SEPARATION OF MENTHYL (HYDROXYMETHYL)-PHENYL PHOSPHINATE USING MOLECULARLY IMPRINTED POLYMERS

by

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SEPARATION OF MENTHYL (HYDROXYMETHYL)-PHENYL PHOSPHINATE USING MOLECULARLY IMPRINTED POLYMERS

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ABSTRACT

Molecularly imprinted polymers (MIPs) are advantageous to chemists both in their ability to drive the equilibrium of a reaction toward a desired product and in chromatography. In this project we focused on the use of MIPs in a chromatographic sense to selectively isolate menthyl (hydroxymethyl)-phenyl phosphinate in the S_P form from a mixture of both diastereoisomers. Both R_P and S_P configurations are made in equal proportions but the yield from isolation and crystallization of each pure diastereoisomer is ~25%. Production of a polymer containing pockets specific to the configuration of one diastereoisomer enables an easier method to isolate one diastereoisomer through absorption by the polymer and subsequent release. The potential for MIPs for these P-stereogenic compounds lies in the increased yield of pure crystals and therefore decreased cost of production.

ACKNOWLEDGEMENTS

It is with the deepest of gratitude that I thank Dr. Jean-Luc Montchamp for his guidance and expertise throughout this project. Without his original idea, support and instruction I would not have accomplished any of the following research. Dr. Montchamp truly made me into the scientist I am today and taught me the values of resilience and curiosity in the laboratory setting. I would also like to thank both Dr. David Minter and Dr. Ron Pitcock for their encouragement and insight into the development of my thesis. I am blessed by the instruction of such wonderful professors at TCU, along with many others who have shaped my career over the past four years. I want to thank Rachel Butler of Montchamp Phosphorus Research Group for aiding in synthesis of the template and original diastereoisomer mixture. I would also like to thank the Science and Engineering Research Center and Montchamp Phosphorus Research Group for providing funds to make this project a reality.

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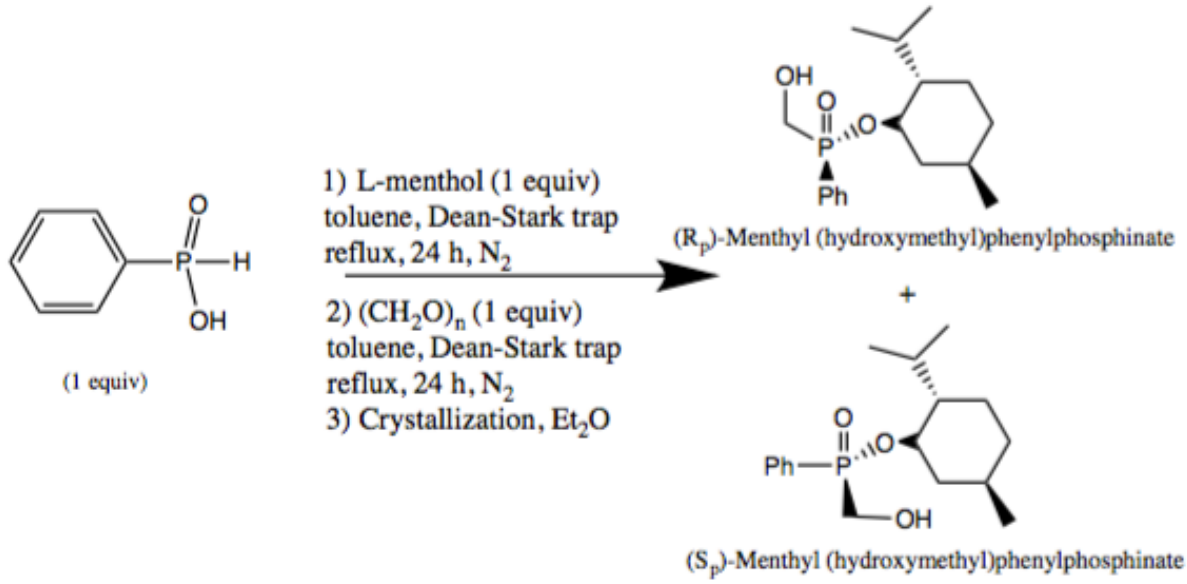
INTRODUCTION

Molecularly imprinted polymers have a wide array of uses in chromatography and selective chemical reactions. Polymers are synthesized around a template molecule to form a pocket, which acts similar to natural molecular recognition. Monomer units with favorable interaction towards the template are used to produce a network structure around the molecule. This selectivity of the network for the template is further increased by the addition of a cross-linking agent that increases the density and complexity of the network. Once the polymer synthesis is completed the template can be removed to leave a specific pocket that in principle should only allow the template molecule entry in the future. The selective pockets act as a "sponge" during chromatography to remove the molecules identical to the template from a mixture by allowing entry and binding to the pockets in a lock and key sense, which then removes the desired molecule from solution.

Polymers are also advantageous in increasing the selectivity of chemical reactions. In our research we focused on the phosphorus compound menthyl (hydroxymethyl)-phenyl phosphinate. The reaction to synthesize the molecule produces two diastereoisomers as shown in Figure 1. Procedure for synthesis can be found in the experimental section at the end of the paper. The current yield of the R_P compound is 15% after crystallization and workup. The current yield of the S_P compound is 24% of the total product after crystallization and workup. Either diastereoisomer is used in further compound synthesis, however the pure template produced by group member Rachel Butler was in fact the S_P diastereoisomer. In any NMR of the mixture or pure sample the S_P compound is noted at 36.2 ppm (right-hand peak) whereas the R_P compound is noted at 36.8 ppm (left-handed peak). The original focus of the project was intended to be menthyl (hydroxymethyl)-H phosphinate due to its innate utility to serve as a

universal starting material for other P-stereogenic menthyl phosphinates. However the H-phosphinate compound proved to be more difficult to produce a selective polymer in the initial stages. The phenyl phosphinate compound was then selected for its bulkier structure from the phenyl group that may create a larger difference between the structures of each diastereoisomer, and covalent interactions from the phenyl ring, once in the polymer pocket. The phenyl phosphinate is also more stable and cannot be oxidized as easily as the H phosphinate.

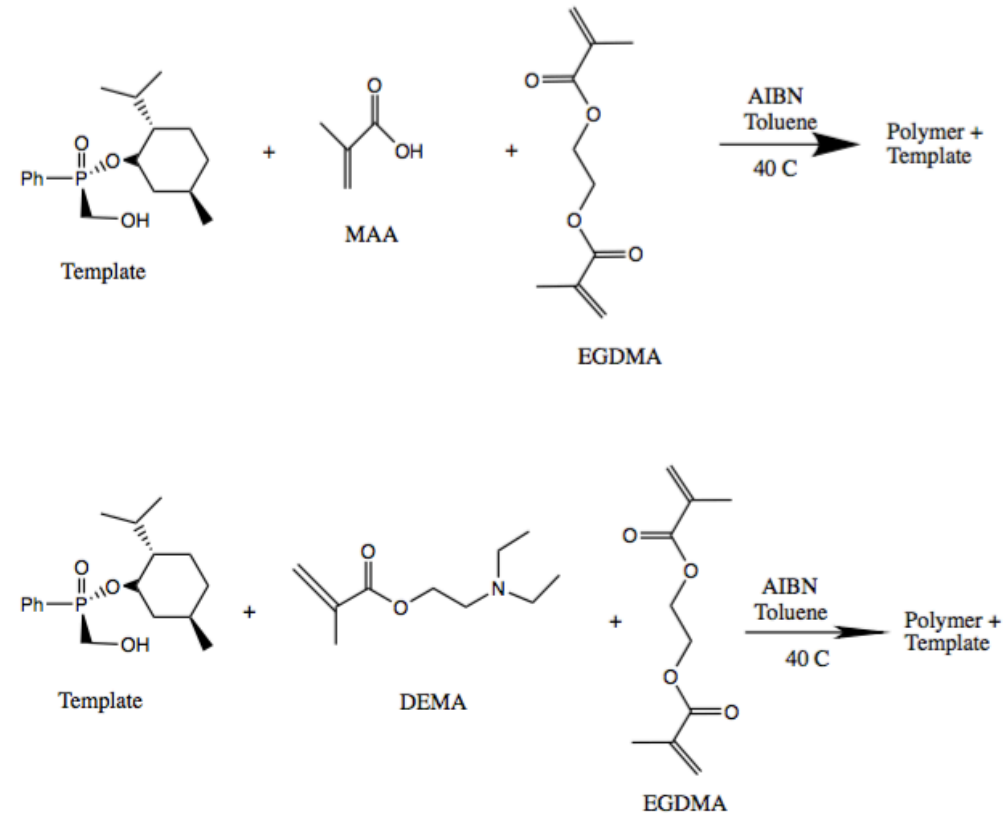
Once selective polymers are synthesized they can be used in a variety of ways. One of the original uses we discussed was during the synthesis of the two diastereoisomers, in the presence of the polymer, to theoretically push the equilibrium of synthesis towards the compound used as the template. Essentially the polymer would act as a sponge soaking up the select diastereoisomer, removing it from the mixture, driving the equilibrium towards increasing the yield of that one molecule. The molecularly imprinted polymer can also be used in a chromatography method to isolate the select compound from a mixture. Instead of using recrystallization directly, the mixture could be added to a solution of the polymer causing one of the diastereoisomers to be absorbed selectively. This diastereoisomer can then be washed from the polymer in high purity for direct crystallization. In a perfect world the polymer would be able to separate the two diastereoisomers completely after a few rounds of soaking and washing. Due to the powder nature of the polymer it can be applied to both column chromatography and the production of plates for radial chromatography (“chromatotron”).



Scheme 1: Reaction utilized to produce the diastereoisomers of menthyl (hydroxymethyl)-phenyl phosphinte

Polymers are synthesized based on a procedure by Soo-Hwan Cheong et al.[2]. Their method focuses on the use of two separate sets of monomer and cross-linker combinations. The monomers were methacrylic acid (MAA) and (diethylamino)ethyl methacrylate (DEMA). Each of these monomers was paired separately with the cross-linker ethylene glycol dimethacrylate (EGDMA). The polymerization reaction proceeds in the presence of non-covalent interactions between the monomers and the template. The cross-linking of the monomers by EGDMA forms a dense polymer surrounding the template for a selective pocket complementary to the template. The polymerization reaction is shown in Scheme 2. Additional procedures for polymerization can be found in the experimental section at the end of the paper. The ratio of monomer to cross-linker plays one of the largest roles in producing selective polymers that are still able to release the template molecule. Ratios higher in favor of the cross-linker are noted as more selective but also more difficult to release the template from due to the increased density caused by cross-linking. In contrast, the ratios that are more nearly equal favoring of the monomer are

significantly less selective and allow both diastereoisomers to enter and leave the binding pockets more freely.



Scheme 2: Polymerization reactions for MAA and DEMA with EGDMA using AIBN as initiator and toluene as solvent.

During the early trials of the polymerization the amount of solvent and choice of solvent was altered to increase the boiling point of the solution to prevent evaporation of the solvent. The paper[2] suggests using $CHCl_3$ as the solvent for smaller particle size, as the solvent creates pores within the polymer. The size of the pores affects the selectivity of the polymer as larger solvent molecules create larger holes for the molecules to enter and exit. With smaller solvent molecules the polymer is more difficult to escape from once it has formed around the template. Due to

complication of releasing the template after polymerization the solvent was changed to toluene. The larger molecular size of the toluene creates bigger pores, and the template washes out more easily. Toluene also has a higher boiling point, which allows the polymerization to take place completely without solvent evaporation.

Another important role in the reaction is filled by the initiator 1,1'-azobis(isobutronitrile) (AIBN), which actually begins the polymerization process. Two separate compounds, AIBN and ABCN (1,1'-azobis(cyclohexane)carbonitrile), filled the role of initiator throughout the project. AIBN proved to be the most successful due to the inherent lower temperature required to initiate the polymerization ($t_{1/2}$ = 1 h at 80°C). This lower temperature allowed the reaction to occur at a slower rate to ensure complete polymerization without "overcooking" the polymer. However, partway through the project we ran out of AIBN and switched to ABCN as the initiator due to inability to obtain more AIBN at the time. ABCN has a higher temperature of activation ($t_{1/2}$ = 1 h at 105°C) to begin the polymerization reaction, which posed a few problems. The solvent was also switched from chloroform to toluene. The toluene allowed for a higher boiling point to avoid evaporating solvent while activating the initiator. AIBN was obtained again due to the generous funding from SERC and proved to be the more successful initiator in producing the final polymer.

The final polymer was prepared using a combination of methacrylic acid and ethylene glycol dimethacrylate in a 1:2 ratio, respectively. The solvent of choice was toluene to allow for a higher boiling point to prevent the potential evaporation of solvent and overheating of the polymer. The toluene also created larger pores that allowed easier removal of the template after polymerization. A larger amount of solvent was used than described in the paper[2] to prevent overheating the polymer, which was noted in earlier reactions that produced "harder" polymers.

AIBN was used as the initiator due to the ability to start the polymerization reaction without the potential of the condenser popping off at higher temperatures. This slowed the reaction down enough to give a more complete polymerization throughout the entire 16-24 hours the reaction was heated.

Once the polymerization was completed the majority of the solvent was either contained in the polymer or removed through vacuum filtration. The polymer itself came out as a wet crystalline-like solid with an off-white color. Once dried the polymer was ground in a mortar to obtain a fine white powder that was dried additionally under vacuum to remove residual toluene. After being removed from vacuum the polymer was washed using a soxhlet extractor and 100-mL ethanol in a 150-mL round-bottom flask. The polymer was placed in alpha cellulose cotton linter thimbles, which are then inserted into the chamber of the soxhlet extraction. The ethanol was refluxed into the top chamber of the soxhlet and condensed back into a liquid to run through the polymer and wash out the template. The soxhlet was extremely advantageous to the project as it allows a continuous extraction with pure ethanol running through the polymer each time it cycles. The released template stays in the flask as the solvent is evaporated up again. This allowed only a single wash to be performed and saved a great deal of time as each extraction was run for 24 h. Before use of the soxhlet wash steps were run two or three times in a round bottom flask fitted with a condenser for 24 h. This method was more difficult because as the ethanol became saturated with released template, it became more difficult for the remainder to exit their pockets.

The polymer was dried once again to remove any excess ethanol before being tested to analyze the selectivity. An approximate 1:1 ratio test sample of the two diastereoisomers was used to show the selectivity trend of the polymer. Two mmol of the mixture was added to 100-

mL of acetonitrile (NMR taken of initial ratio seen in Figure 9) and combined with the entire mass of polymer in a 150-mL flask. The flask was placed under N_2 to stir for 24 h. After removing the solution the polymer was separated from the acetonitrile using gravity filtration and subsequent vacuum filtration. The remaining solution was analyzed using ^{31}P NMR to determine what was left from the original mixture. If the polymer was selective enough the right hand peak should be decreased as the polymer soaks up the S_P compound. The polymer was then washed using the soxhlet extraction as previously noted but with acetonitrile as the solvent instead of ethanol. ^{31}P NMR was then used to analyze the remaining solution to determine what had been soaked out of the mixture by the polymer.

RESULTS AND DISCUSSION

As noted in Tables 1 and 2 there were numerous trials for combinations of variables in both MAA and DEMA polymers. In each case the monomer to cross-linker ratio (mmol monomer/mmol cross-linker) was altered according to the results of previous experiments. When a polymer proved not to be very selective but released the template easily, the ratio was changed to higher cross-linker amounts. Increasing the amount of cross-linker in comparison to the monomer proved to produce greater selectivity. One of the other parameters that changed was switching from chloroform to toluene. This change created easier template release as pore size in the polymer increased and counteracted the increased density of ratios with high amounts of cross-linker. In the methacrylic acid polymers we also switched back to the AIBN initiator for the final trial. This proved to allow a more complete polymerization and provided the most selective polymer.

Some of the initial polymer trials were either too dense due to a higher amount of cross-linker or simply did not polymerize. The ratios below 0.45 did not allow release of the template regardless of the solvent. It was also noted that polymers with ratios above 1 were more difficult to synthesize. For the two polymers in trials 20 and 33, which were around 0.5 ratios, the initiators used most likely caused the difference in polymerization. The ABCN requires a higher temperature for activation than AIBN, and in a solvent like chloroform for trial 20 the temperature must be set lower to avoid evaporation. Once the solvent was switched to toluene and AIBN was used the polymerization proceeded without a problem.

Experiment # - Solvent	Initiator	MAA (mmol)	EGDMA (mmol)	Ratio	Template Removal
7 - CHCl3	AIBN	8	25	0.32	None
19 - CHCl3	AIBN	20	18	1.11	Incomplete Polymer
20 - CHCl3	ABCN	10	18	0.55	Incomplete Polymer
21 - Toluene	ABCN	8	18	0.44	None
22 - Toluene	ABCN	20	20	1	400mg wet
24 - Toluene	ABCN	15	20	0.75	600mg with residue
26 - Toluene	ABCN	15	20	0.75	400mg with residue
27 - Toluene	ABCN	17.5	20	0.875	400mg with residue
33 - Toluene	AIBN	10	20	0.5	300mg

Table 1: Methacrylic Acid polymer experiment ratios of monomer to cross-linker.

The DEMA polymers seemed to be far less selective than the MAA polymers and easily released the template. One of the major reasons we stopped using DEMA was that higher amount of cross-linker did not seem to make a difference in ease of template was removed. Neither initiator nor solvent alterations produced different results. In both the case of MAA and DEMA polymers the template removal after washing the polymers was analyzed by NMR to locate a single peak corresponding to the template molecule in the ^{31}P NMR spectrum. The wash solution was also rotoevaporated in order to remove the solvent to weigh the amount of template and

residue. In most cases the polymerization of the DEMA experiments was not complete as some starting material was left in the wash solution. This prevented the template from recrystallizing.

Experiment # - Solvent	Initiator	DEMA (mmol)	EGDMA (mmol)	Ratio	Template Removal
8 - CHCl3	AIBN	8	25	0.32	Wash 1
10 - CHCl3	AIBN	8	35	0.23	Wash 1 + 2
11 - CH3CN	AIBN	8	25	0.32	500mg with residue
15 - CH3CN	ABCN	8	35	0.23	600mg with residue
16 - Toluene	ABCN	8	25	0.32	Wash 1 + 2

Table 2: 2-(Diethylamino)ethyl methacrylate polymer ratios of monomer to cross-linker.

After the template was removed from each polymer, the polymer was subjected to testing with a mixture of both diastereoisomers. For the DEMA polymers an original mixture produced by Rachel Butler was used. An NMR spectrum was taken before the soaking began to establish a base ratio (1:1.6) to determine the change in concentration of the molecules following each step. "After soak ratios" refer to the mixture left over when the polymer is removed. These often had very similar ratios to the original mixture. The only promising DEMA polymer was experiment 11, which had a diastereoisomer ratio decrease from 1.78 to 1.64. This decrease meant that there was an indication for selectivity of the S_P compound. However when the polymer was washed, and solvent analyzed, the ratio had decreased below either of the previous numbers indicating that there was really no selectivity for the S_P diastereoisomer.

Figure 1 is a graphic representation of the data in Table 3 for the DEMA polymers. The ideal trend should be a V-shape with the right side being higher than the left. This shape starts from the initial ratio being a base point. The ratio after soaking should decrease as the S_P compound is removed from solution. This is followed by a prominent increase to an even higher ratio number, as the major compound should be the S_P diastereoisomer. None of the DEMA

experiment trend lines show this shape and therefore did not help to provide results that affirmed the use of MIPs for chromatography.

Experiment	Starting ratio - Left	Starting ratio - Right	Total starting ratio	After soak - Left	After soak - Right	Total after soak ratio
8	1	1.53	1.53	1	1.57	1.57
10	1	1.53	1.53	1	1.55	1.55
11	1	1.78	1.78	1	1.64	1.64
15	1	1.64	1.64	1	1.75	1.75
16	1	1.48	1.48	1	1.57	1.57

Wash – Left	Wash – Right	Total wash ratio
1	1.58	1.58
1	1.61	1.61
1	1.59	1.59
1	1.74	1.74
1	1.52	1.52

Table 3: NMR integration ratios of menthyl (hydroxymethyl)-phenyl phosphinate mixture from testing of DEMA polymers (Right and Left designate S_P and R_P peaks respectively).

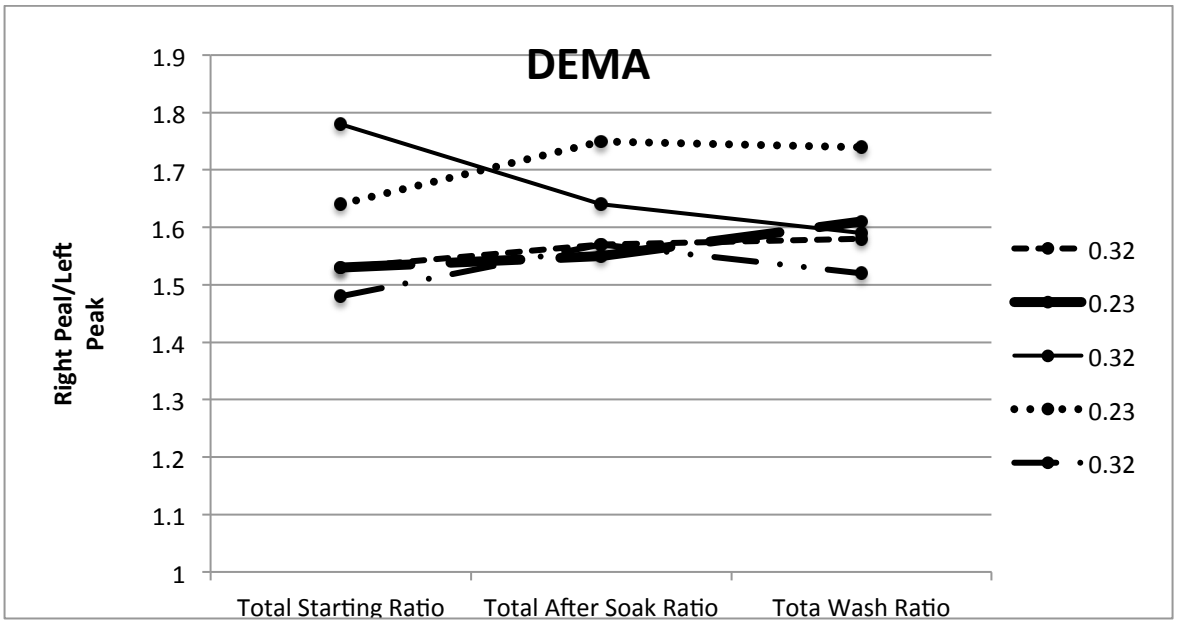


Figure 1: Graphic representation of Table 3 (NMR integration ratios of menthyl (hydroxymethyl)-phenyl phosphinate mixture from testing of DEMA polymers).

The MAA polymers proved to be far more successful in the end of the project. The most significant results that showed the V trend were from experiments 24 and 33. However, while the results of 24 seem to be the most significant they were discounted due to a few discrepancies in the trial. First, the condenser popped off of the flask after approximately 6 hours, which caused the polymerization to be halted early. Second, in an effort to fix the condenser issue the experiment was repeated in trial 26 and the results of the complete polymerization showed that there was no selectivity for the S_P compound. Experiment 22 should also be noted as having the highest final ratio, but the spectrum for that sample was so noisy, due to a small amount of mixture being obtained, that the integration was significantly thrown off.

In the end, the most promising experiment was 33 with a 0.5 ratio of MAA to EGDMA. This polymer made with AIBN as the initiator and toluene as the solvent provided to most complete polymerization and skewed V trend. The ratio began as 0.93 and dipped down to 0.79 indicating that more of the S_P compound was being removed from solution than R_P. The ratio then jumped back up to 1.02 indicating that there was in fact more S_P present in this solution than in the original. These results indicate that there is an increased selectivity for the S_P compound used as the template. In Figure 2 the trend line for experiment 33 is the very bottom one, which exhibits the V trend.

Experiment	Starting ratio - Left	Starting ratio - Right	Total starting ratio	After soak - Left	After soak - Right	Total after soak ratio
22	1	1.5	1.5	1	1.66	1.66
24	1	1.61	1.61	1	1.55	1.55
26	1	1.43	1.43	1	1.48	1.48
27	1	0.9	0.9	1	0.91	0.91
33	1	0.93	0.93	1	0.79	0.79

Wash - Left	Wash - Right	Total wash ratio
1	2.09	2.09
1	1.78	1.78
1	1.42	1.42
1	0.97	0.97
1	1.02	1.02

Table 4: NMR integration ratios of menthyl (hydroxymethyl)-phenyl phosphhinate mixture from testing of MAA polymers (Right and Left designate S and R peaks respectively).

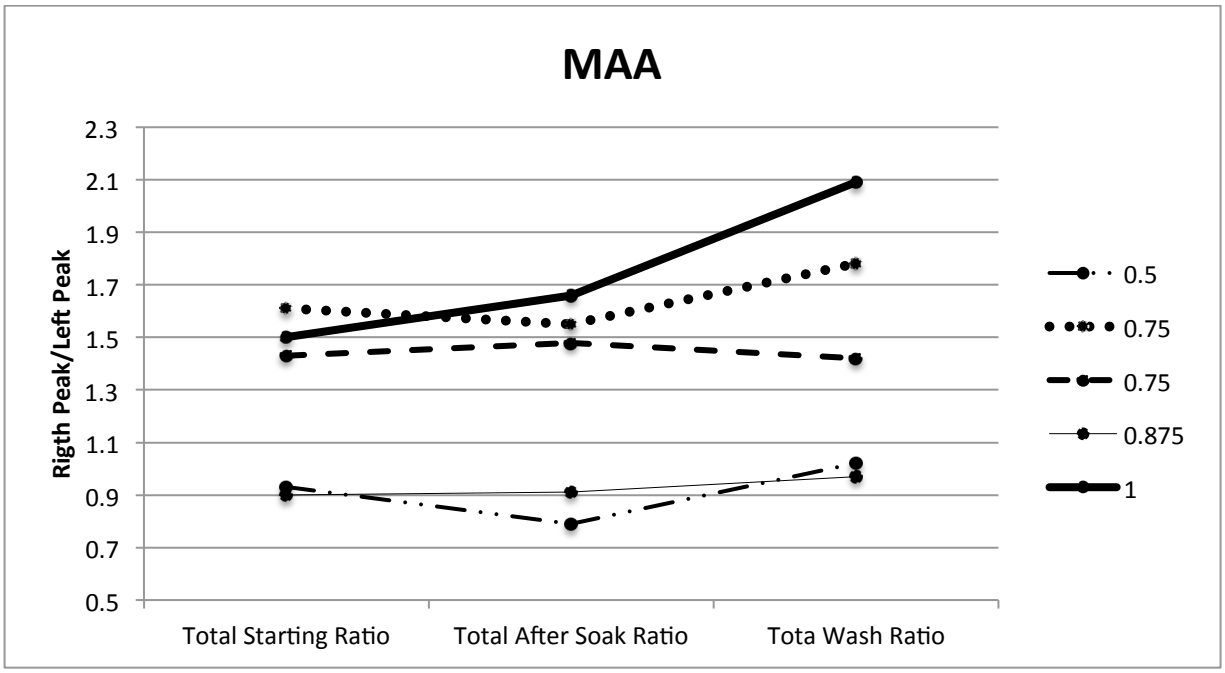


Figure 2: Graphic representation of Table 4 (NMR integration ratios of menthyl (hydroxymethyl)-phenyl phosphhinate mixture from testing of MAA polymers).

CONCLUSION

While the project proceeded for nearly a year there is still additional work to be completed. The final polymer obtained was useful in proving that the project was headed in the correct direction as the polymer was in fact more selective for the S_P compound template. However, narrowing the conditions to the best compromise between selectivity and template release did not give good results. There are a number of variables that can be altered in order to refine the selectivity of the polymer. For example the solvent used in the polymerization reaction plays a large role in the selectivity and release of the template molecule. If we proceeded to change the solvent from toluene back to chloroform, or another small solvent molecule the selectivity might be enhanced by requiring higher match to the shape of the pockets in order to enter the network. However the problem with decreasing the solvent molecule size then becomes the release of the template molecule once polymerization or soaking has occurred.

Another important variable is the ratio of monomer to cross-linker. We believed that we had found the "sweet spot" in the ratio, however the polymer still proved to not be selective enough. In fact the monomer itself could be changed to have a greater non-covalent interaction with the template. The use of monomers such as styrene or ethyl acrylates might produce a more selective orientation for the template within the pocket. These variables can also be combined to produce even further changes in the selectivity. Therein lies the problem of finding the perfect polymer for this particular molecule in the allotted amount of time. The intrinsic competition between the template release and selectivity is a very fine line to walk. Too much cross-linker is like breaking the key inside the lock. Not enough shows no selectivity. One might even want to

repeat the literature procedure to evaluate the concept on a tested basis. Ultimately once a polymer that is highly selective for menthyl (hydroxymethyl)-phenyl phosphinate is produced the goal would be to return to producing a polymer for menthyl hydroxymethyl-H phosphinate. The production of a polymer for this compound would help to reduce the cost of synthesizing nearly every P-stereogenic compound produced from the H-phosphinate.

EXPERIMENTAL SECTION

Materials: The following reagents were used without further purification. Phenylphosphinic acid, L-menthol, paraformaldehyde, toluene, diethyl ether, 1,1'-azobis(isobutyronitrile) (AIBN), methacrylic acid (MAA), 2-(diethylamino)ethyl methacrylate (DEMA), ethylene glycol dimethacrylate (EGDMA) (98%), ethanol 1,1'-azobis(cyclohexane)carbonitrile (ABCN). Departmental Bruker 400-spectrometer was used for NMR analysis (^{31}P).

Preparation of menthyl (hydroxymethyl)-phenyl phosphinate mixture for testing: In a round bottom flask with 75-mL of toluene was added phenylphosphinic acid (10.14 g, 1 eq) and L-menthol (11.86 g, 1 eq). The flask was then set up with a Dean-Stark trap under N_2 and the mixture stirred at reflux at 100 °C for 24 h. Reaction mixture was removed from heat and allowed to cool to room temperature before the addition of paraformaldehyde (2.26 g, 1 eq). Reaction mixture was then returned to reflux under N_2 for 24 h. Reaction turned out to be incomplete as noted by the NMR in Figure 3. Addition of paraformaldehyde (2.26 g, 1eq) to the mixture was followed by reflux at 100 °C for an additional 24 h under N_2 to obtain a more pure mixture as noted in Figure 4.

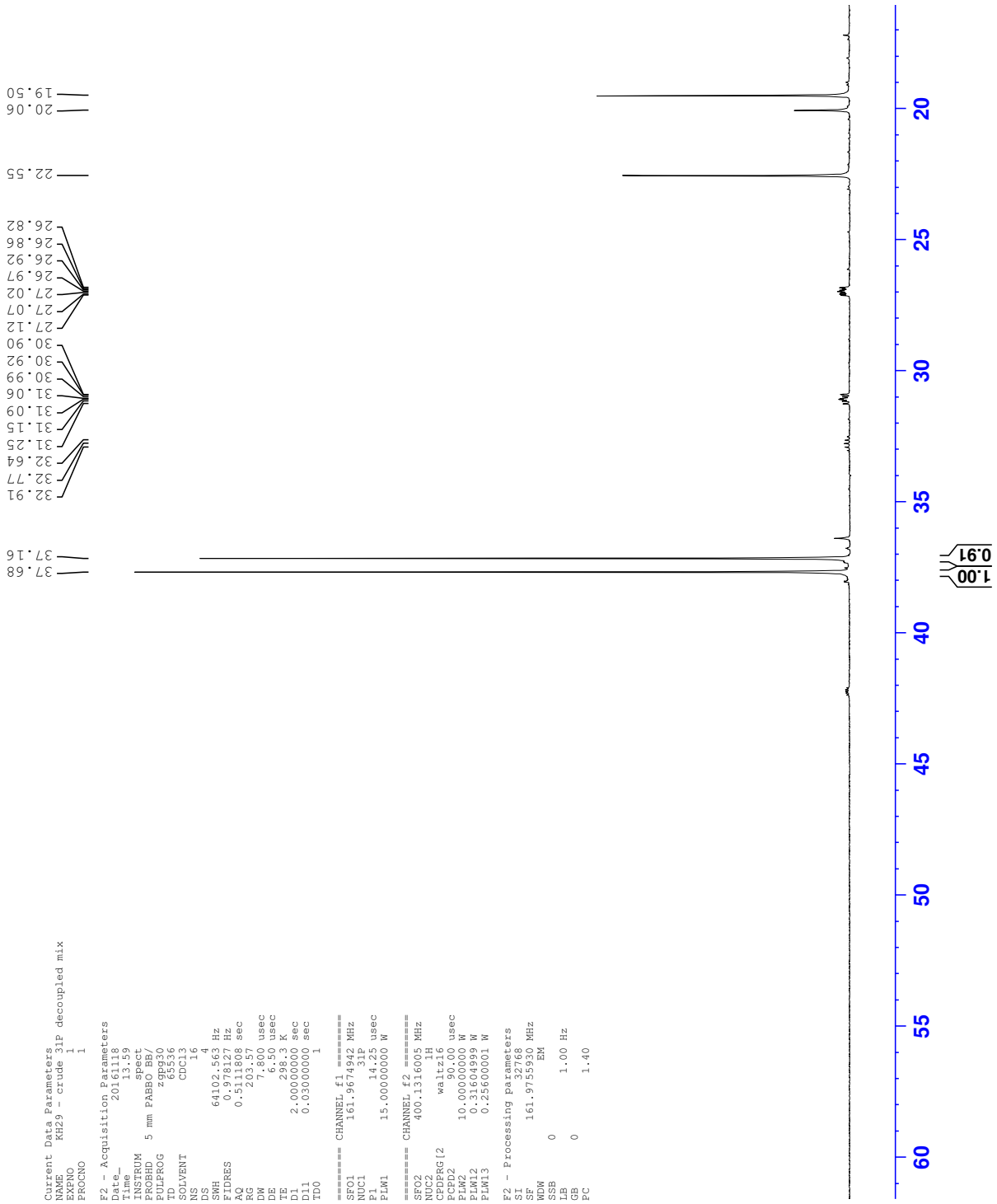


Figure 3: NMR analysis of initial menthyl (hydroxymethyl)-phenyl phosphinate mixture after addition of paraformaldehyde and reflux for 24 h.

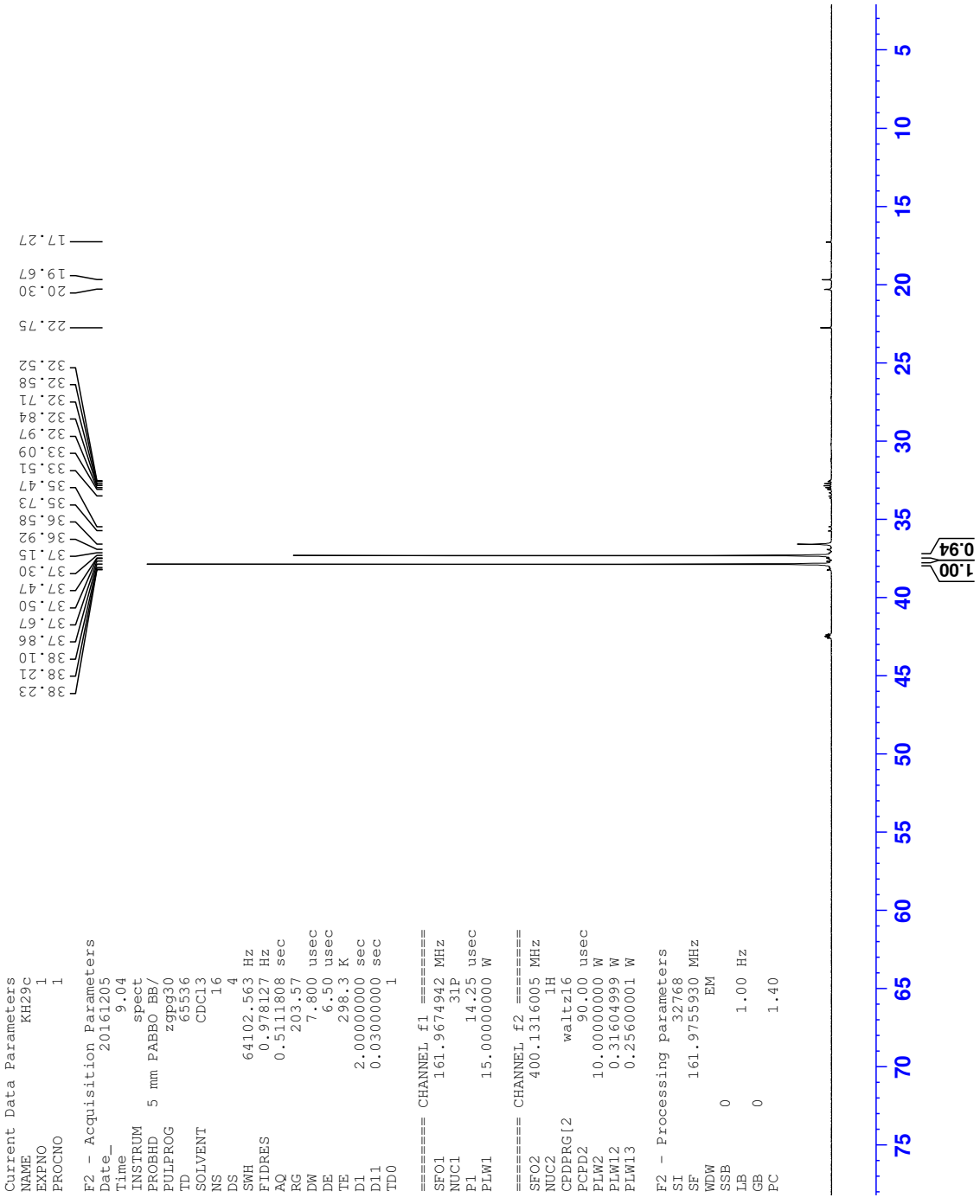


Figure 4: NMR analysis of final menthyl (hydroxymethyl)-phenyl phosphinate mixture after second addition of paraformaldehyde and reflux for 24 h.

Preparation of (S_P)-menthyl (hydroxymethyl)-phenyl phosphinate: Additional work up from the reaction above was done by Rachel Butler of Montchamp Phosphorus Research Group in order to isolate a nearly pure sample of the S_P diastereoisomer. Directions were to crystallize from diethyl ether at room temperature. NMR can be noted in Figure 5.

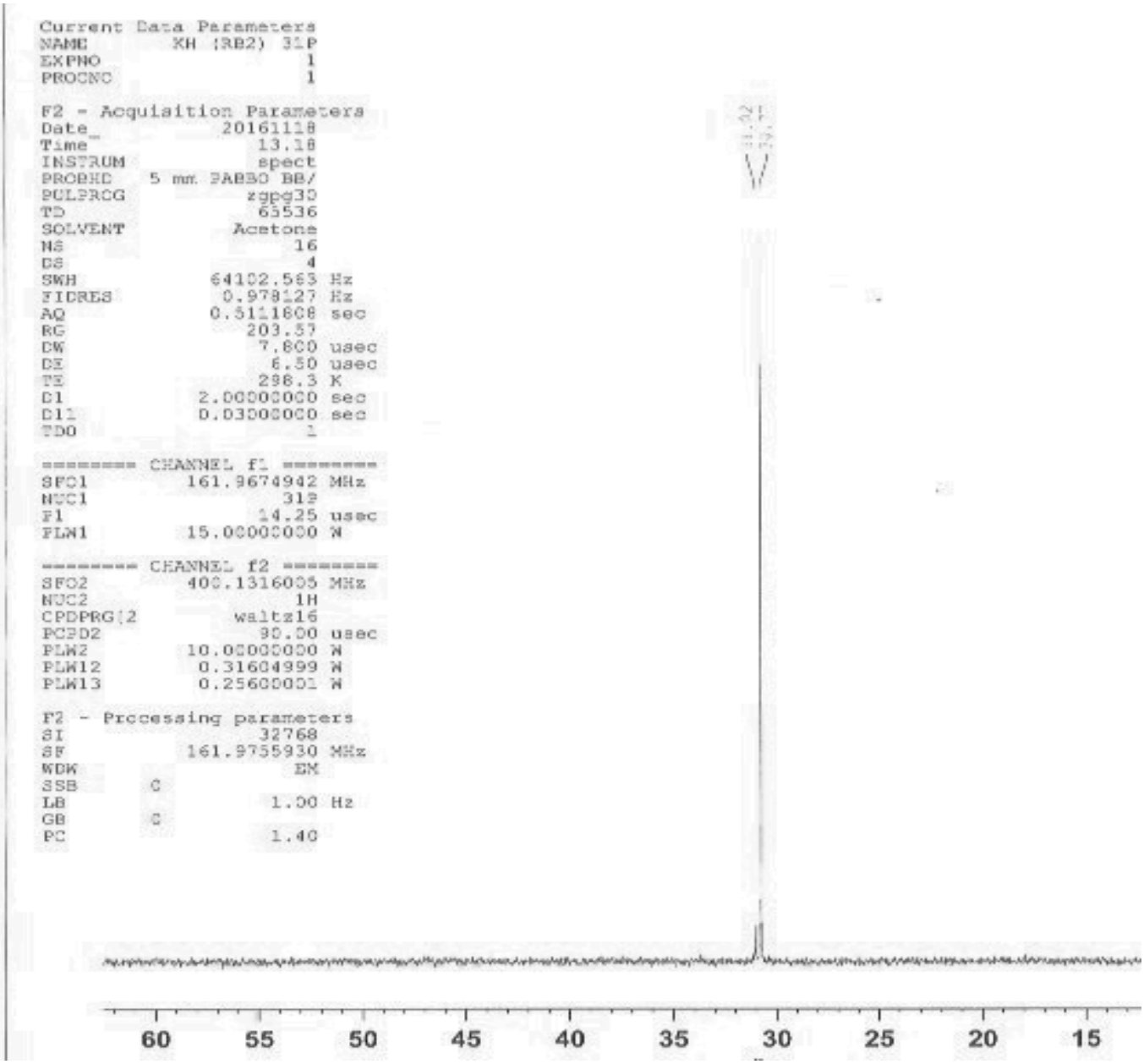


Figure 5: NMR of (S_P)-menthyl (hydroxymethyl)-phenyl phosphinate used as template.

Preparation of MAA Polymer: Polymers were prepared at different ratios as noted in Table 1. In general: In a 100-mL round bottom flask containing 40-mL of solvent (toluene or chloroform), 1 mmol of (S_P)-menthyl (hydroxymethyl)-phenyl phosphinate was combined with designated mmol of methacrylic acid and ethylene glycol dimethacrylate followed by 1mmol of initiator (AIBN or ABCN). Mixture was placed under N_2 to reflux for approx. 16 h at 40 °C with constant stirring. The polymer obtained was a solid network that was removed from the flask and dried by vacuum filtration. The polymer was then crushed with a mortar and pestle to afford a fine white powder. The polymer was then dried under vacuum for 24 h and placed in freezer when not being utilized. Template was removed from the polymer by using a Soxhlet apparatus, which can be noted in Figure 6. Using a 150-mL flask with approx. 100-mL of ethanol, the polymer was placed in a thimble within the soxhlet and washed as the ethanol was refluxed at approx. 80 °C for 24 h. Polymer was then removed from the Soxhlet and dried first under vacuum filtration and then under vacuum for 24 h. Polymer was then ready for testing.

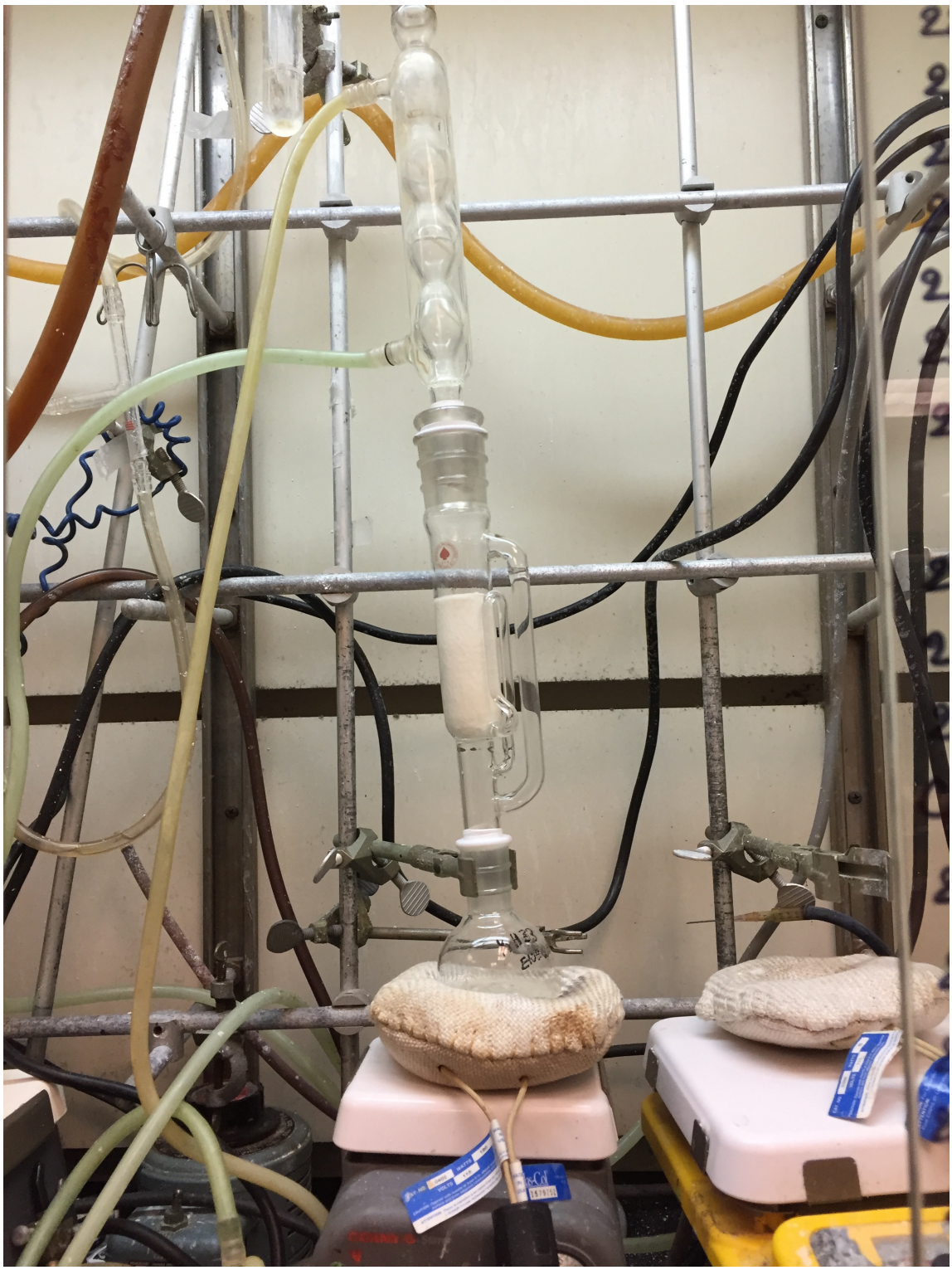


Figure 6: Soxhlet Apparatus shown with condenser and polymer contained in thimble.

Preparation of DEMA polymers: Polymers were prepared at different rations as noted in Table 1. In general: In a 100-mL round bottom flask containing 40-mL of solvent (toluene or chloroform), 1 mmol of (S_P)-menthyl (hydroxymethyl)-phenyl phosphinate was combined with designated reaction amount of 2-(diethylamino)ethyl methacrylate and ethylene glycol dimethacrylate followed by 1mmol of initiator (AIBN or ABCN). Mixture was placed under N_2 to reflux for approx. 16 h at 40 °C with constant stirring. The polymer obtained was a solid network that was removed from the flask and dried by vacuum filtration. The polymer was then crushed with a mortar and pestle to afford a fine white powder. The polymer was then dried under vacuum for 24 h and placed in freezer when not being utilized. Template was removed from the polymer by using a Soxhlet apparatus, which can be noted in Figure 6. Using a 150-mL flask with approx. 100-mL of ethanol, the polymer was placed in a thimble within the soxhlet and washed as the ethanol was refluxed at approx. 80 °C for 24 h. Polymer was then removed from the soxhlet and dried first under vacuum filtration and then under vacuum for 24 h. Polymer was then ready for testing.

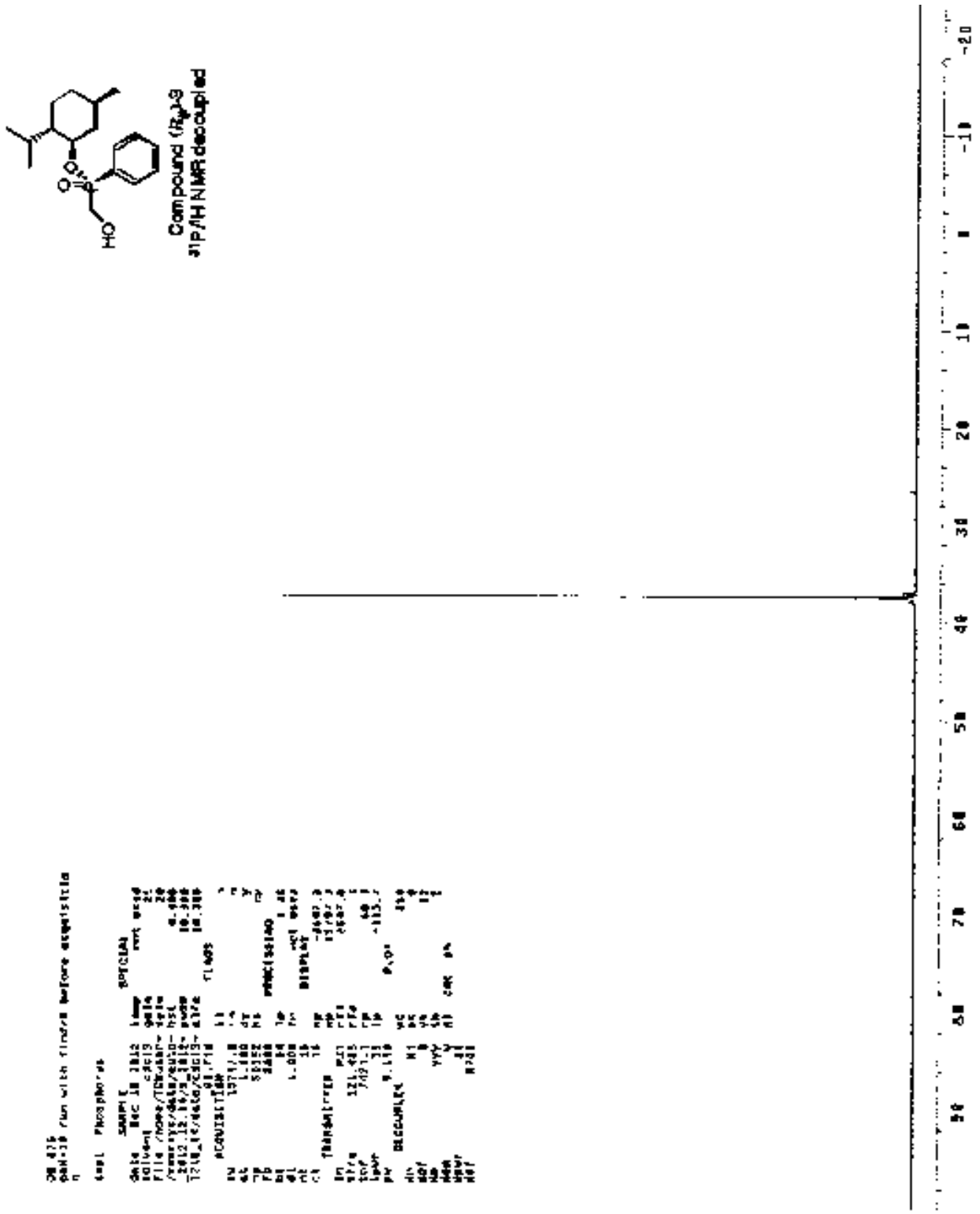


Figure 7: R_P menthyl (hydroxymethyl)-phenyl phosphinate reference NMR

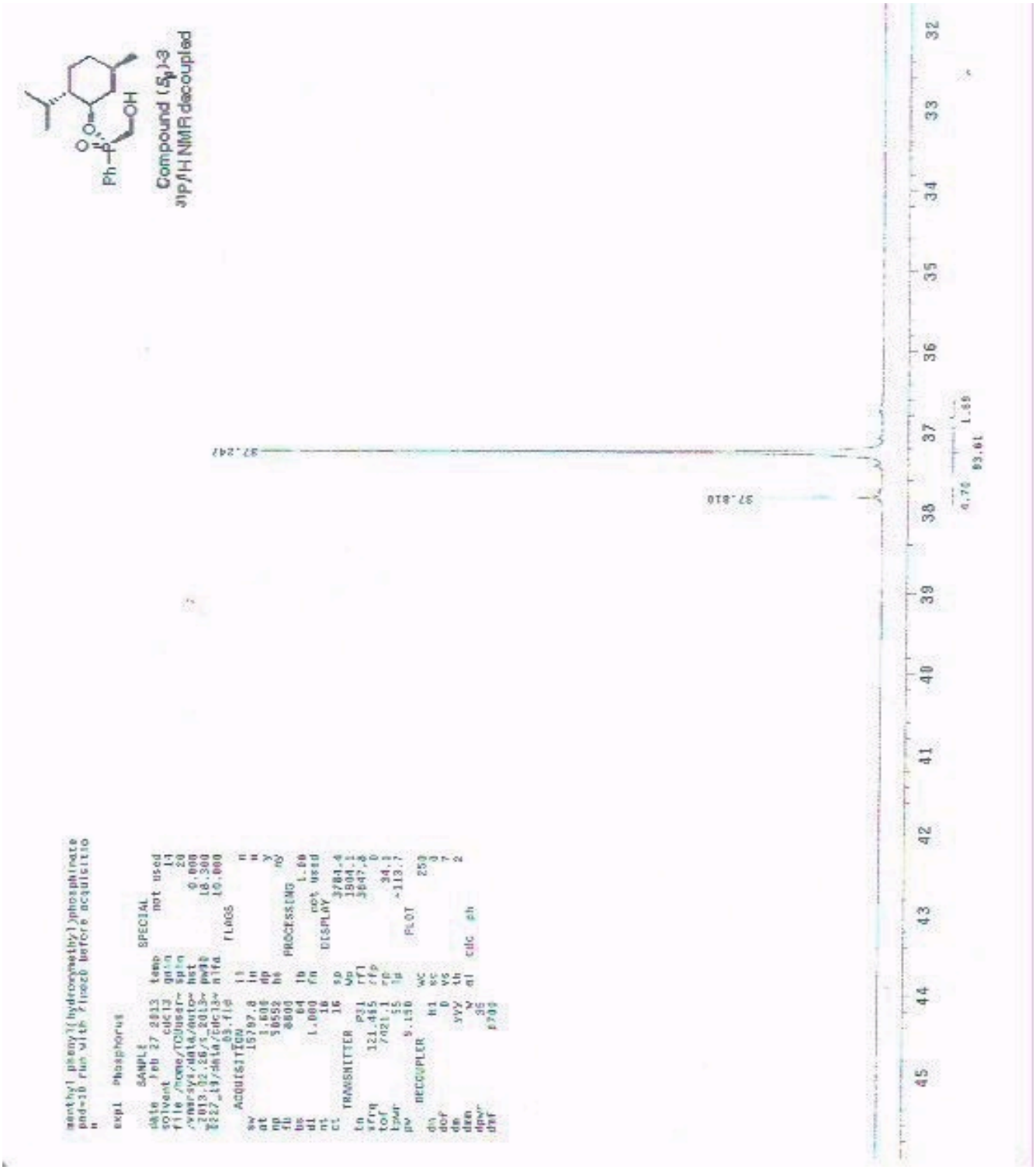


Figure 8: S_P menthyl (hydroxymethyl)-phenyl phosphinate reference NMR

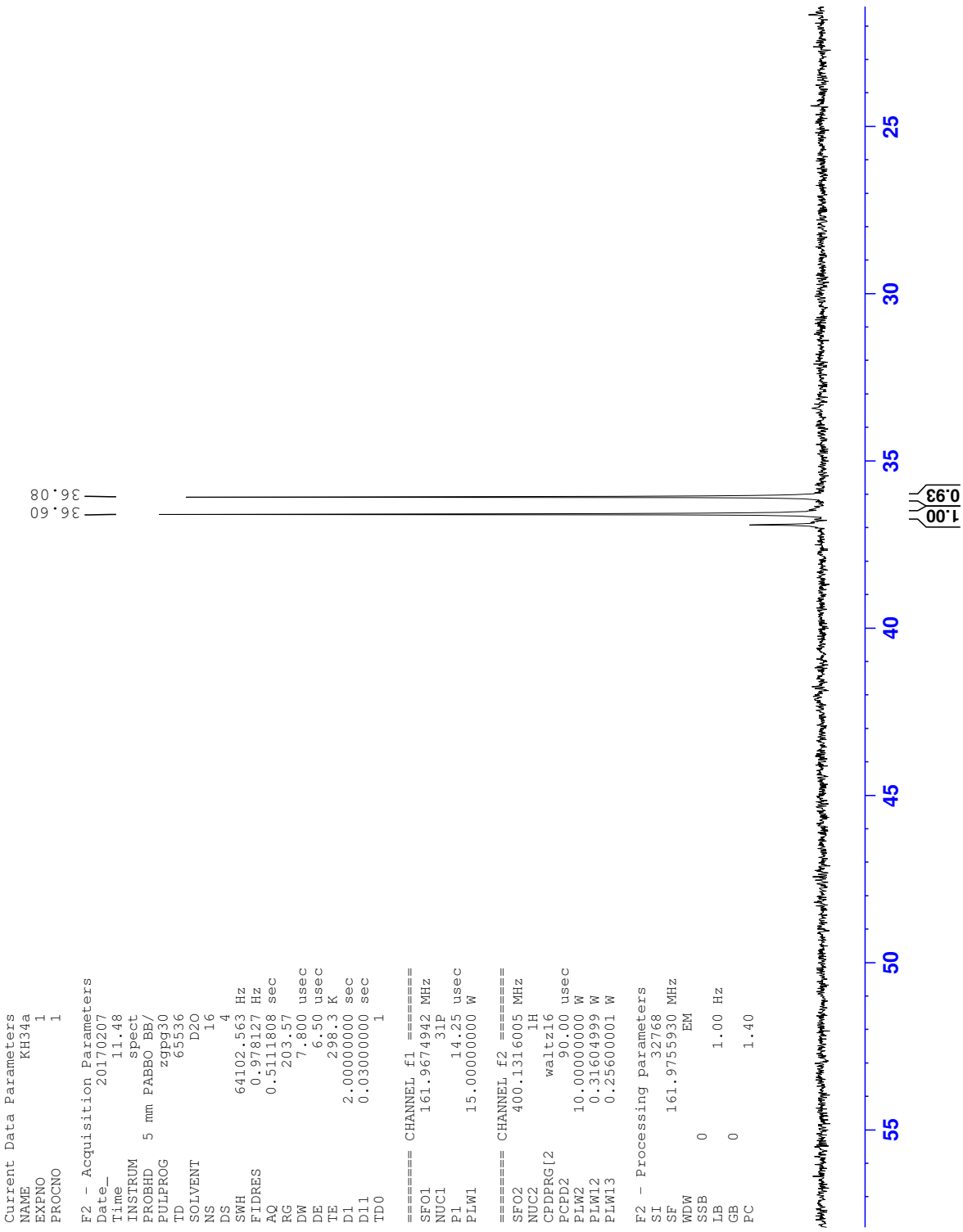


Figure 9: NMR of mixture of diastereoisomers before soak step (exp. 33)

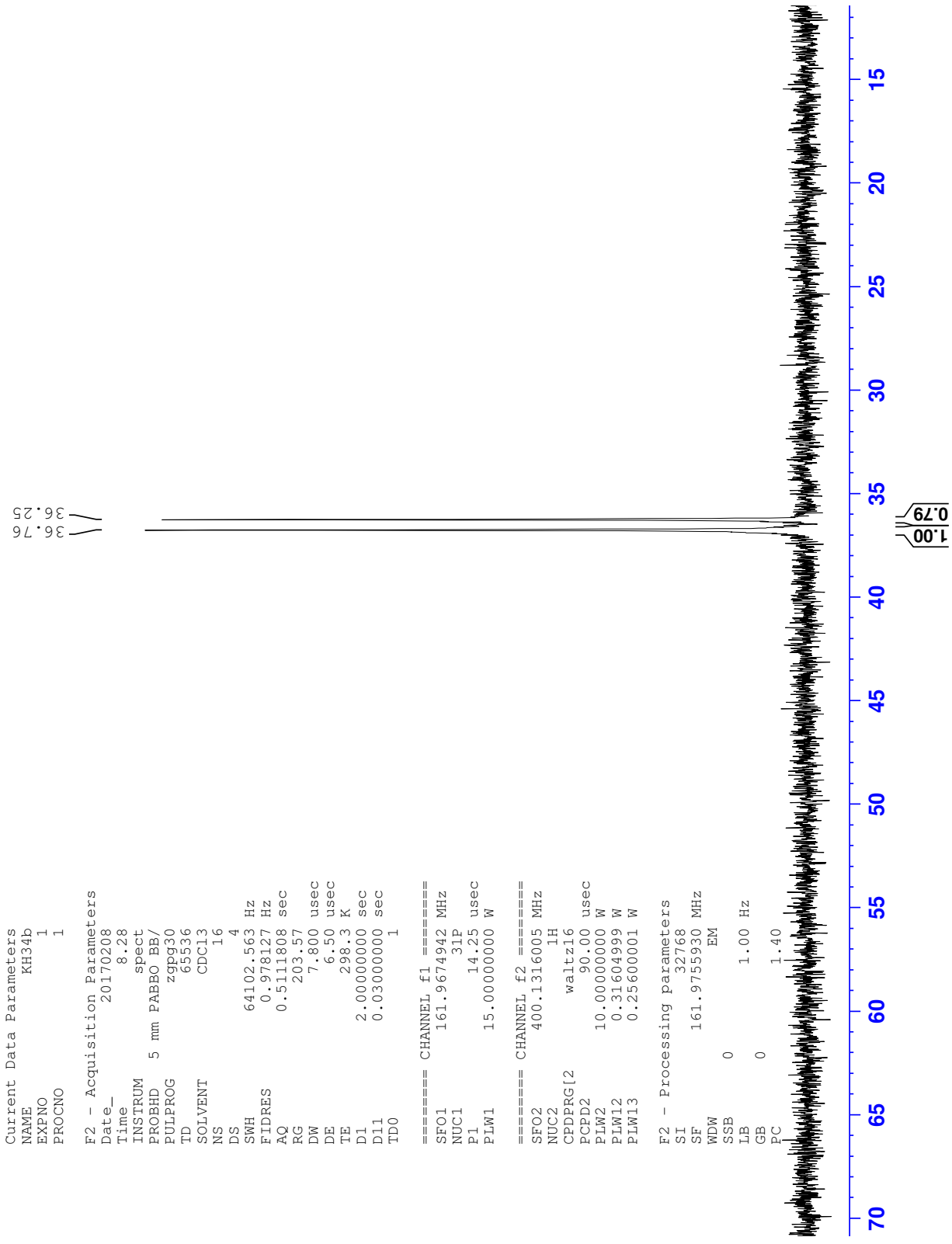


Figure 10: NMR of mixture of diastereoisomers after polymer removal (exp. 33)

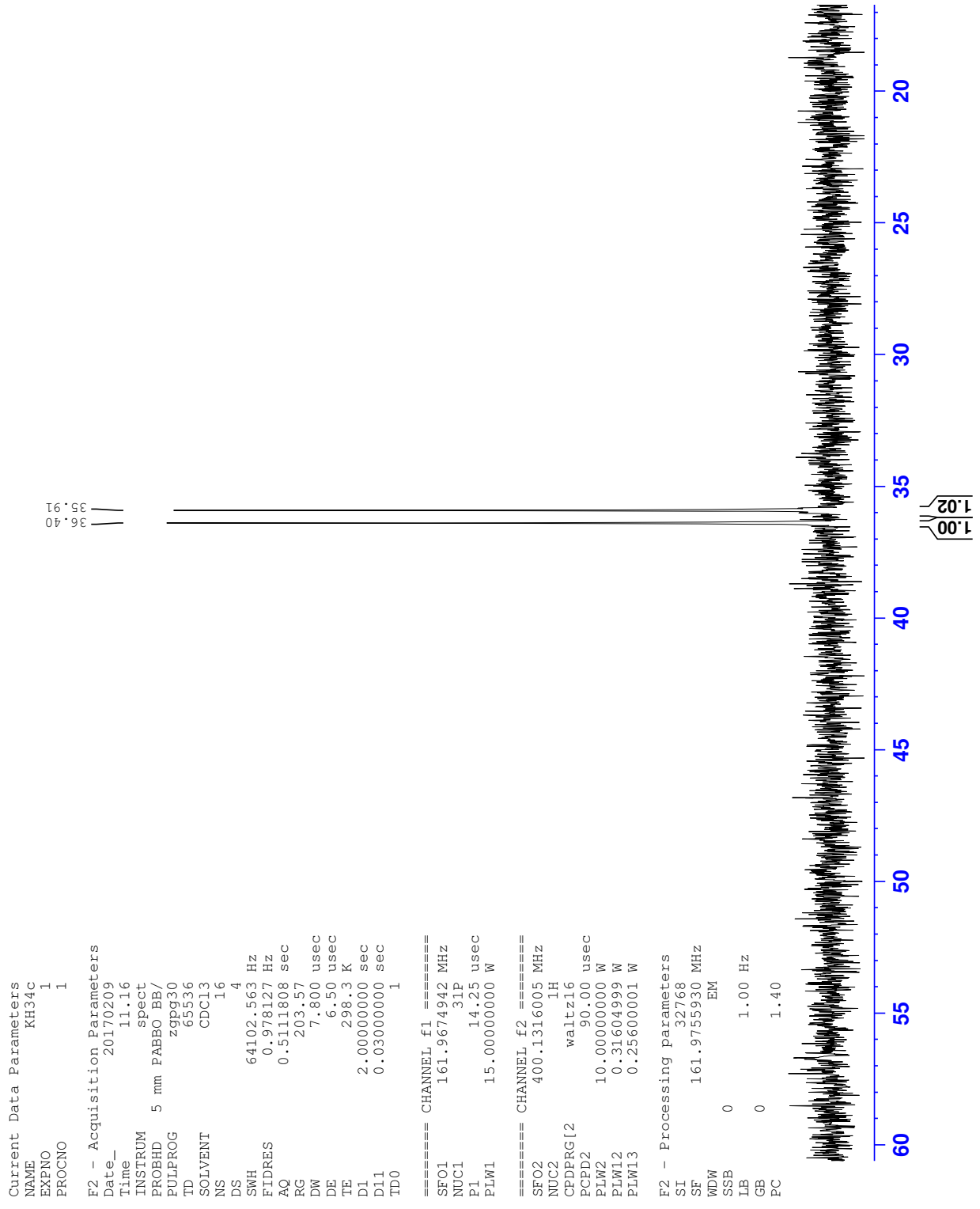


Figure 11: NMR of diastereoisomers after final wash of polymer (exp. 33)

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