FORMATION OF ENAMINES AND 1,2-DIFUNCTIONALIZED OLEFINS VIA CATALYTIC DEHYDROGENATION BY PINCER-Ir COMPLEXES

By

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Alan S. Goldman

And approved by

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ABSTRACT OF THE DISSERTATION

FORMATION OF ENAMINES AND 1,2-DIFUNCTIONALIZED OLEFINS VIA CATALYTIC DEHYDROGENATION BY PINCER-Ir COMPLEXES

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Dissertation Director:

Alan S. Goldman

Efficient pincer-ligated-iridium catalysts are reported for the dehydrogenation of amines to give enamines and for the dehydrogenation of 1,2-difunctionalized C-C linkages to give the corresponding 1,2-difunctionalized olefins. Isotope effect studies indicate that the rate-determining step is β-C-H bond cleavage following a pre-equilibrium cleavage of the α-C-H bond.

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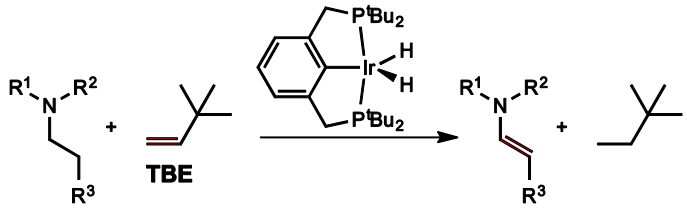
INTRODUCTION

The ability to effect selective catalytic conversions of typically unreactive C-H bonds has emerged as one of the major frontiers in organic chemistry in recent years, offering the promise of simple atom-economical methods for the synthesis of valuable functionalized organic compounds.[1] Pincer-ligated iridium complexes have been studied intensively in this context,[2] mostly as highly active and robust catalysts for the dehydrogenation of alkanes, but also for the dehydrogenation of aliphatic C-C linkages in molecules other than alkanes. Our laboratory has previously reported the synthesis of enamines via dehydrogenation of the corresponding tertiary amines catalyzed by (^{tBu4}PCP)Ir [**1**, ^{R4}PCP = κ^3-C_6H_3-2,6-$(CH_2PR_2)_2$],[3] using a hydrogen acceptor (**Scheme 1**).[4] Enamines are highly valuable synthons, used extensively as nucleophiles for the selective formation of C-C bonds by Michael reactions, as Diels-Alder dienophiles, and in a wide range of other reactions.[5]



Scheme 1. Reported synthesis of enamines via catalytic dehydrogenation

Subsequent to the early pincer-Ir dehydrogenation work with precursors of (^{tBu4}PCP)Ir,[3, 6] it was found that precursors of (^{iPr4}PCP)Ir (**2**) and derivatives are often catalytically more active for alkane dehydrogenation.[7] It was later found in our lab that (^{iPr4}PCP)IrH_n (n = 2, 4),[8] and the corresponding *para*-methoxy-substituted derivative (MeO-^{iPr4}PCP)IrH_n (**3**)[9] are significantly more effective than (^{tBu4}PCP)IrH_2 as catalysts for

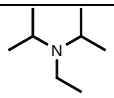
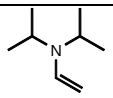
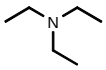
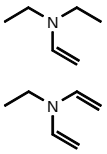
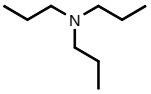
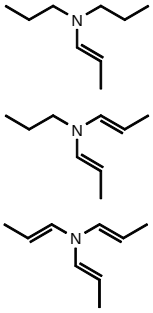
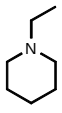
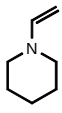
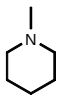
dehydrogenation of tertiary amines to enamines.[10] In this work, we find that with the sterically unhindered **2** and the *para*-methoxy substituted derivative **3**, we are able to dehydrogenate sterically crowded 1,2-difunctionalized saturated C-C linkages. This represents a novel approach to the corresponding 1,2-difunctionalized olefins which are attractive precursors for further functionalization reactions, leading to advanced building blocks that cannot be efficiently synthesized via known methods. These 1,2-difunctionalized olefins are often electron-rich alkenes, and may undergo further chemical manipulations like cycloaddition reactions,[11] such as [2+1] cycloaddition (cyclopropanation, Simmons-Smith type reaction),[12] [2+2],[13] [3+2][14] and [4+2] cycloadditions,[15,16] to afford various compounds as novel building blocks for organic synthesis.

RESULTS AND DISCUSSION

In our lab's previous report of the transfer-dehydrogenation of tertiary amines catalyzed by (^{tBu4}PCP)IrH_2,[4] we found that a relatively high catalyst loading was generally required for good yields. With (^{iPr4}PCP)IrH_2 and the same substrates as investigated previously, using NBE as hydrogen acceptor, satisfactory yields were generally achieved with a catalyst loading of only 2%, although higher temperatures and somewhat longer times were generally required (**Table 1**).[10] Note that with the same reaction temperatures and time, the yields of the reactions with (^{tBu4}PCP)IrH_2 were actually lowered, not improved. The need for higher temperature with (^{iPr4}PCP)Ir is likely a result of stronger bonding of olefin (acceptor or enamine) to the catalyst. Very high yields with (^{iPr4}PCP)Ir, much higher than with (^{tBu4}PCP)Ir, have also been reported for alkane

transfer-dehydrogenation using the strongly-binding hydrogen acceptors ethylene and propylene; in this case the optimal temperatures (>200 °C) are significantly higher than that found with (^{tBu4}PCP)Ir.[7c]

Table 1. Catalytic dehydrogenation of tertiary amines: (MeO-^{iPr4}PCP)IrH_2 vs. (^{tBu4}PCP)IrH_2[10]

			(MeO-^{iPr4}PCP)IrH_2		**(^{tBu4}PCP)IrH_2**	
Entry	Substrate (0.1 M)	Product	Conditions (120 °C)	Yield (%)	Conditions (90 °C)	Yield (%)
1			48 h, 2 equiv NBE, 1% cat.	90	5 h, 2 equiv TBE, 10% cat. 24 h, 2 equiv TBE, 2% cat.	98 65
2			32 h, 2 equiv NBE, 2% cat.	95	24 h, 2 equiv TBE, 10 % cat.	65
3			32 h, 4 equiv NBE, 2% cat.	53 40	24 h, 3 equiv TBE, 10% cat.	25 75
4			32 h, 4 equiv NBE, 2% cat.	40 38 6	24 h, 2 equiv TBE, 10 % cat.	43 11 -
5			32 h, 2 equiv NBE, 2% cat.	39	24 h, 2 equiv TBE, 10 % cat.	10
6			48 h, 2 equiv NBE, 2% cat.	90	24 h, 3 equiv TBE, 10% cat. 24 h, 2 equiv NBE, 10% cat.	67 92
7			48 h, 2 equiv NBE, 2% cat.	N.R.	24 h, 2 equiv TBE, 10 % cat., 110 °C	N.R.

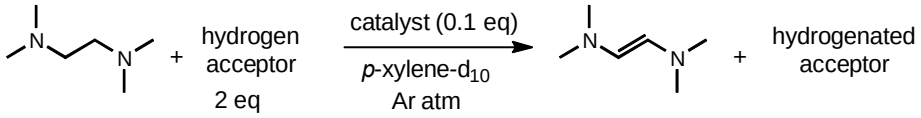
Note: all reactions were conducted in *p*-xylene-d_{10} solvent and were monitored by ^{31}P NMR and ^{1}H NMR spectroscopy over the course of the reaction. Yields were determined by ^{1}H NMR spectroscopy.

In general, the same patterns of reactivity were observed with (MeO-^{iPr4}PCP)Ir as with (^{tBu4}PCP)Ir. This includes complete selectivity for dehydrogenation of an *N*-ethyl group versus a *N*-i-propyl group (entry 1) and the failure to dehydrogenate the piperidine ring in either *N*-methylpiperidine or *N*-ethylpiperidine. The greater effectiveness of (MeO-^{iPr4}PCP)Ir as compared with (^{tBu4}PCP)Ir, however, was much more marked for the dehydrogenation of *n*-propyl groups (entry 4) and the *i*-Pr group (entry 5). This is likely attributable to increased importance of the lesser crowding at the metal center of (MeO-^{iPr4}PCP)Ir in the case of dehydrogenation of C-C linkages more crowded than the ethyl group.[10]

As observed in (^{tBu4}PCP)Ir-catalyzed reactions, all of the enamine products degraded, usually within several hours, after being isolated from the catalyst (via vacuum transfer of enamine and solvent); this behavior is consistent with the known instability of simple enamines.[5a, 17] Thus it is quite remarkable that the enamines are stable at the high temperature (120 °C) at which they are formed.[10] In view of that stability it is not surprising that the enamines are indefinitely stable – while still in the presence of the catalyst – at room temperature. As previously proposed, it seems probable that the catalysts inhibit chain reactions leading to loss of the enamine.[4]

1,2-Difunctional olefins are of great interest as versatile substrates for various cycloadditions in organic synthesis. In this context we studied the catalytic dehydrogenation of *N*,*N*,*N*',*N*'-tetramethylethylene-1,2-diamine (TMEDA) (**Scheme 2**). Various conditions were screened, including the use of three different alkenes as

hydrogen acceptors (**Fig. 1**). Significant yields of the desired product were achieved only with NBE.[18]



Scheme 2. Reaction model in screening reaction parameters for 1,2-difunctional olefins

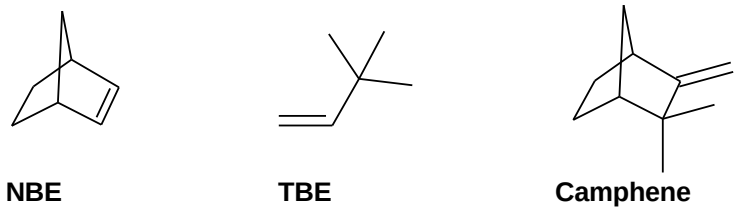


Figure 1. Hydrogen acceptors screened in this work

Catalysts **1**-**5** (**Fig. 2**) were screened for the model reaction (**Scheme 2**); among these catalysts, **2** and **3** are similar and are both proved to be effective. Catalyst **1** gave no observable product, presumably highlighting the importance of steric factors for dehydrogenation of this sterically hindered substrate. Catalyst **4** gave some product, but less than **2** or **3**. Catalyst **5** apparently polymerized the hydrogen acceptor (NBE)[19] and the desired dehydrogenation products were not detected.

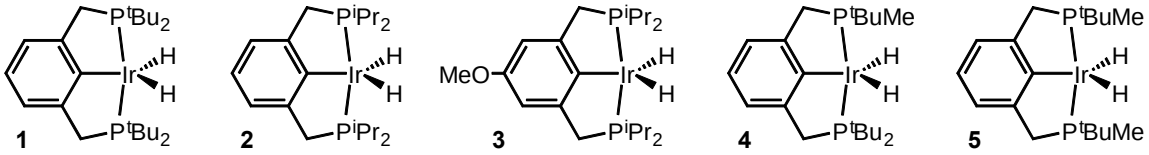
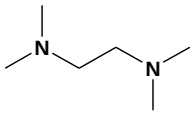
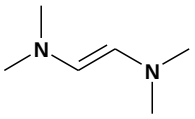
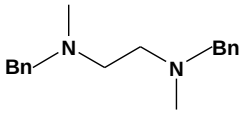
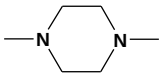
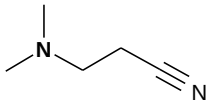
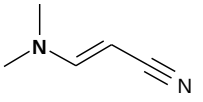
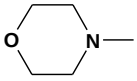
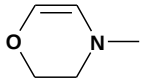
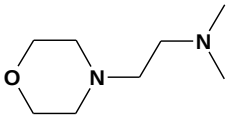
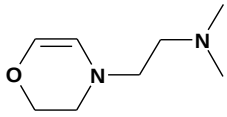
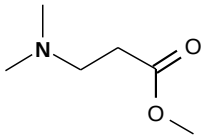
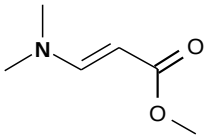
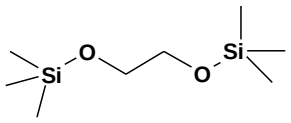
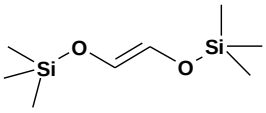


Figure 2. Pincer-iridium catalysts screened in this work

Entries 1, 4, 5, 6, 7 and 8 in Table 2 represent new chemical transformations and only a single isomer (*E*) was observed for entries 1, 4 and 7. *N*,*N*'-Dimethyl-*N*,*N*'-dibenzyl-ethylene-1,2-diamine (entry 2) did not undergo any reaction, which is likely

attributable to steric hindrance by the benzyl substituents as compared with the methyl groups.

Table 2. Dehydrogenation reactions catalyzed by **2** with NBE as hydrogen acceptor [a]

Entry	Substrate	Product	Conditions	Yield (%)
1			**A** **B**	64% 98%
2			**A**	N. R.
3			**A**	N. R.
4			**A**	84
5			**A** (150 ^{o}C/24 h)	90
6			**A**	85
7			**A** (110 ^{o}C/55 h)	27
8			**A** (110 ^{o}C/40 h) (110 ^{o}C/70 h)	96 *E*/*Z* = 6.5/1 100 *E*/*Z* = 10/1
9	**$CH_3(CH_2)_3CN$**		**A**	N. R.
10	**$NCCH_2CH_2CN$**		**A**	N. R.

(a) All reactions were run in *p*-xylene-d_{10} and NBE was used as hydrogen acceptor. All yields were determined by ^{1}H NMR spectroscopy. **A**: 0.05 mmol substrate, 2.3 eq (0.1115 mmol) NBE, 15 mol% (4.0 mg) **2**, 143 °C, 45 h. **B**: 0.05 mmol of substrate, 2.0 eq (0.10 mmol) NBE, 25 mol% (6.6 mg) **2**, 143 °C, 24 h.

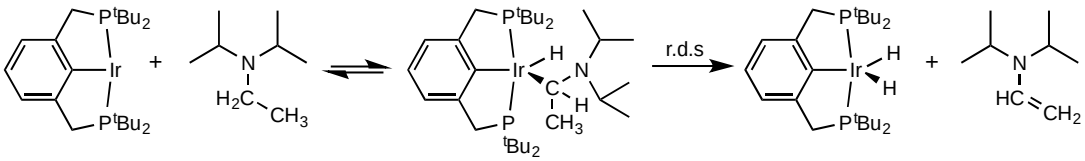
1,4-Dimethylpiperazine (entry 3) did not undergo dehydrogenation, in accord with the failure of either (MeO-^{iPr4}PCP)IrH_2 or (^{tBu4}PCP)IrH_2 to dehydrogenate *N*-methyl and *N*-ethyl piperidine at the ring position. Vinyl acrylates have been found to form stable, catalytically inactive, adducts with (^{tBu4}PCP)Ir.[20] Therefore, we were pleasantly surprised that some, albeit limited, catalytic dehydrogenation of methyl 3-(dimethylamino)propanoate (entry 7) was achieved, likely thanks to steric hindrance preventing the formation of such adducts. Relatedly, nitriles appear to coordinate fairly strongly to (PCP)Ir fragments, but a very good yield (84%, entry 4) was obtained with the substrate 3-(dimethylamino)propanenitrile. Previous attempts in our laboratory to dehydrogenate ethers have for the most part been unsuccessful apparently due to the formation of vinyl ether adducts. Some success has been achieved with ether dehydrogenation;[21] most notably in the context of this work, Brookhart and co-workers recently found that (^{iPr4}PCP)Ir could affect dehydrogenation of acyclic ethers.[22] With the bulky diether substrate of entry 8 excellent dehydrogenation yields were obtained. The apparently high reactivity of the acyclic amine substrates, as indicated by the good product yields, was confirmed in a competition experiment between cyclooctane (600 mM) and *N*,*N*-di(isopropyl)ethylamine (60 mM);[10] the cyclooctane substrate is frequently used in alkane dehydrogenation studies because of its anomalously low enthalpy of dehydrogenation. The ratio of cyclooctene to vinylamine remained roughly constant at 1 : 2.0, even from the earliest reaction times, indicating that the observed product ratio reflects a kinetic, not thermodynamic, product distribution. Dehydrogenation of the aminoethyl group was thus found to be 20 times more rapid

than dehydrogenation of COA on a per mol basis; on a per C-C bond basis the ratio is therefore 160.[10]

Competition experiments between *N*,*N*-di(alkyl)ethylamines reveal that reactivity is dependent upon the ancillary *N*-alkyl group as follows: *i*-propyl > ethyl > methyl in the ratio of ca. 140 : 7: 1.[10] This trend is opposite what would be expected based on consideration of steric factors. It is not obvious how it would be reconciled with the generally accepted pathway for alkanes which proceeds via oxidative-addition followed by β-hydrogen elimination.[2, 7b, 23]

We considered that the unusually high reactivity of the tertiary amines, and the more highly substituted amines in particular, might be attributed to a mechanism involving electron-transfer (oxidation of the amine). In this context the following kinetic isotope effect experiments were conducted.[10] *N*,*N*-di(isopropyl)ethylamine isotopomers $^{i}Pr_2N(CD_2CD_3)$, $^{i}Pr_2N(CD_2CH_3)$ and $^{i}Pr_2N(C_2H_5)$ were synthesized. In a competitive catalytic reaction **2** (10.2 mM), TBE (250 mM), $^{i}Pr_2N(C_2H_5)$ (30.7 mM) and $^{i}Pr_2N(C_2D_5)$ (61.4 mM) were allowed to react; k_{C2H5}/k_{C2D5} was found to be 7.0. A stoichiometric competition reaction of (^{tBu4}PCP)Ir(H)(Ph) (which is known to act as an effective precursor of the fragment (^{tBu4}PCP)Ir even at or below room temperature[24]) with $^{i}Pr_2N(C_2H_5)$ (146 mM) and $^{i}Pr_2N(CD_2CD_3)$ (291 mM) gave a KIE of k_{C2H5}/k_{CH2CD3} = 3.7. In another stoichiometric competition reaction, the reaction of (PCP)Ir(H)(Ph) with $^{i}Pr_2N(C_2H_5)$ (146 mM) and $^{i}Pr_2N(CD_2CH_3)$ (291 mM), the value of k_{C2H5}/k_{CD2CH3} was found to be 2.0. Thus k_{C2H5}/k_{C2D5} is equal to the product of the KIE values k_{C2H5}/k_{CH2CD3} and k_{C2H5}/k_{CD2CH3}.

The results of these isotope effect experiments clearly imply that C-H bond cleavage is involved in the rate-determining reaction step; thus electron-transfer from the amine is presumably not rate-determining. The value of 2.0 for k_{C2H5}/k_{CD2CH3} is consistent with an equilibrium isotope effect (preceding a rate-determining step) while the value of 3.7 for k_{C2H5}/k_{CH2CD3} indicates a rate-limiting kinetic isotope effect.[25] These isotope effects are thus consistent with a pathway of reversible oxidative addition of the α-C-H bond followed by rate-determining β-H-elimination (**Scheme 3**).[10]



Scheme 3. Dehydrogenation pathway by **1** consistent with observed isotope effects

EXPERIMENTAL SECTION

All NMR spectra were recorded on a Varian 500- or 400-MHz spectrometer. Screw-cap NMR tubes were used for catalytic dehydrogenation reactions. *p*-Xylene-d_{10} was used as solvent for all catalytic dehydrogenation reactions. *p*-Xylene-d_{10}, TBE, *N*,*N*,*N*',*N*'-tetramethylethylene-1,2-diamine (TMEDA), and 4-methylmorpholine were purified by treating with Na-K alloy, followed by vacuum distillation. All other substrates were stored over molecular sieves before use.

Typical procedure for catalytic dehydrogenation. All substrates, hydrogen acceptors, catalysts, and solvents were loaded into a screw-cap NMR tube in a glovebox at argon atmosphere. The mixture became a light brown solution. The capped NMR tube was removed from the glovebox. A ^{1}H NMR spectrum was acquired at time zero (t_0) and the capped NMR tube was heated in an oil-bath. The reaction progress was monitored by ^{1}H NMR spectroscopy. Yields were calculated based on the relevant peak areas in the ^{1}H NMR spectrum.

Preparation of *N,N'*-Dimethyl-*N,N'*-dibenzylethylenediamine:

A 50-mL round-bottom flask equipped with a magnetic stir bar and septum was degassed and refilled with N_2. Tetrahydrofuran (anhydrous, 20 mL) was added via syringe under N_2 atmosphere. The starting material, *N,N'*-dimethyl-ethylenediamine (0.89 g, 10 mmol) was added via syringe under N_2. The mixture was cooled to -20 ^{o}C in brine/dry ice bath under N_2. n-BuLi (2.5 M in hexane, 8.8 mL, 22 mmol) was added via

syringe over 20 minutes under N_2. The mixture was warmed to 15 ^{o}C over 30 minutes and was then cooled to -20 °C; benzyl bromide (4.3 g, 25 mmol) was then added via syringe over 10 min. The cooling bath was removed. The batch was stirred at ambient temperature for 1.5 h. Brine (10 mL) was added to quench the reaction. THF was removed on a rotary evaporator *in vacuo*. iPrOAc (20 mL) and water (20 mL) was added to the residue. The batch was transferred to a separatory funnel. The aqueous layer was separated and discarded. The organic layer was extracted with 1 N HCl (2 x 20 mL). The combined aqueous layer was treated with 4 N NaOH to reach pH 12. The batch was extracted with iPrOAc (2 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator *in vacuo* to afford product (2.35 g) as pale oil, in 87% yield.

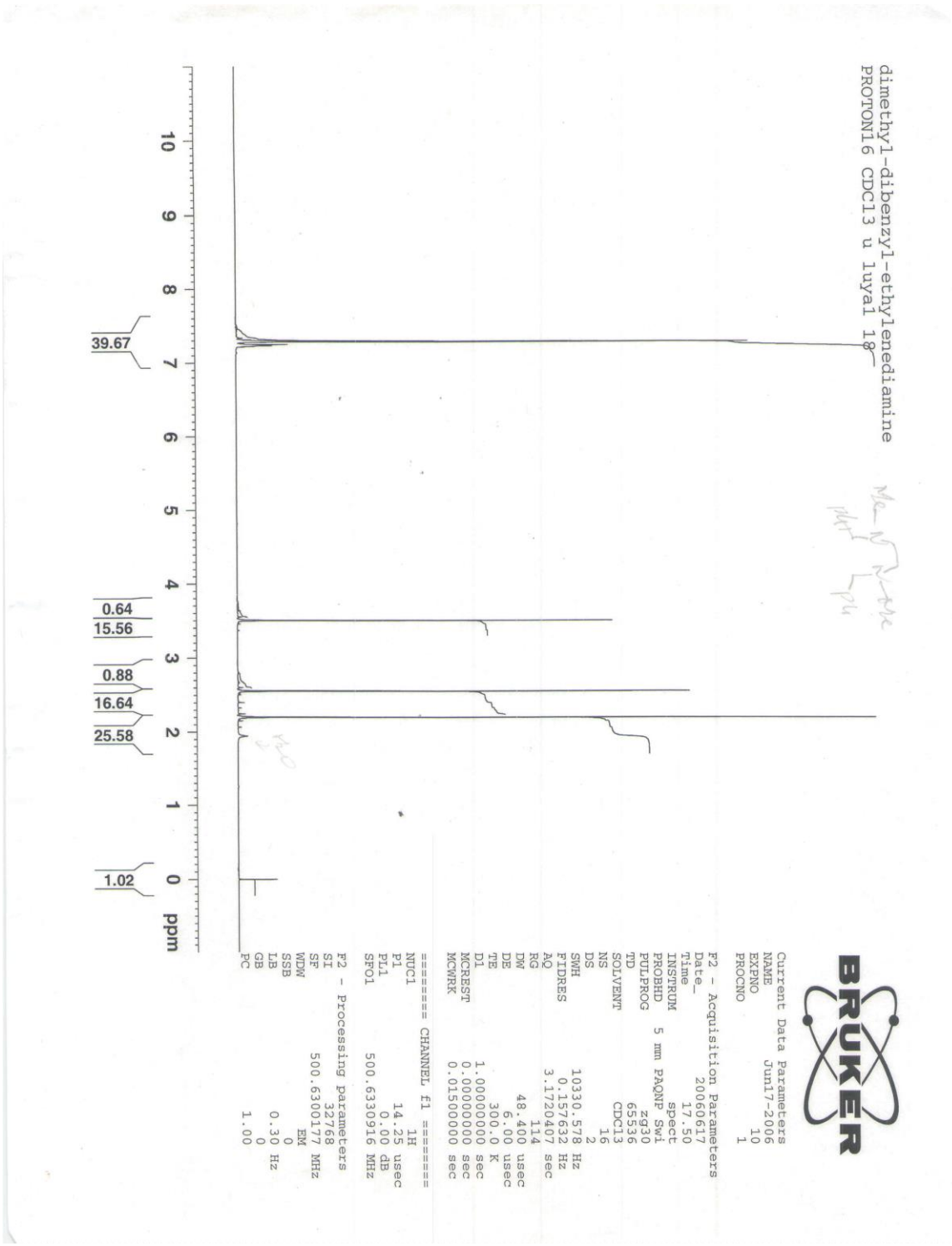


Figure 3. The ^{1}H NMR spectrum of *N,N'*-Dimethyl-*N,N'*-dibenzylethylenediamine

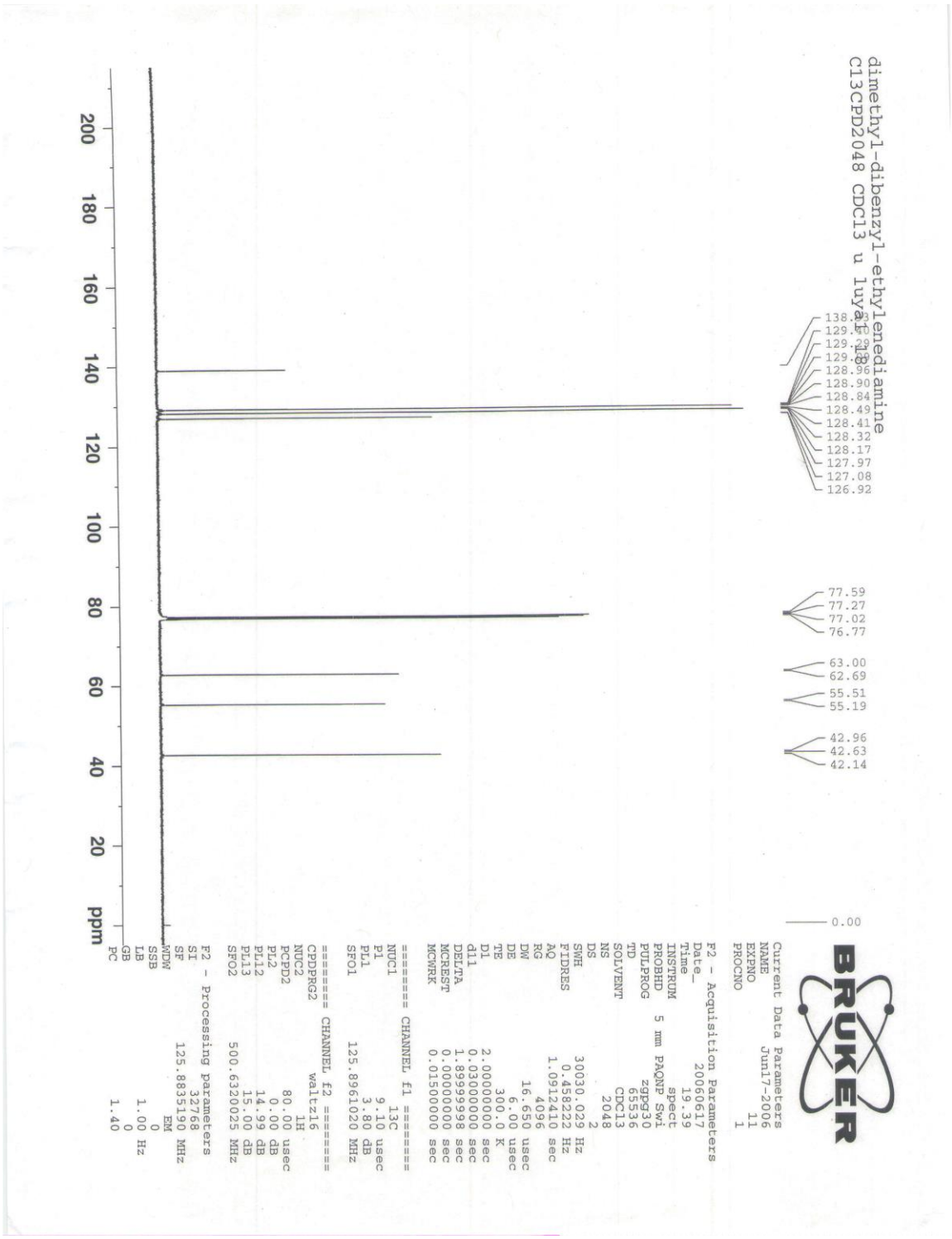


Figure 4. The ^{13}C NMR spectrum of *N,N'*-Dimethyl-*N,N'*-dibenzylethylenediamine

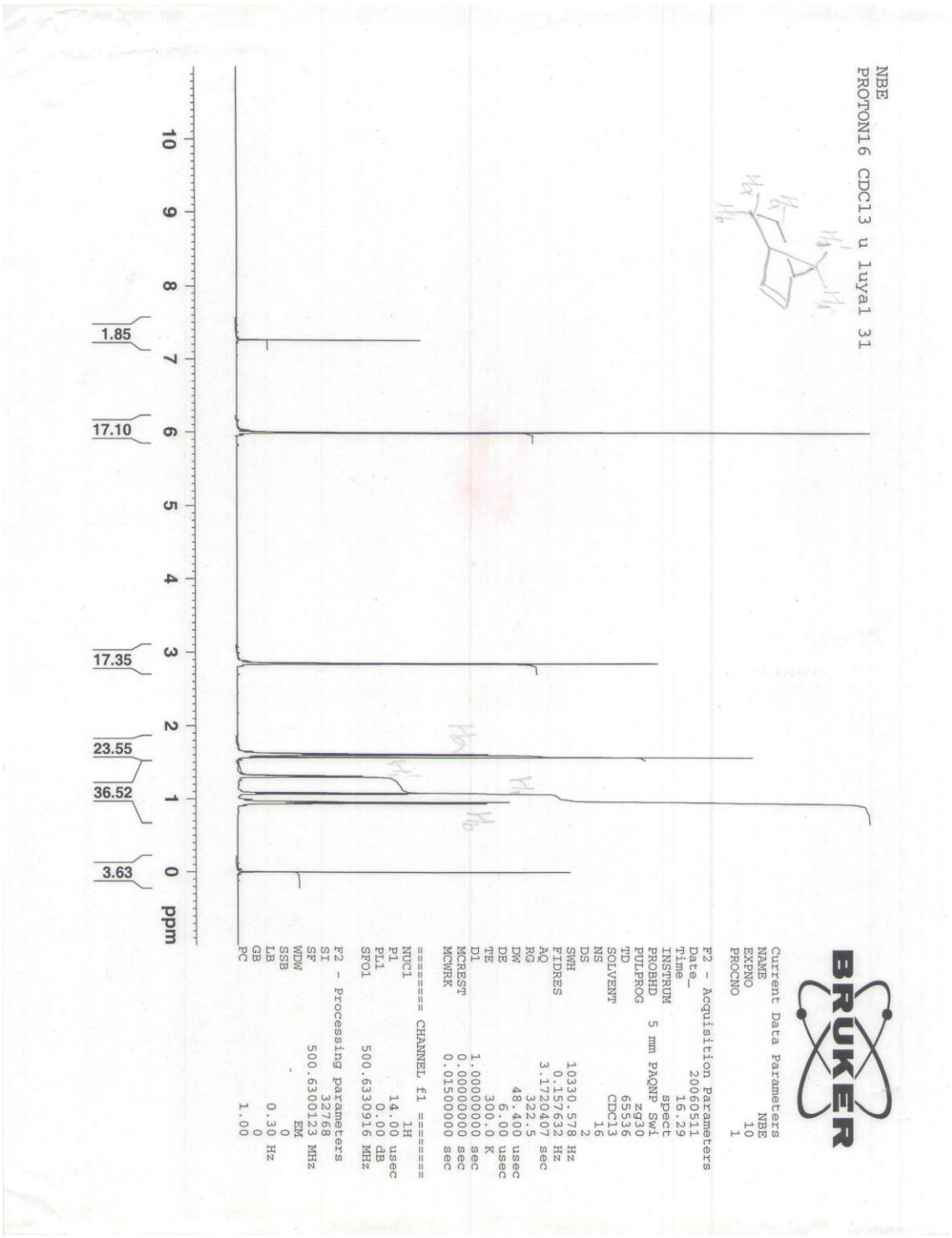


Figure 5. The ^{1}H NMR spectrum of norbornene (NBE)

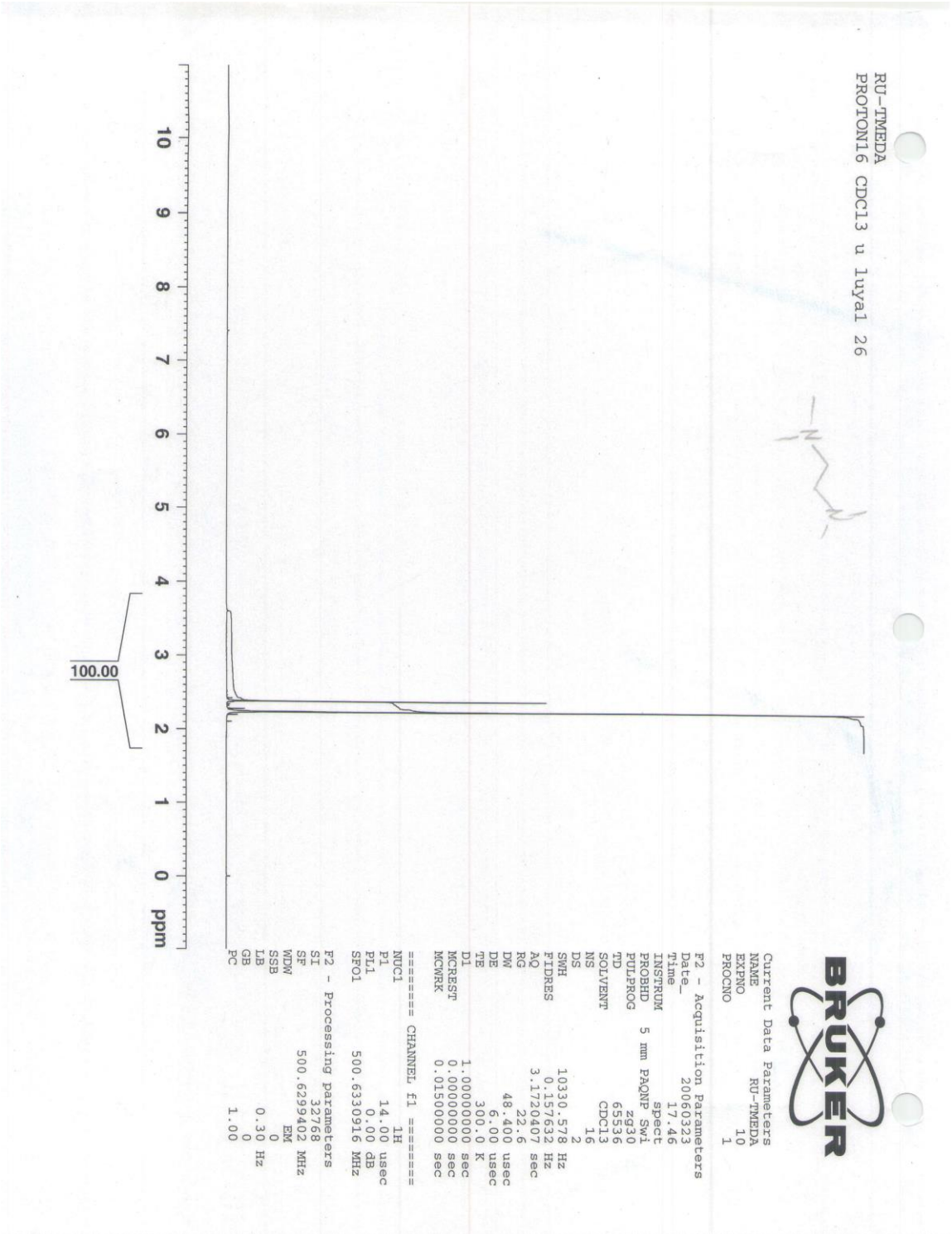


Figure 6. The ^{1}H NMR spectrum of TMEDA

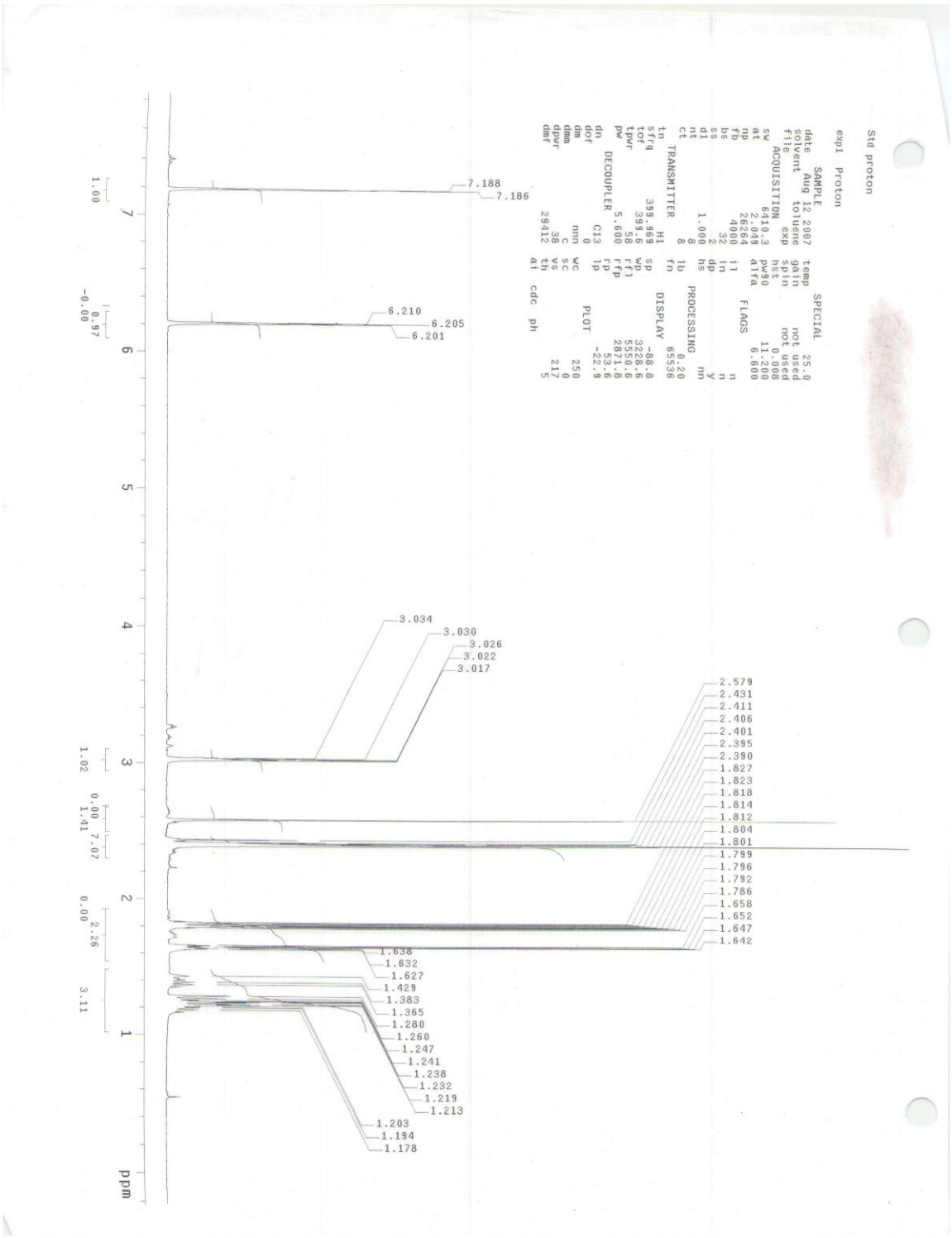


Figure 7. The ^{1}H NMR spectrum at t_0 for reaction mixture of entry 1 in table 2

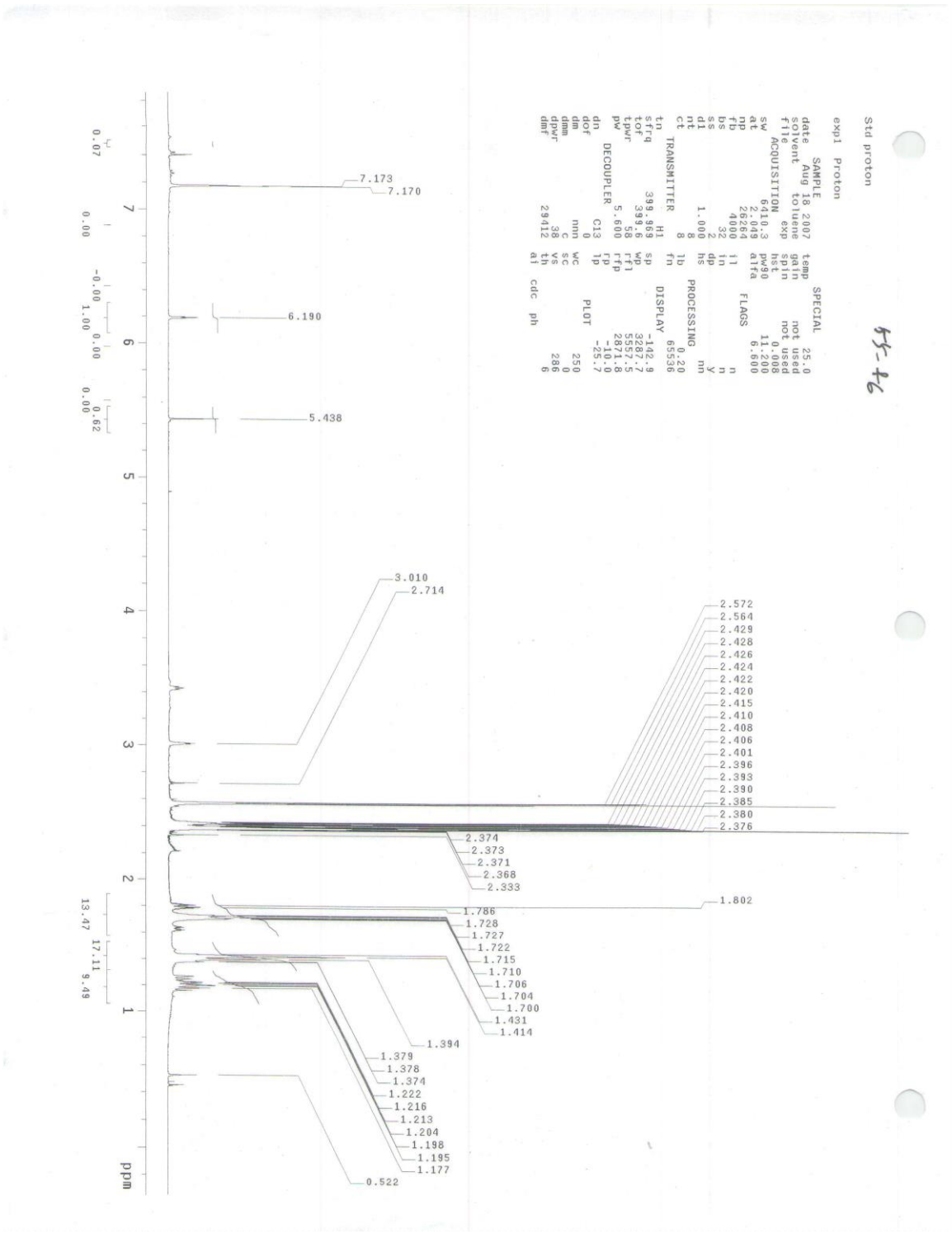


Figure 8. The ^{1}H NMR spectrum for reaction mixture of entry 1 (**A**) in table 2

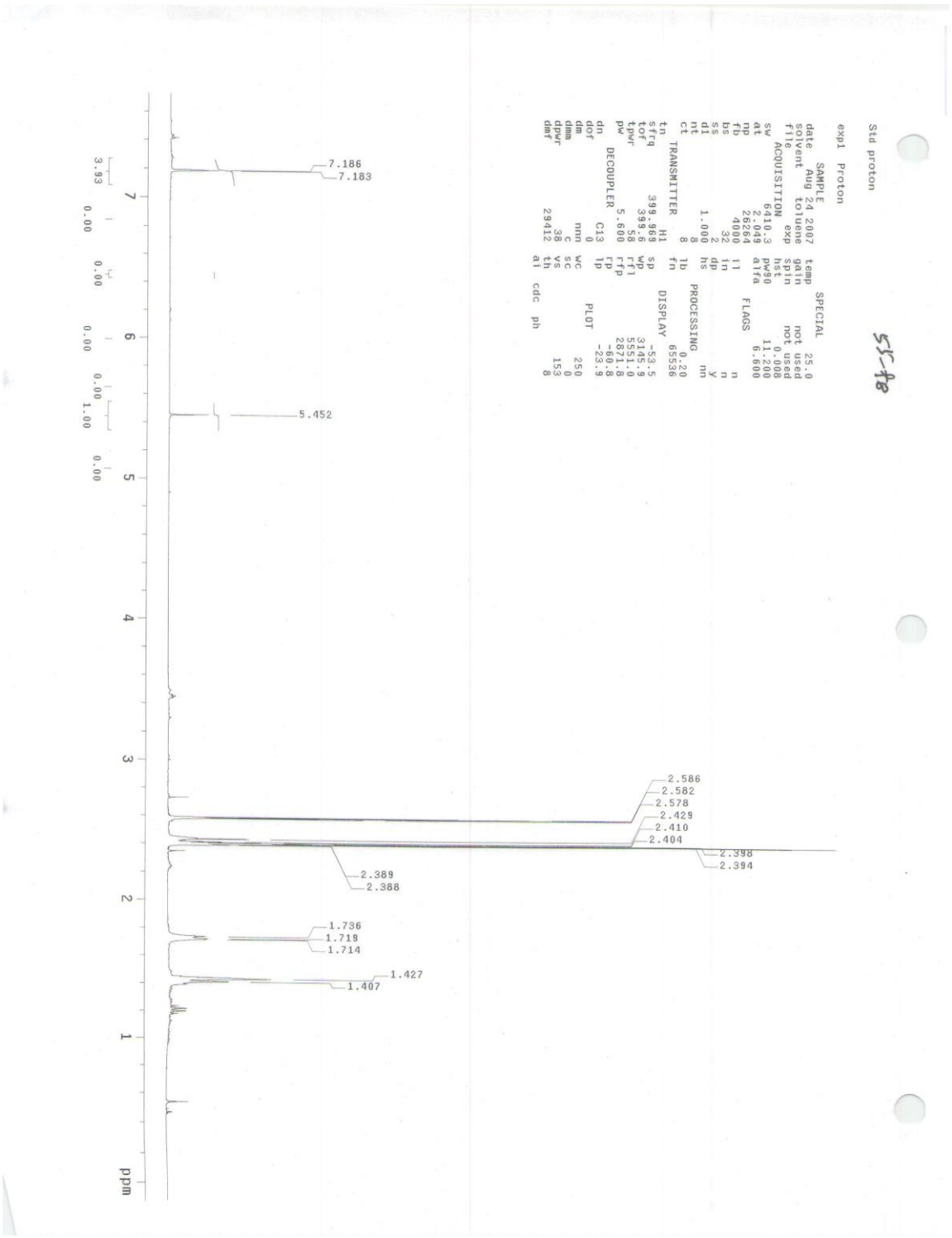


Figure 9. The ^{1}H NMR spectrum for reaction mixture of entry 1 (**B**) in table 2

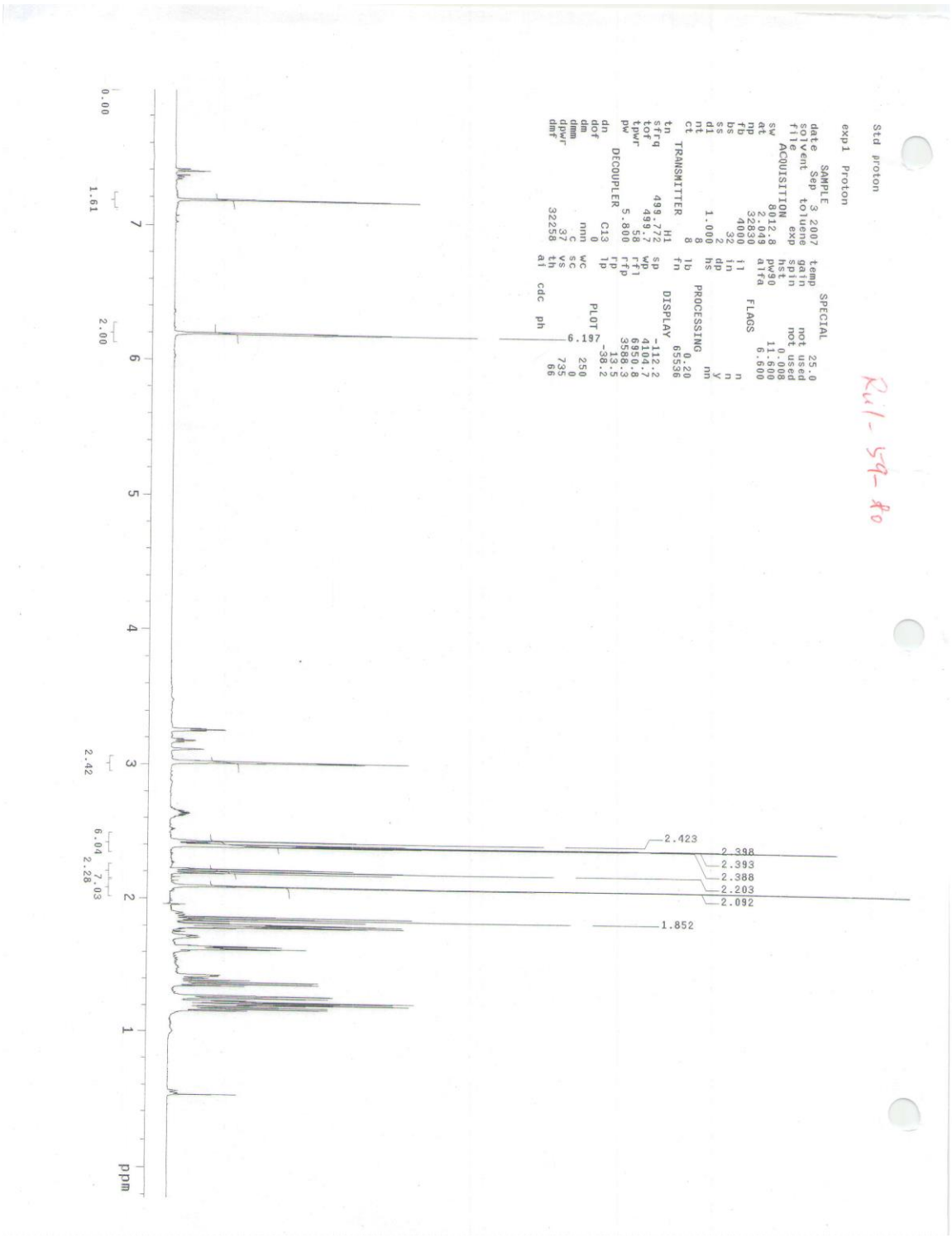


Figure 10. The ^{1}H NMR spectrum at t_0 for reaction mixture of entry 4 in table 2

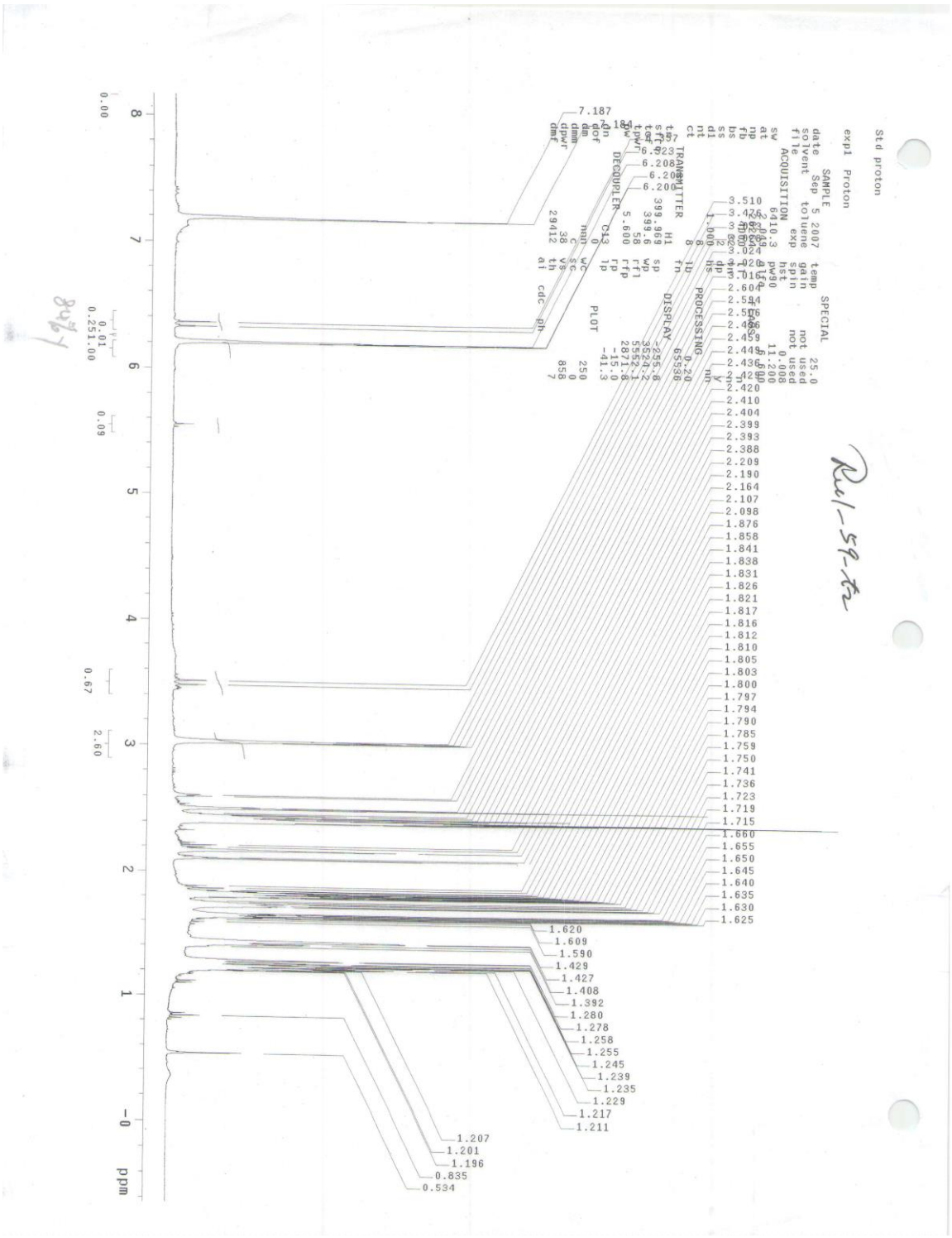


Figure 11. The ^{1}H NMR spectrum for reaction mixture of entry 4 in table 2

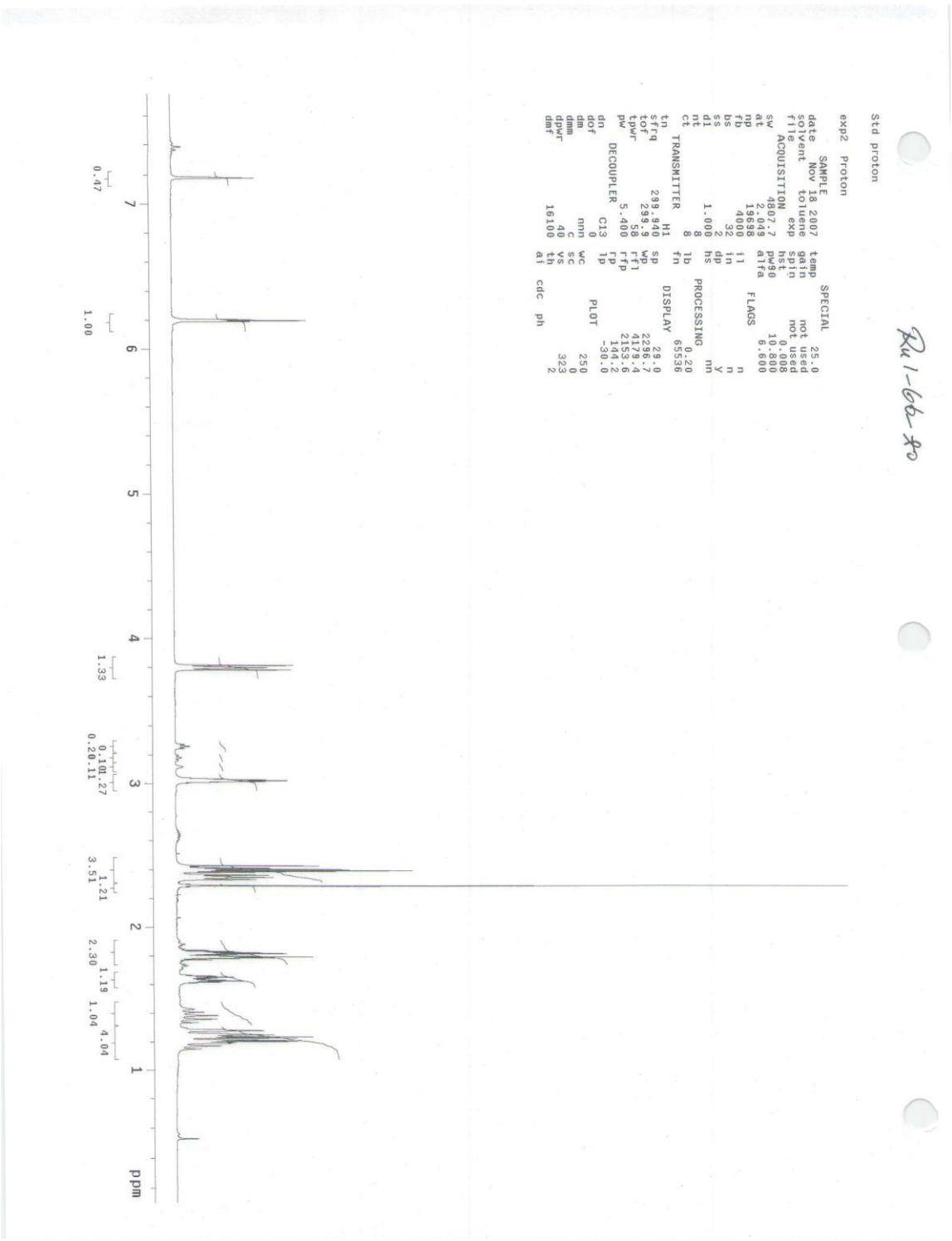


Figure 12. The ^{1}H NMR spectrum at t_0 for reaction mixture of entry 5 in table 2

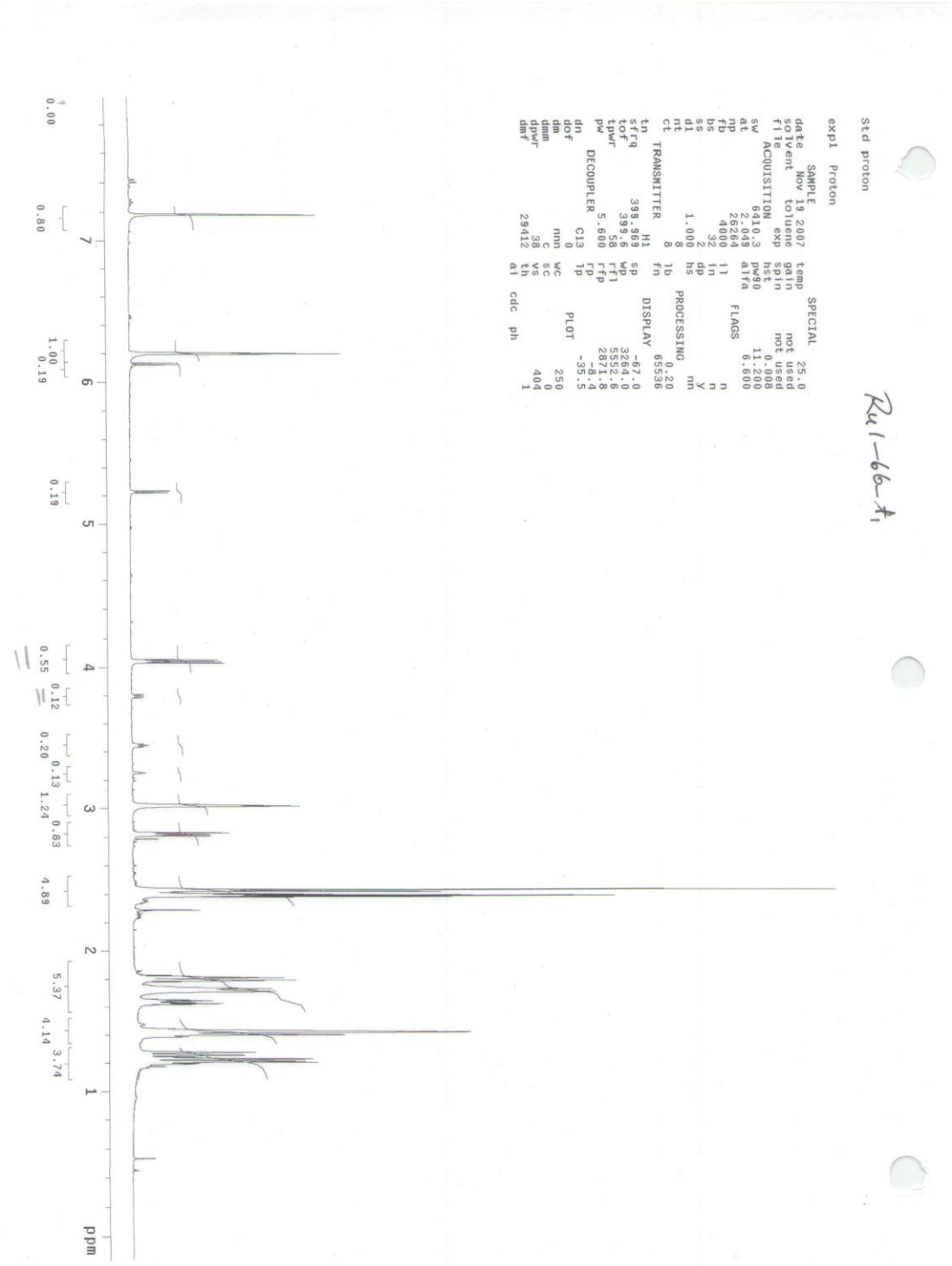


Figure 13. The ^{1}H NMR spectrum for reaction mixture of entry 5 in table 2

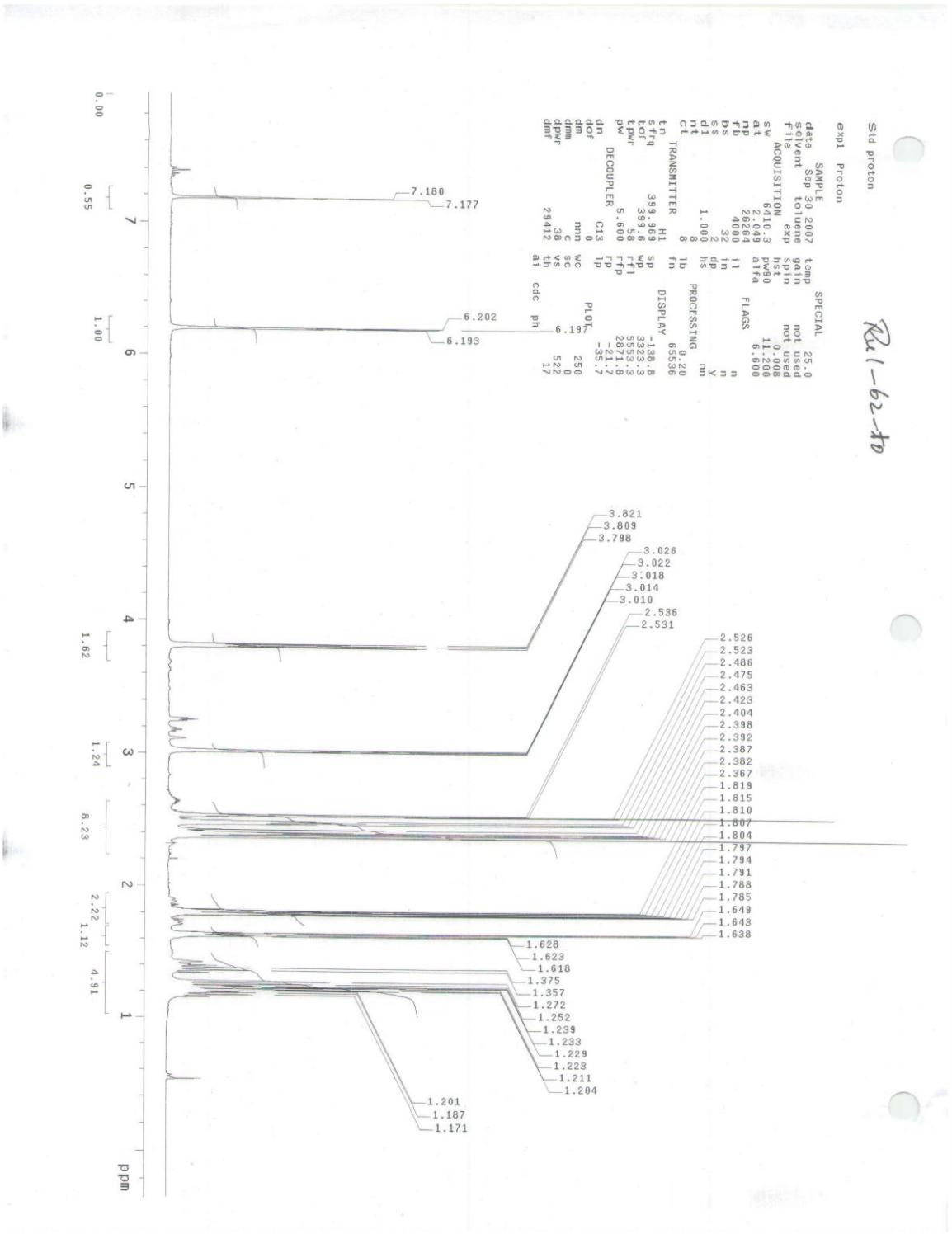


Figure 14. The ^{1}H NMR spectrum at t_0 for reaction mixture of entry 6 in table 2

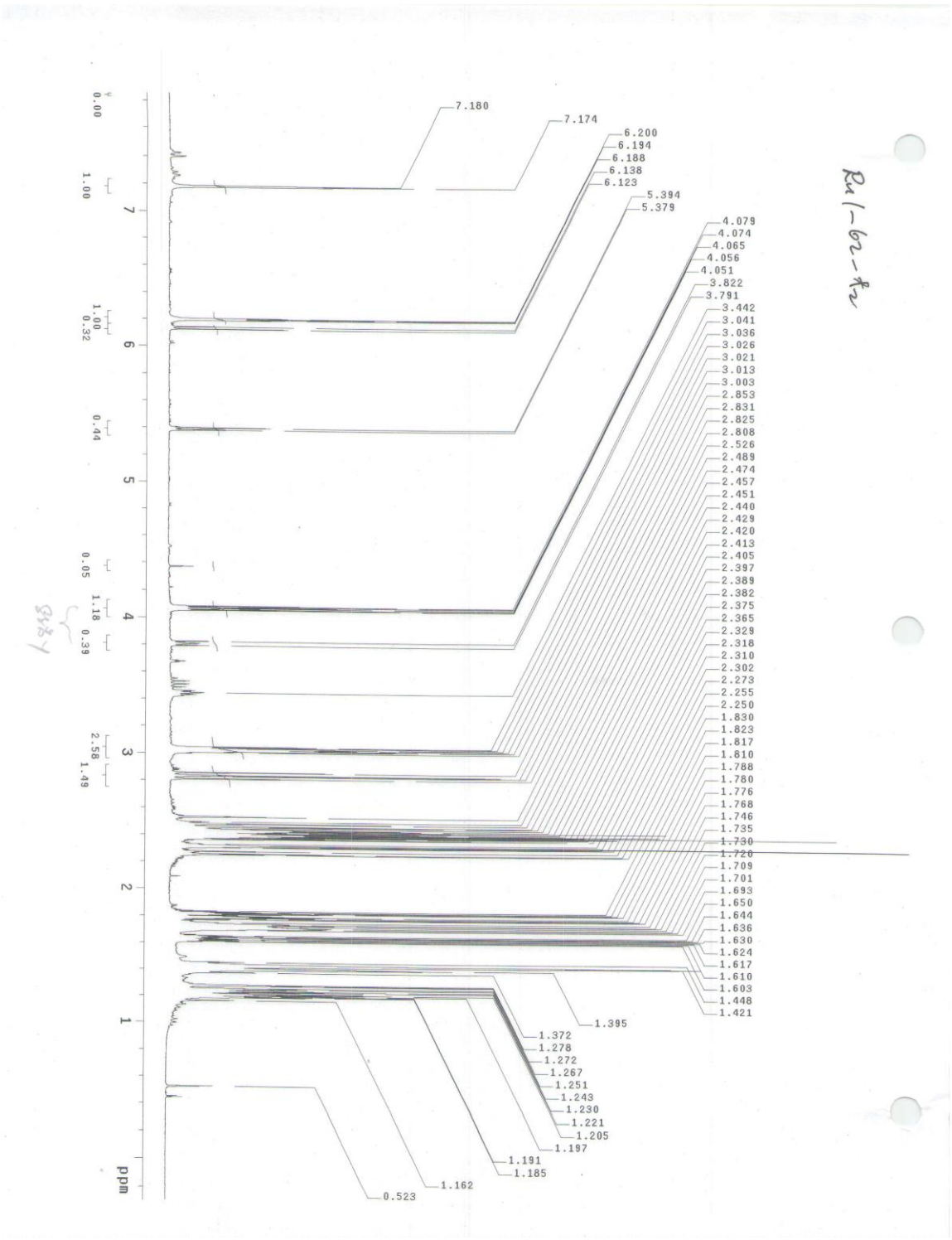


Figure 15. The ^{1}H NMR spectrum for reaction mixture of entry 6 in table 2

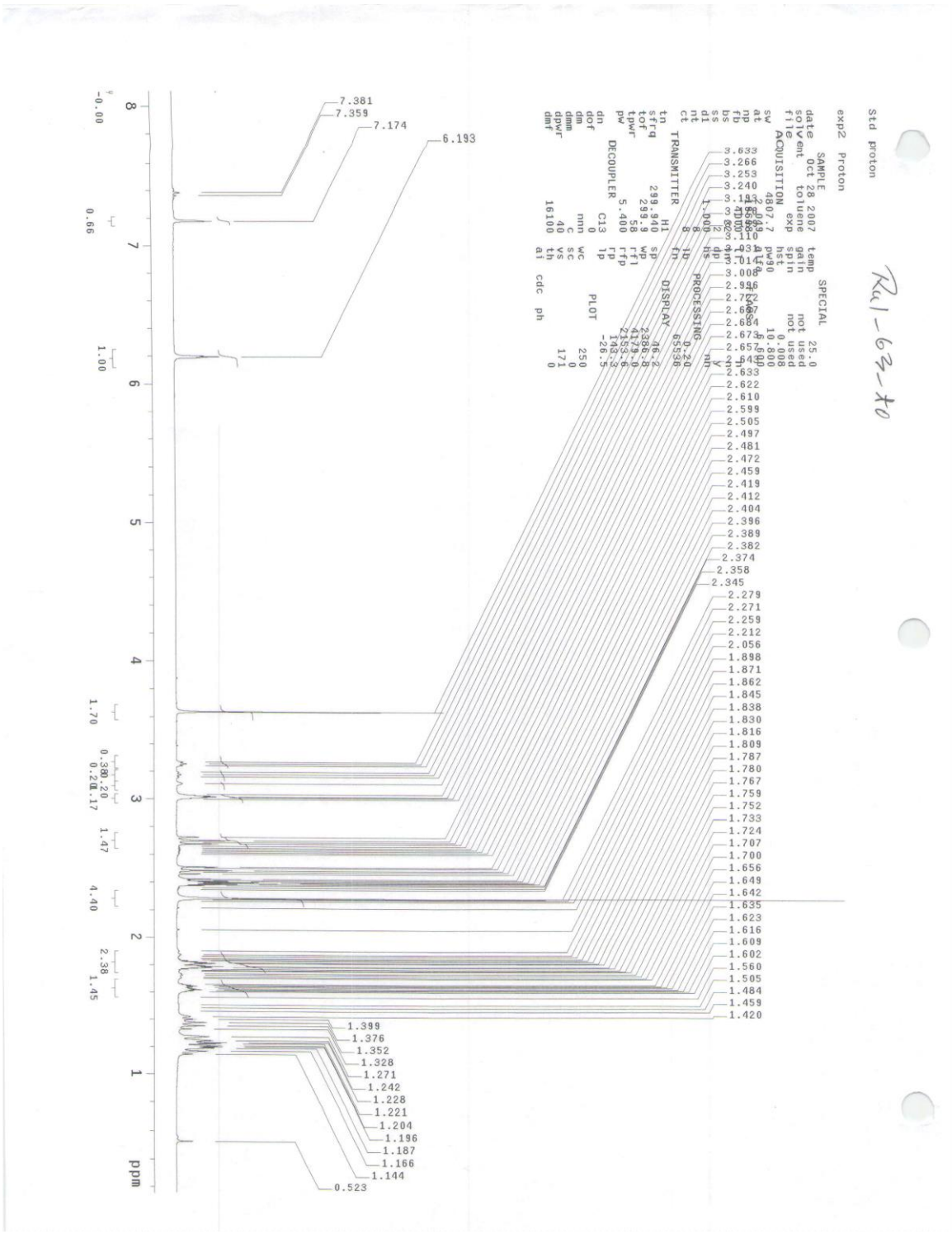


Figure 16. The ^{1}H NMR spectrum at t_0 for reaction mixture of entry 7 in table 2

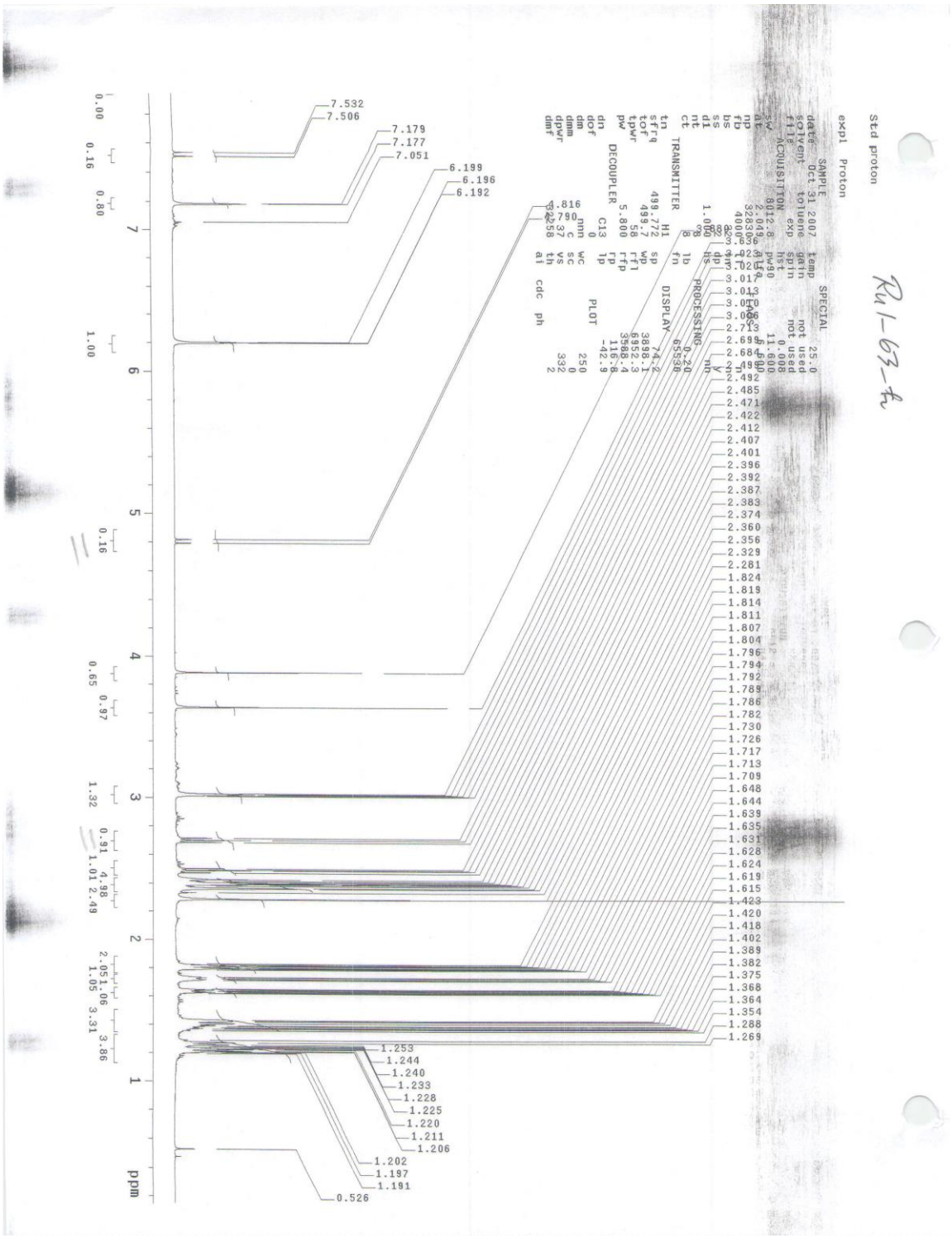


Figure 17. The ^{1}H NMR spectrum for reaction mixture of entry 7 in table 2

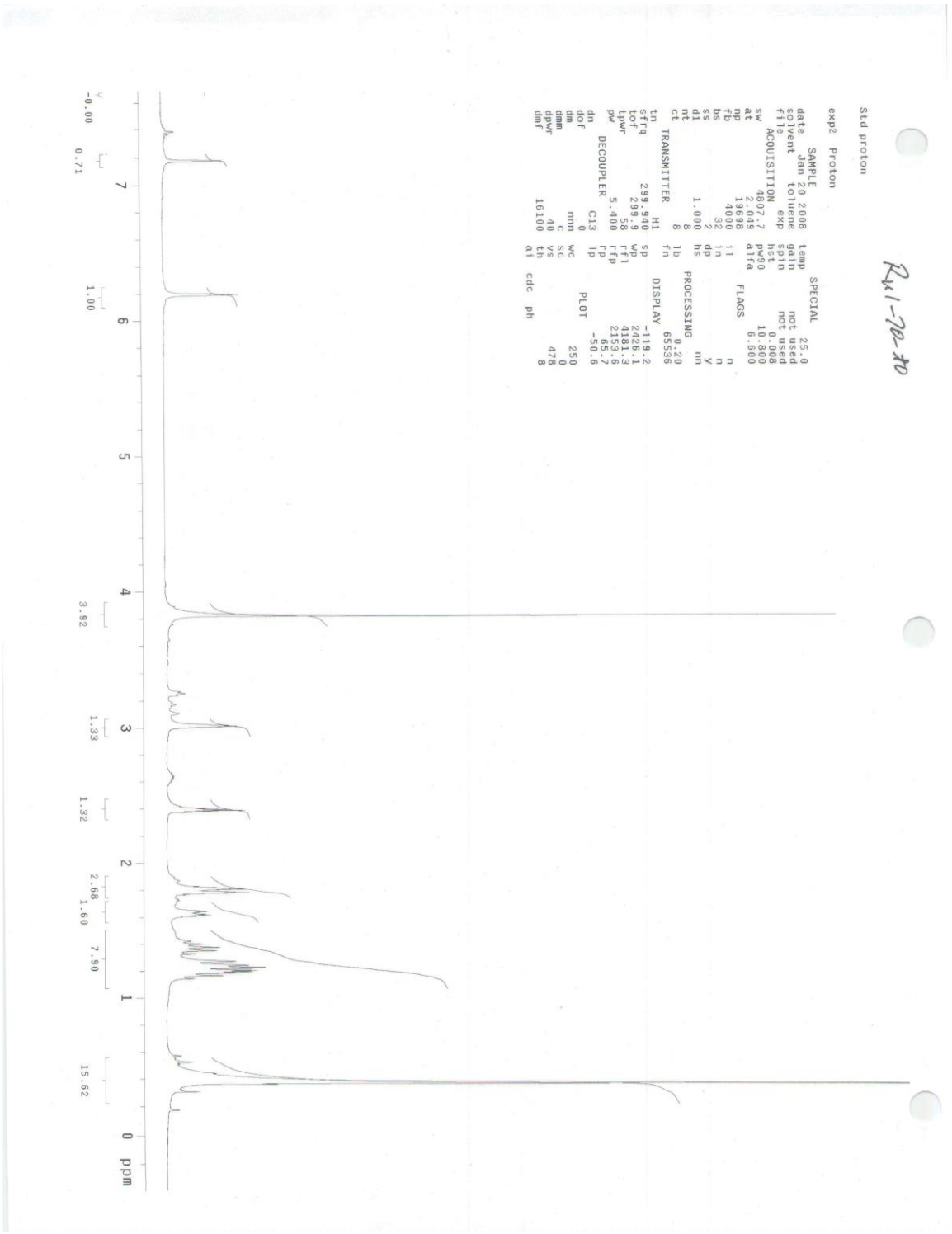


Figure 18. The ^{1}H NMR spectrum at t_0 for reaction mixture of entry 8 in table 2

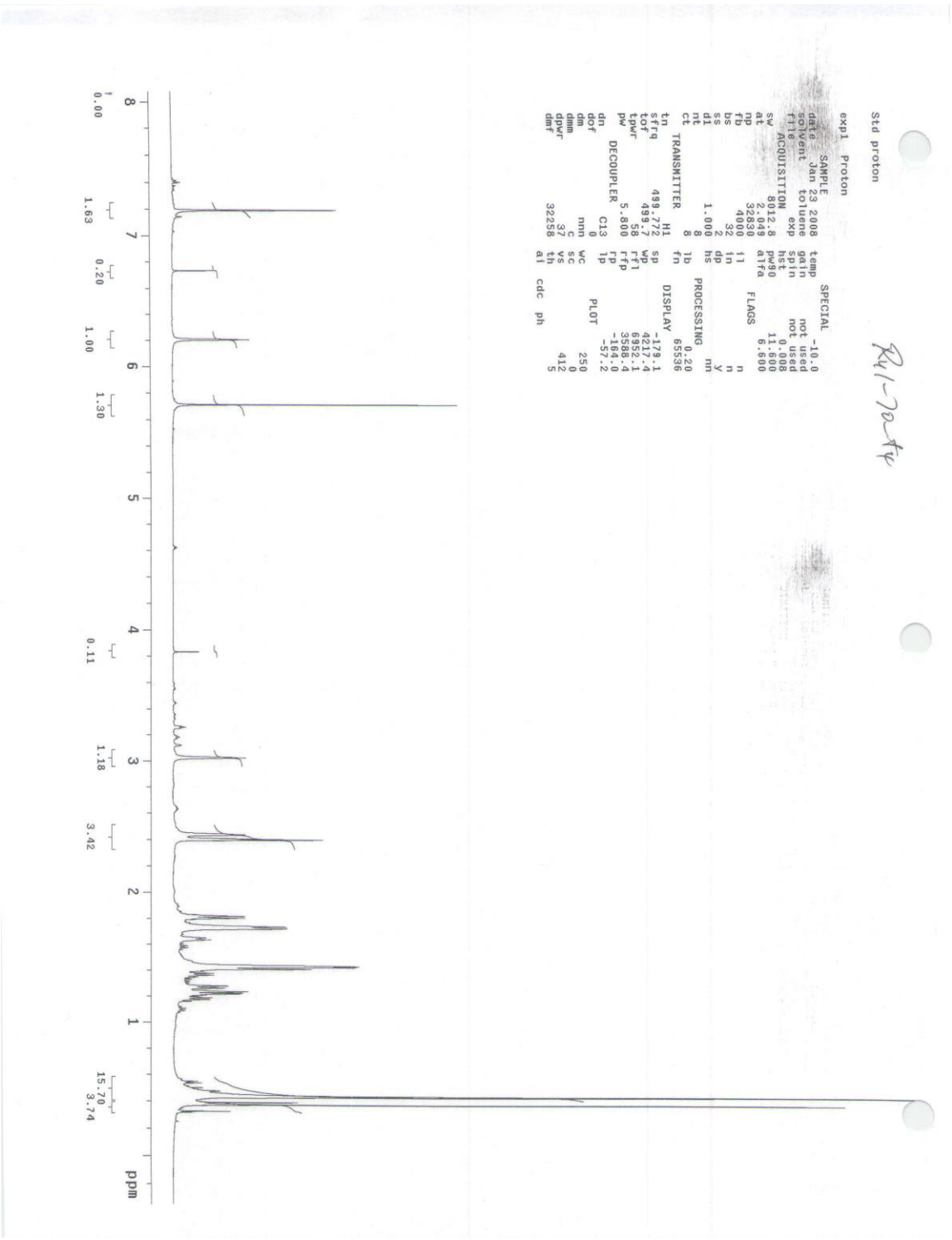


Figure 19. The ^{1}H NMR spectrum for reaction mixture of entry 8 (40 h) in table 2

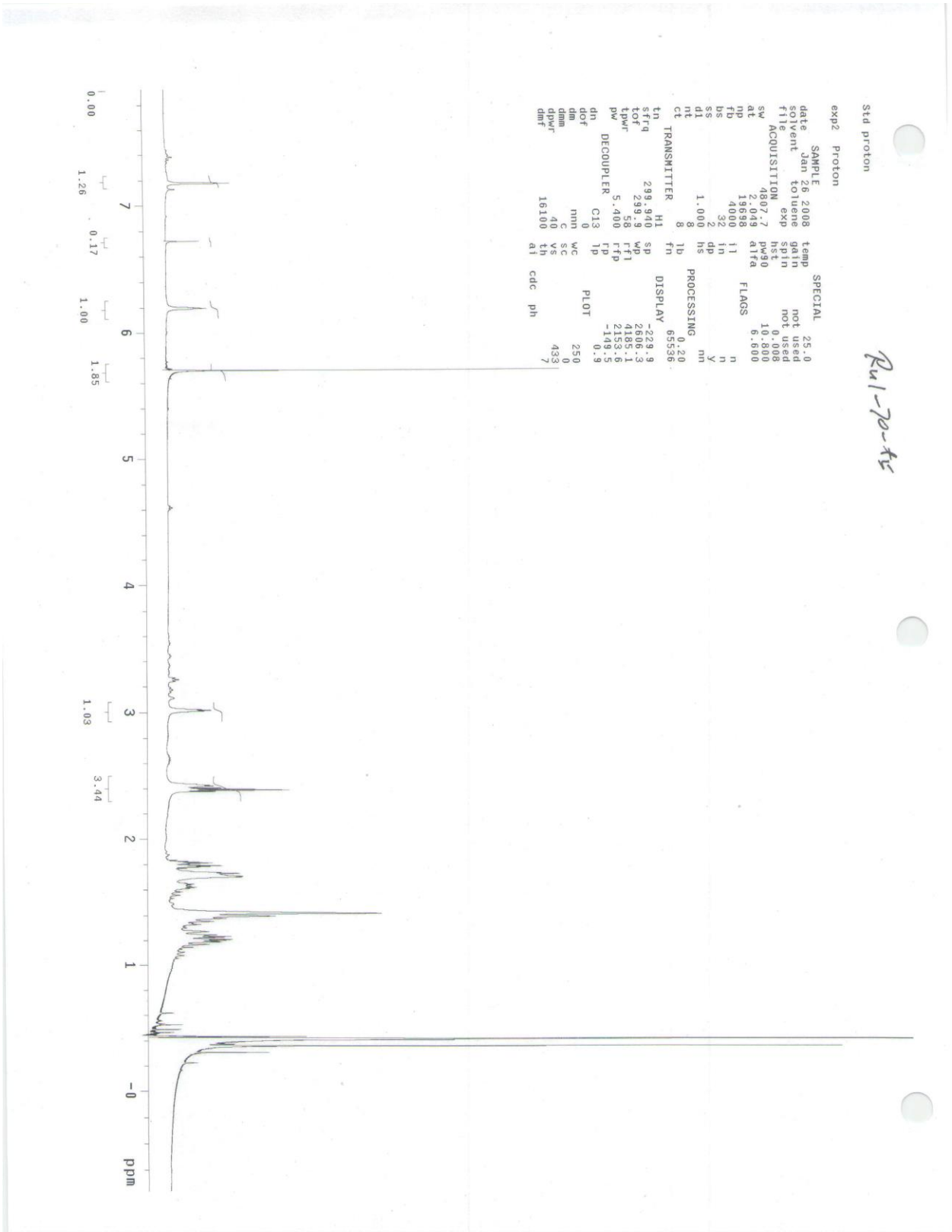


Figure 20. The ^{1}H NMR spectrum for reaction mixture of entry 8 (70 h) in table 2

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18. Typical reaction conditions included 10 mM catalyst, 100 mM substrate, and 200 mM hydrogen acceptor in *p*-xylene-d_{10} solvent.
19. Loss of NBE was revealed by ^{1}H NMR spectroscopy, while the formation of a thread-like precipitate was observed.

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