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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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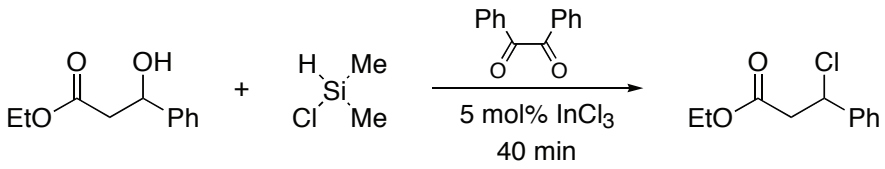
DIRECT CHLORINATION OF ALCOHOLS: SYNTHESIS OF ETHYL 3-CHLORO-3-PHENYLPROPANOATE

[Benzenepropanoic acid, β-chloro-, ethyl ester]



Submitted by Makoto Yasuda, Satoshi Yamasaki, Yoshiyuki Onishi, and Akio Baba.[1]

Checked by John R. Heemstra, Jr. and Scott E. Denmark.

1. Procedure

Caution! This reaction generates hydrogen (H_2) gas and therefore should be conducted in an efficient hood.

A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stir bar, a glass stopper, a Teflon-coated thermocouple, and a Leibig reflux condenser fitted with an inert gas inlet tube that is attached to a nitrogen manifold. The flask is flame-dried under vacuum, (0.2 mmHg) flushed with nitrogen, cooled to room temperature, and maintained under a slightly positive pressure of nitrogen. The flask is charged with $InCl_3$ (0.775 g, 3.5 mmol) (Note 1), which is then dried by heating the bottom of the flask with a hot air gun under vacuum (0.2 mmHg) for 2 min (Note 2). The flask is then refilled with nitrogen and kept under a slightly positive pressure. The glass stopper is removed and to the flask are added benzil (14.7 g, 70 mmol) (Note 3), dichloromethane (140 mL) (by syringe) (Note 4), and ethyl 3-hydroxy-3-phenylpropanoate (by syringe) (13.6 g, 70 mmol) (Note 5). Chlorodimethylsilane ($HSiMe_2Cl$) (7.28 g, 77 mmol) is added to the resulting mixture by syringe through an open neck while stirring (Note 6). The stopper is replaced and gentle evolution of gas (H_2) starts in a few minutes (Note 7). The extent of the gas evolution gradually increases and the reaction temperature slowly increases (Note 8).

After 35 min, gas evolution ceases (Note 9), indicating the end of the reaction. The solution is stirred for 5 min further (40 min total after addition of chlorodimethylsilane), whereupon water (100 mL) is added to the flask and the mixture is transferred into a 1-L separatory funnel containing diethyl ether (200 mL). After the mixture is shaken, the organic layer is separated and the aqueous layer is extracted with diethyl ether (1 x 100 mL, 1 x 60 mL). The combined organic extracts (yellow solution) are dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and concentrated at reduced pressure by rotary evaporation (30 °C/14 mmHg). The residue is diluted with hexane (20 mL) and cooled in an ice-bath to give a precipitate, which is filtered (Note 10). The filtrate is concentrated at reduced pressure by rotary evaporation (30 °C/14 mmHg) to afford a yellow oil.

The oil is loaded onto a column (4 cm diam x 14 cm height) of 100 g of silica gel (Note 11) with hexane. Using compressed air, the column is eluted with hexane (250 mL) (Note 12) and then ethyl acetate (300 mL) (Note 13). The ethyl acetate fraction (yellow solution) is concentrated by rotary evaporation (30 °C/14 mmHg) to afford 19.08 g of yellow liquid (Note 14). The liquid is distilled at reduced pressure to give 14.0 g (94%) of ethyl 3-chloro-3-phenylpropanoate (90 °C/0.2 mmHg) as a yellow oil (Notes 15-18).

2. Notes

1. $InCl_3$ (98%) was obtained from Aldrich Chemical Company, Inc., and used as received.
2. $InCl_3$ is hygroscopic and this procedure gives dry $InCl_3$.
3. Benzil (98%) was obtained from Aldrich Chemical Company, Inc., and used as received.
4. Dry dichloromethane was obtained from Wako Pure Chemical Industries, Ltd. (Japan), and used as received.
5. The reaction temperature does not change during this process. A yellow solution with a precipitate is observed.
6. Chlorodimethylsilane (98%) was obtained from Aldrich Chemical Company, Inc., and used as received. The bottle of the reagent should be

cooled at –30 °C in freezer before the syringe transfer operation.

7. The evolution of H_2 can be checked by bubbler and is seen in the flask as bubbles.

8. Internal temperatures: 19 °C (0-6 min), 21 °C (10 min), 26 °C (20 min), 30 °C (25 min), 31 °C (30 min), 30-29 °C (35-40 min).

9. The gas (H_2) evolves constantly for about 30 min and ceases at 35 min. The period of the time is shorter for smaller scale reactions.

10. The precipitate is separated by vacuum filtration using 60 mm Büchner funnel. The solid is carefully washed with cold hexane (50 mL). The separated pale yellow solid is pure benzil (10.1 g).

11. Silica gel was purchased from Silicycle (SiliaFlash P60 (40-63 μ, 60 Å pore size)). For TLC analysis, EMD Chemicals, Inc. silica gel 60 F_{254} TLC plates were used, with hexane/Et_2O, 7:3 as eluent. The starting alcohol (ethyl 3-hydroxy-3-phenylpropanoate), the chlorinated product (ethyl 3-chloro-3-phenylpropanoate), and benzil have R_f values of ca. 0.28, 0.66, and 0.57, respectively.

12. The column is eluted with hexane until a few drops of yellow solution come out. This process effectively separates silyl by-product.

13. A yellow-colored solution comes out.

14. The ^{1}H NMR spectrum shows that the liquid contains the desired chloride and benzil (79:21), along with a small amount of silyl species.

15. A forerun (10 drops) is collected and discarded to avoid contamination by silyl species.

16. The purity of the product was found to be 94%. The major contaminants detected by ^{1}H NMR (500 MHz) spectroscopic analysis are benzil (2%) and ethyl 3-phenyl-2-propenoate (4%).

17. The residue after distillation contains mostly benzil. The pure benzil (2.47 g) is recovered from the residue by vacuum filtration and is washed with cold hexane. A total of 12.57 g (86%) of benzil is recovered (Note 11).

18. The checkers obtained an analytically pure sample of the product as follows: a 300-mg portion of the product was purified by silica gel column chromatography (2 cm diam x 11 cm height, 20 g) (Note 12) with hexane/CH_2Cl_2, 2:1 (200-300 mL). In this solvent system the desired

product has an R_f = 0.33 and the elimination product an R_f = 0.23. Concentration of the product-containing fractions (30 °C/14 mmHg) provided 275 mg of ethyl 3-chloro-3-phenylpropanoate, which was purified by bulb-to-bulb distillation to afford 133 mg of analytically pure material. Physical properties of the purified product are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.1 Hz, 3 H), 3.03 (A<u>B</u>X, J_{AB} = 15.9 and J_{BX} = 5.8 Hz, 1 H), 3.17 (<u>A</u>BX, J_{AB} = 15.9 and J_{AX} = 9.1 Hz, 1 H), 4.16 (m, 2 H), 5.35 (dd, J = 5.9 and 9.0 Hz, 1 H), 7.30−7.43 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 44.8, 58.1, 60.9, 126.9, 128.67, 128.74, 140.2, 169.5; IR (neat) cm^{-1}: 3454 (m), 3066 (m), 3034 (m), 2983 (s), 2938 (s), 2906 (m), 2360 (w), 1955 (w), 1883 (w), 1740 (s), 1604 (m), 1587 (m), 1495 (m), 1455 (m), 1367 (s), 1333 (s), 1272 (s), 1196 (s), 1159 (s), 1097 (m), 1021 (s), 948 (s); MS (EI, 70 eV) m/z (%): 212 (M^+, 43), 183 (28), 167 (17), 149 (19), 138 (84), 125 (89), 105 (100), 91 (14), 77 (47), 63 (11); HRMS (EI, M^+) *m/z* calcd for $C_{11}H_{13}ClO_2$: 212.0604, found: 212.0596. Anal. calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16; Cl, 16.67. Found: C, 62.17; H, 6.16; Cl, 16.56.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described herein provides a useful method for chlorination of alcohols under mild and neutral conditions.[3] Even an acid sensitive hydroxy ester (ethyl 3-hydroxy-3-phenylpropanoate) is cleanly converted into the desired chloride. For this substrate, conventional chlorination methods[4] in which strong protic acids are generated *in situ* using PCl_3 or PCl_5 give low yield of the chloride contaminated with ethyl 3-phenyl-2-propenoate that forms through β-elimination.[3]

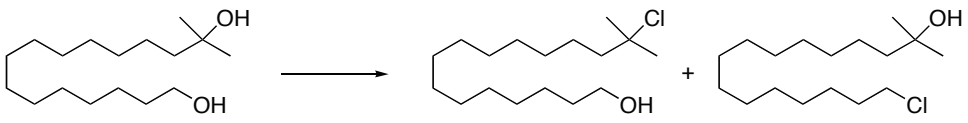
Indium trichloride ($InCl_3$) has moderate Lewis acidity and oxophilicity as compared with typical Lewis acids such as aluminum halides or boron halides.[5-7] This character enables $InCl_3$ to catalyze the reactions of carbonyls or alcohols.[8,9]

In the alcohol/$HSiMe_2Cl$/$InCl_3$/benzil system, role of benzil is significant. When benzil is not included, hydro-dehydroxylation (reduction) occurs through the formation of the hydrodimethylsilyl ether with release of HCl.[10] The addition of benzil changes the reaction pathway to form the chlorodimethylsilyl ether with release of H_2. Although benzil is used as an equimolar additive, about 80% of the benzil can easily be recovered. The amount of benzil can be reduced for certain substrates, but the use of a stoichiometric amount leads to faster reaction rates, higher yields, and broader substrate scope.

The generality of this chlorination method is summarized in Table 1. Various secondary and tertiary alcohols are converted into the corresponding chlorides in high yields (entries 1-6). A primary alcohol (2-phenylethanol) does not give the desired product (entry 7). However, effective transformation proceeds in the reaction with benzylic alcohols which bear electron-withdrawing or donating substituents (entries 8-10). Nitro and ester groups tolerate these reaction conditions to furnish the corresponding chlorides (entries 11 and 12). The enantiomerically pure alcohol (1-phenylethanol) gives racemic 1-phenylethyl chloride (entry 13). These results suggests that the reaction proceeds via a carbocationic intermediate.

Selective chlorination at the tertiary site of a diol that contains both primary and tertiary alcohols illustrates the unique selectivity of this chlorination system (Scheme 1). On the contrary, conventional chlorination systems such as PPh_3/CCl_4 or PCl_5 afford the primary chloride.

Scheme 1



$HSiMe_2Cl$/benzil/cat. $InCl_3$	56%	0%
Ph_3P/CCl_4	0%	80%
PCl_5	0%	45%

Table 1. Chlorination of Various Alcohols

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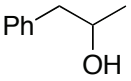
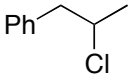
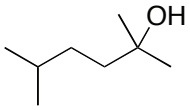
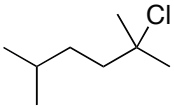
2		15		68
3		9		100
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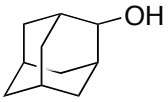
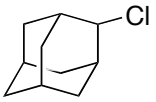
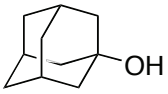
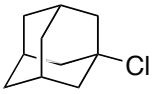
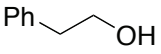
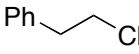
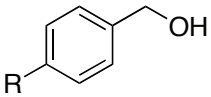
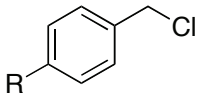
5		91		98
6		82		93
7		24		0
8	 R = H	1		80
9	R = Cl	2.5		92
10	R = Me	0.7		83
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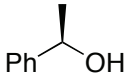
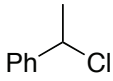
13		2.5		91 (<2% ee)

1. Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

$InCl_3$: Indium chloride; (10025-82-8)

Benzil: Diphenylethanedione; (134-81-6)

Ethyl 3-hydroxy-3-phenylpropanoate: Benzenepropanoic acid, β-hydroxy-, ethyl ester; (5764-85-2)

Chlorodimethylsilane; (1066-35-9)

Ethyl 3-chloro-3-phenylpropanoate: Benzenepropanoic acid, β-chloro-, ethyl ester; (77085-24-6)

JRHIV20

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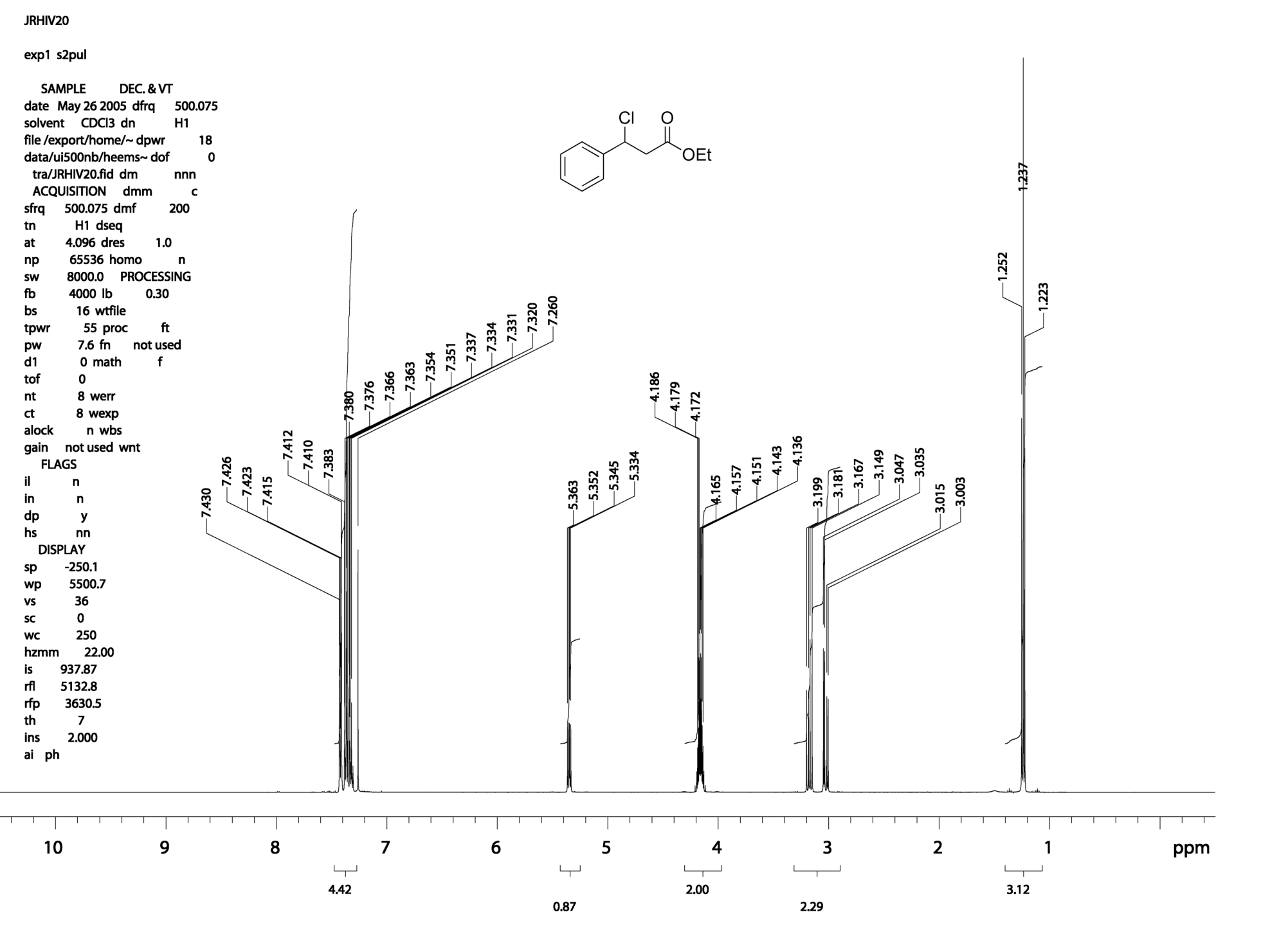

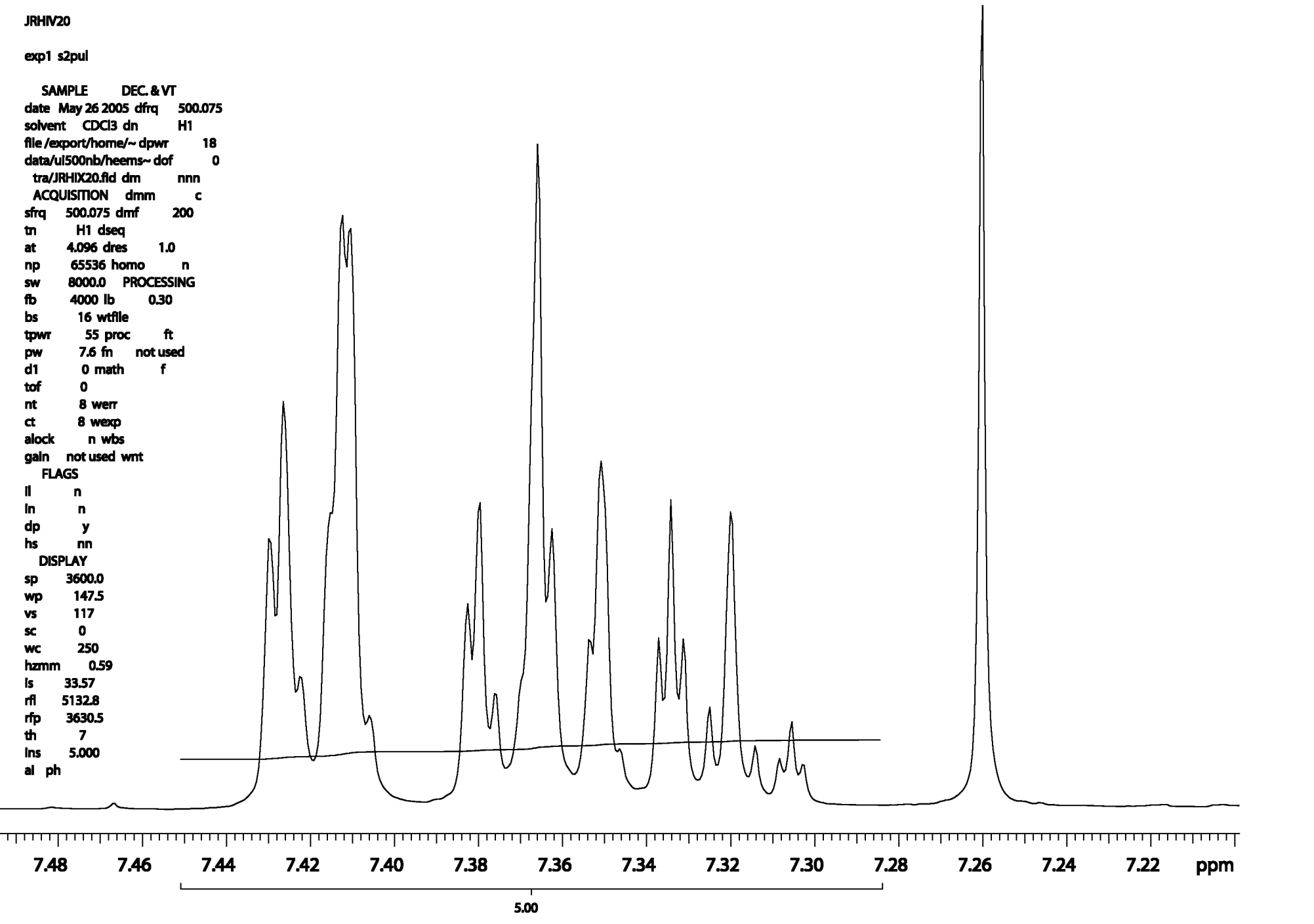
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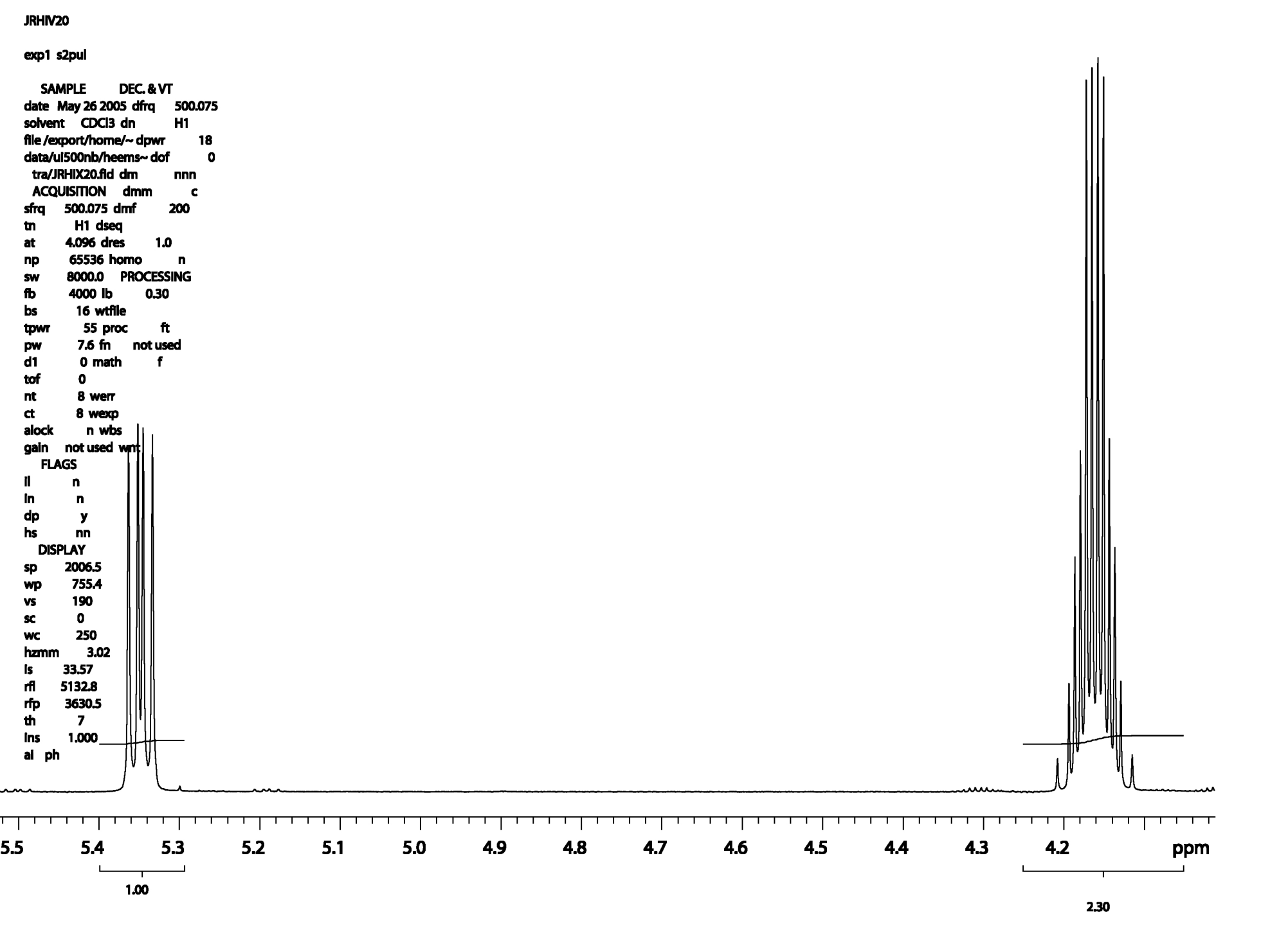
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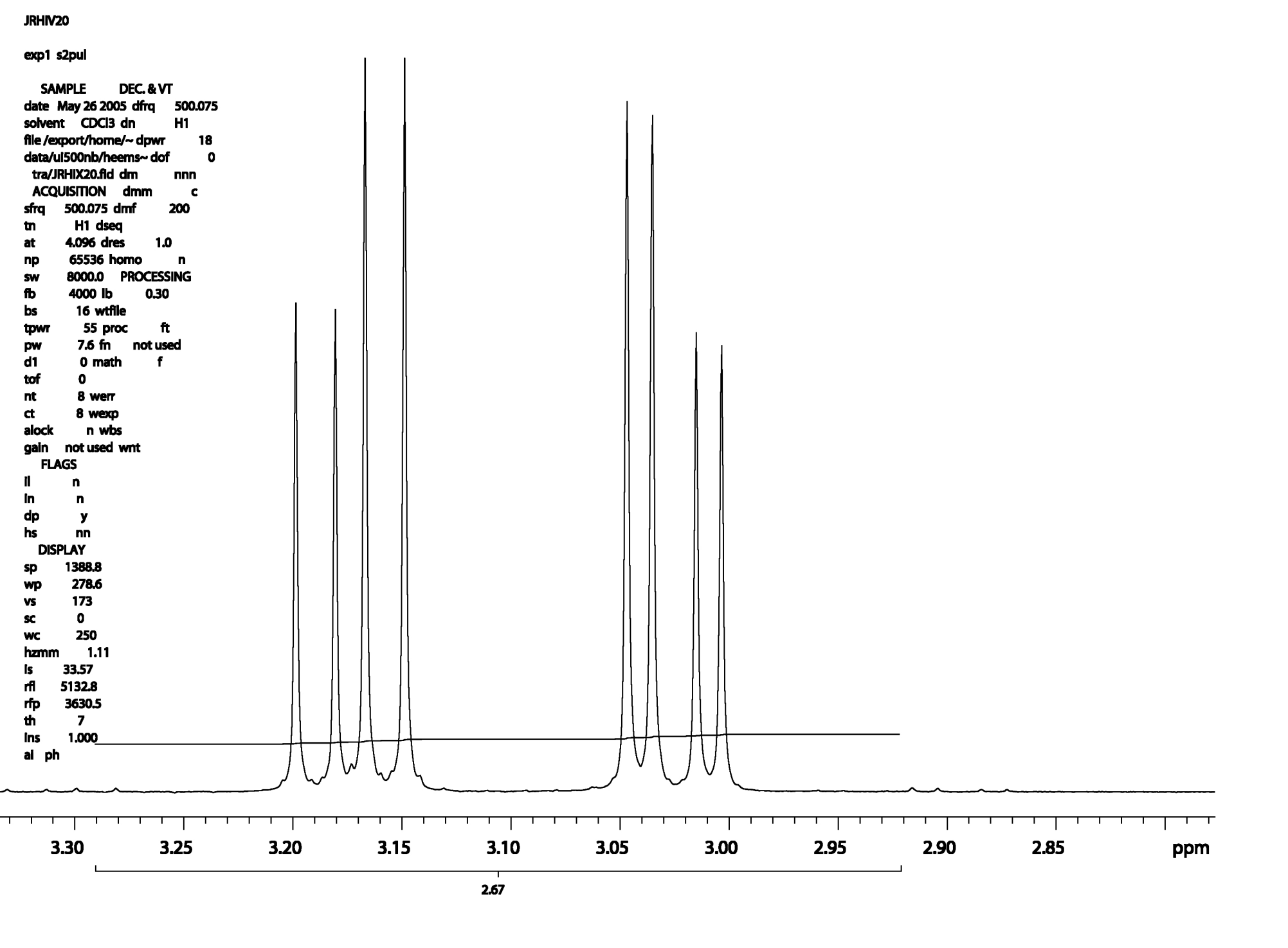
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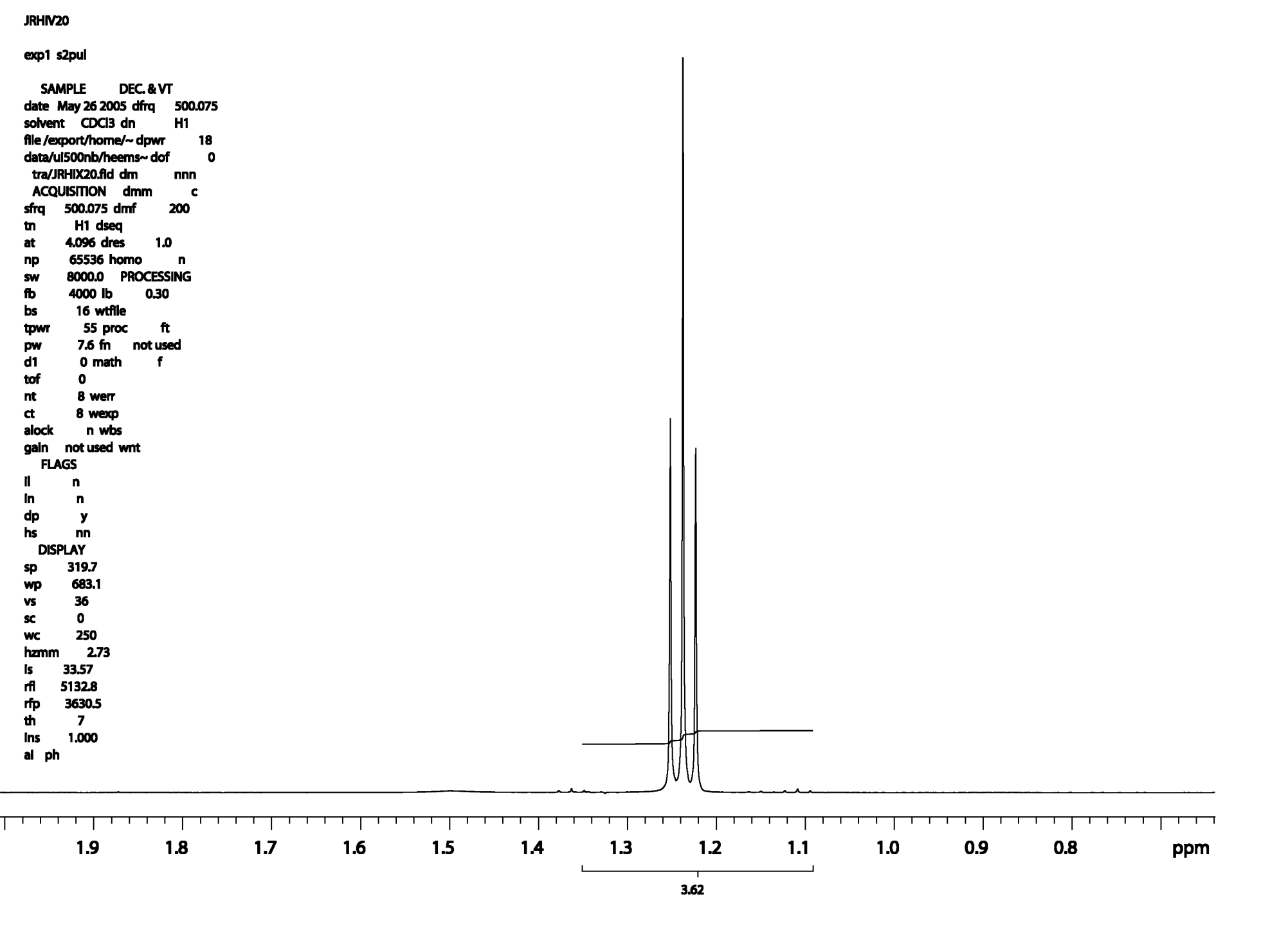
ppm
2.67


JRHIV20
exp1 s2pul
SAMPLE DEC. & VT
date May 26 2005 dfrq 500.075
solvent CDCl3 dn H1
file /export/home/~ dpwr 18
data/ul500nb/heems~ dof 0
tra/JRHIX20.fid dm nnn
ACQUISITION dmm c
sfrq 500.075 dmf 200
tn H1 dseq
at 4.096 dres 1.0
np 65536 homo n
sw 8000.0 PROCESSING
fb 4000 lb 0.30
bs 16 wtfile
tpwr 55 proc ft
pw 7.6 fn not used
d1 0 math f
tof 0
nt 8 werr
ct 8 wexp
alock n wbs
gain not used wnt
FLAGS
ll n
ln n
dp y
hs nn
DISPLAY
sp 319.7
wp 683.1
vs 36
sc 0
wc 250
hzmm 2.73
ls 33.57
rfl 5132.8
rfp 3630.5
th 7
lns 1.000
al ph
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
ppm
3.62