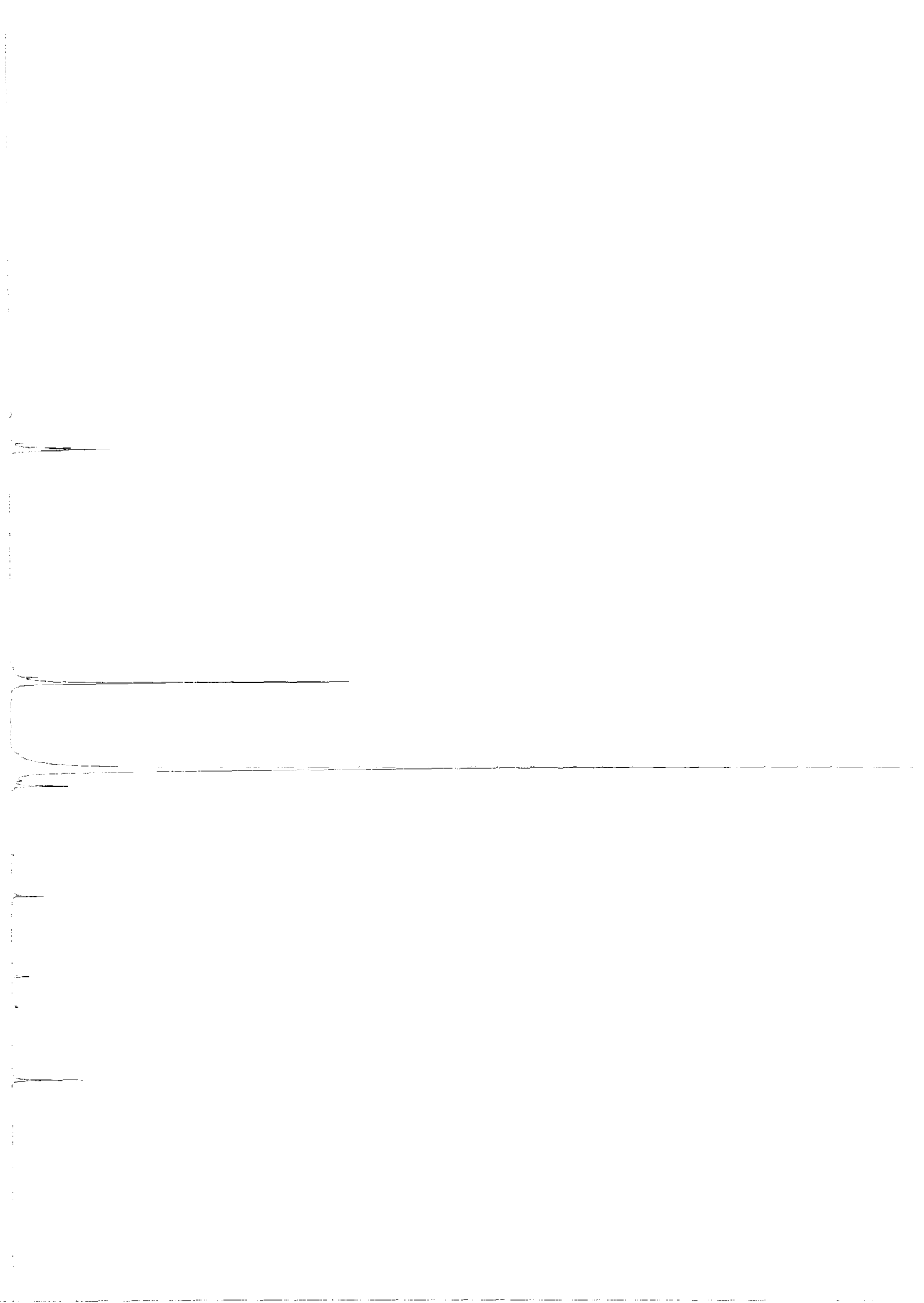
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2.0

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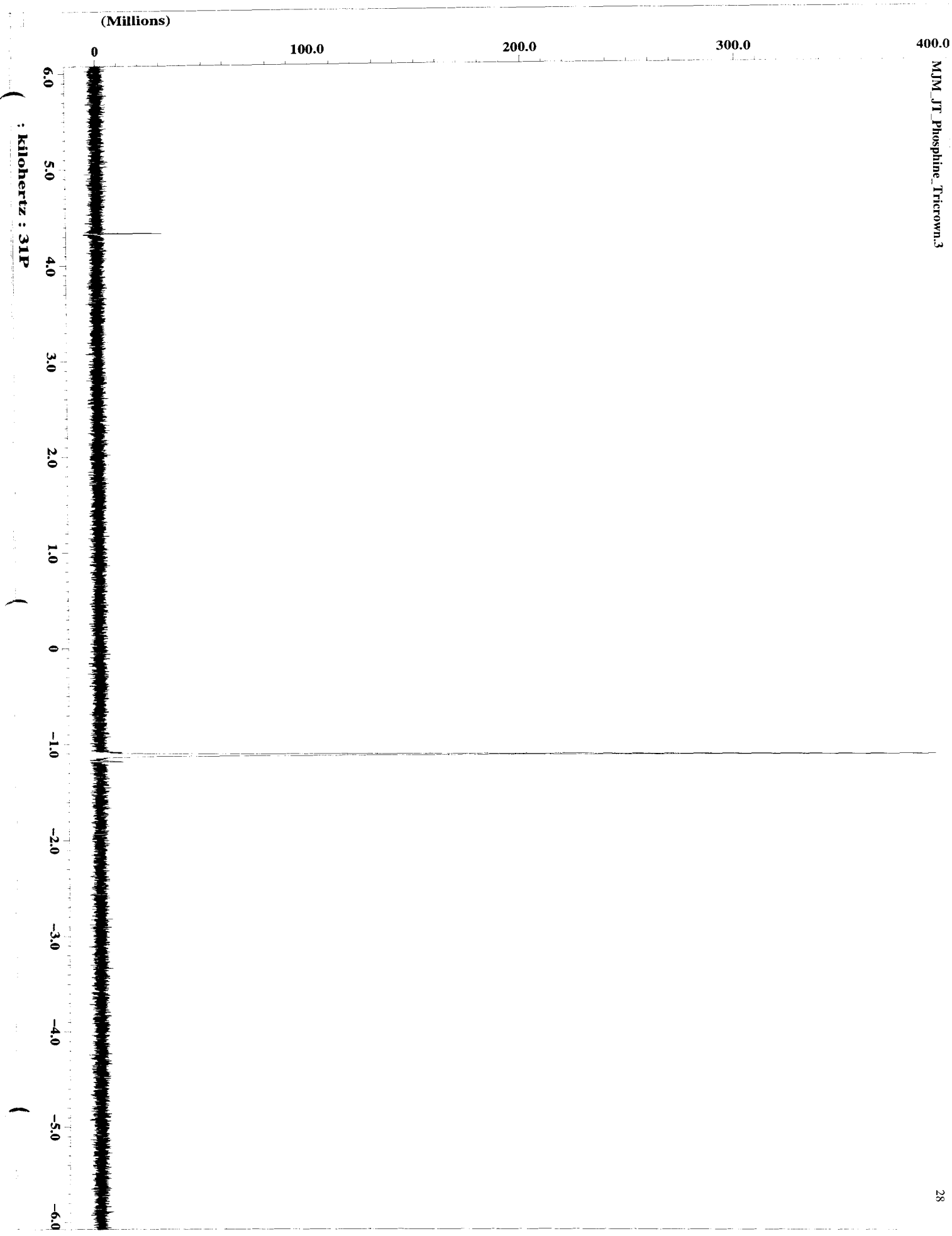
-1.0



Appendix 5

³¹P NMR of Fluorocrown Phosphine

This spectrum labeled PHOSPHINE TRICROWN shows a clean sample of the tris-crown phosphine.



**ABSTRACT OF A PAPER SCHEDULED TO BE PRESENTED AT THE JUNE MEETING OF
THE ACS JOINT CENTRAL/GREAT LAKES REGIONAL MEETING. June 11-13. Grand
Rapids, Mich.**

“THE SYNTHESIS AND STUDY OF PHOSPHINE-FUNCTIONALIZED CROWN ETHERS WITH FLUORINE IN POSITIONS TO ASSIST WITH ION BINDING”, Michael J. Murcia, Bruce N. Storhoff and Jeanette M. Tower, Department of Chemistry, Ball State University, Muncie, IN, 47306

Phosphine-crown ethers based on 1,3-xylyl-18-crown-5 units with fluorine atoms in the 2 positions and P(III) donors in the 5-positions have been synthesized and characterized. The starting materials for the crown ether portions of the molecules were 4-bromo-2,6-dimethylaniline, NaBF₄, NBS and tetraethylene glycol. The P(III) moieties have been introduced by generating the carbanions at the 5-positions by way of Br-Li exchange reactions. The procedures used during the syntheses along with the spectroscopic characteristics of the intermediates and final products will be discussed. The properties of these new molecules will be compared to those of the related systems with H or OMe groups in place of F atoms.