

Continuous Nitration of Alcohols in a Freon Flow

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1. General information

Materials. Alcohols **1a-c** were supplied by Acros Organics and Freon R134a (1,1,1,2-tetrafluoroethane) by Linde Gas (Russia). Dinitrogen pentoxide was synthesized by known method.¹

Instruments. The ¹H, ¹³C, and ¹⁴N NMR spectra were recorded on a Bruker, AM-300 (300.13, 75.47 and 21.69 MHz, respectively). The FTIR spectra were obtained on a Simex FT-801 spectrometer.

The experiments were carried out on a specially designed installation for flow nitration processes (Figure 1). The main element of the system was the reactor unit, which consisted of two static mixers (M_1 and M_2) connected with a helix-shaped steel pipe with inner diameter of 0.03". The used pipes had lengths of 0.5, 1.0 or 2.0 m and volumes of 0.25, 0.5 or 1.0 cm³ respectively. The reaction temperature was controlled with two sensors: TS_1 located at M_1 where the alcohol mixes with the nitrating agent and TS_2 – at M_2 where alkali solution is added. TFE feed was delivered from cylinder **I** or one of collection vessels **IX** by plunger pump **II** with integrated cooling Peltier thermoelectric modules. The DNP solution in TFE was preliminary prepared in auxiliary cell **III** ($V = 50 \text{ cm}^3$) equipped with two look-through sapphire glasses. The prepared DNP solution and neat alcohol flows were continuously delivered to mixer M_1 by syringe pumps **IV** and **V**, respectively. Both pumps provided constant flow rates with accuracy of 10^{-5} mL/min and maximum deviation of 0.3%. An aqueous alkali flow was simultaneously delivered into mixer M_2 by plunger pump **VI**. The operating pressure was maintained by the automatic back pressure regulator (ABPR) **VII** with working elements made of corrosion resistant materials (PTFE or stainless steel AISI316, etc.). The installation also comprised separator **VIII** for separation of gaseous TFE from liquid products, two condensation vessels (**IXa** and **IXb**) and adsorption tube **X** filled with molecular sieves 4A / granulated sodium hydroxide for purification of the recovered TFE before its reuse. All the elements were interconnected with stainless steel tubes and valves V_I .

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¹ Audrieth, L. F., Ed. Inorganic Syntheses, Vol. III; McGraw-Hill Book Company: New York, 1950.

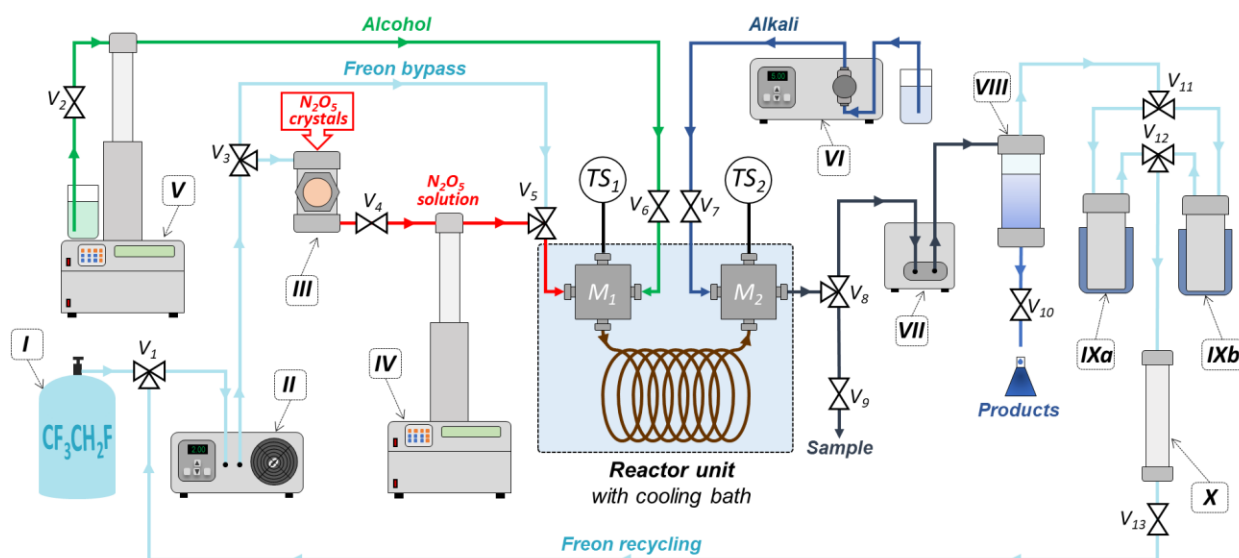


Figure 1. Flow nitration system: **I** – cylinder with TFE; **II** – fluid pump; **III** – auxiliary cell for N_2O_5 solution; **IV** – syringe pump for pump for supplying N_2O_5 solution; **V** – syringe pump for pump for supplying alcohol; **VI** – pump for supplying alkali solution; **VII** – automated back pressure regulator (ABPR); **VIII** – separator; **IXa** and **IXb** – parallel TFE collection vessels with cooling baths; **X** – sorption tube; **TS** – inlet (1) and outlet (2) temperature sensors; V_{1-12} – valves; M_1 and M_2 – mixers.

2. Experimental procedures

Preparation of DNP solution in TFE. DNP (5.25 g, 48.6 mmol) was placed into stainless steel cell ($V = 50 \text{ cm}^3$) equipped with two look-through sapphire glasses. The cell was sealed, adjusted to 20°C and filled with liquid TFE at 10 bar ($d = 1.228 \text{ g/cm}^3$). Thus, obtained homogeneous solution was transferred through the cell lower port into syringe pump **IV** cooled to 10°C by means of reverse piston movement and due to the temperature difference ($\Delta T = 10^\circ\text{C}$) between the pump **IV** and the cell **III** (the optimal filling rate was 2.5 ml/min). Then, valve V_5 was closed and the pressure inside pump **IV** risen to 10 bar by forward piston movement. Herewith, the DNP solution concentration was adjusted to $1 \text{ mol/L} \pm 2\%$.

Flow nitration (general procedure). Before starting the flow process, the required flow rate and operating pressure values (see Tables 1 and 2) must be carefully set on control panels of pumps **IV – VI** and ABPR **VII**, respectively). Valve V_8 was opened and the installation was filled with liquid TFE through the FREON BYPASS line by means of pump **II**. Then, pumps **IV – VI** were switched on and valves $V_5 – V_7$ were opened. The nitration was quenched in mixer **M₂** by 2M aqueous NaOH flow (for detailed flow rates see Supporting Information). Then the resulting mixture was transferred through ABPR **VII** into separator **VIII**. The gas phase (TFE at 3 bar) was removed from the separator through the upper port to vessel **IXa** where it condensed at 0°C . Upon filling vessel **IXa** with liquid TFE, valve V_{11} was turned to redirect the TFE flow to parallel condensation vessel **IXb**. Then, vessel **IXa** was warmed up to an ambient temperature, gaseous TFE was passed through the adsorption tube **X** to remove aqueous and other impurities and returned to fluid pump **II** for recycling. The liquid phase was periodically poured out of separator **VIII** through the lower port with valve V_{10} to a flask. The organic phase was separated from aqueous solution, washed twice with distilled water to afford nearly pure nitroester **2**

Analysis. To control stability of the flow nitration parameters, two analytical samples were taken in each experiment (~ 5 min after the flow start and ~ 5 min before pumps **IV-VI** turning off). On this purpose, valve V_8 was opened and a micro-sample of the reaction mixture was passed to the analytical capillary ($l = 0.2 \text{ m}$, $V = 0.1 \text{ mL}$). Then valve V_8 was closed and the sample was transferred to a flask at ambient pressure by opening valve V_9 . The analytic capillary volume needs to be at least several times smaller than the helix-shaped tube to avoid interfering with ABPR **VII** operation and retain constant pressure in the system. Therefore, the described procedure must be repeated 5-10 times (depending on the substrate) to collect sufficient for analysis sample amount. The combined sample was dried under

reduced pressure, then acetone-D₆ is added, solid inorganic salts were separated, and the solution was analyzed with ¹H NMR to determine conversion of alcohol **1** and selectivity of the process.

3. The reagents flow calculation

For example, in the Experimental 1 (Table 1) at reactor tube length 2 [m] (volume 1 [cm³]) and the chosen reagents contact time 100 [s] the sum of alcohol F_{alc}^V and N₂O₅ solution F_{nitr}^V volume flow rates is 0.01 [cm³/s]. Also the molar ratio of the reactants is $F_{alc}^n:F_{nitr}^n = 1:1.5$, the alcohol density is $d_{alk} = 0.833$ [g/cm³] and the N₂O₅ solution concentration is $C_{nitr} = 1$ [mol/L] = 10⁻³[mol/cm³]. Then the molar flow rates of the reactants are:

$$F_{nitr}^n = C_{nitr} \cdot F_{nitr}^V,$$

$$F_{alc}^n = \frac{F_{alc}^m}{M_{alc}} = \frac{d_{alk} \cdot F_{alc}^V}{M_{alc}},$$

where F_{alc}^m – the alcohol mass flow rate; M_{alc} – the alcohol molar mass. In accordance with molar ratio of the reactants:

$$1.5 \frac{d_{alk} \cdot F_{alc}^V}{M_{alc}} = (C_{nitr} \cdot F_{nitr}^V),$$

$$F_{alc}^V = \frac{C_{nitr} \cdot M_{alc}}{1.5 \cdot d_{alk}} \cdot F_{nitr}^V.$$

By applying the values:

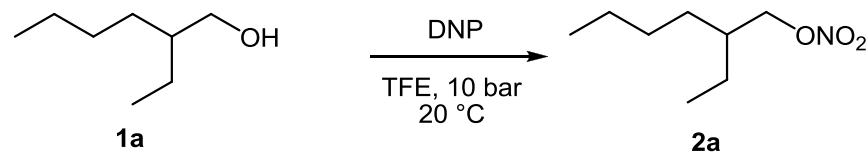
$$F_{alc}^V = \frac{10^{-3} \cdot 130}{1.5 \cdot 0.833} \cdot F_{nitr}^V = 0.104 \cdot F_{nitr}^V.$$

The flow rates of each reactant F_{alc}^V and F_{nitr}^V may be found using the following rate balance equation:

$$0.104 \cdot F_{nitr}^V + F_{nitr}^V = 0.01 \text{ [cm}^3/\text{s]},$$

$$F_{nitr}^V = 0.009058 \text{ [cm}^3/\text{s]} = \mathbf{0.544 \text{ [cm}^3/\text{min}]}, \text{ and}$$

$$F_{alc}^V = 0.104 \cdot 0.009058 \text{ [cm}^3/\text{s]} = 0.000942 \text{ [cm}^3/\text{s]} = \mathbf{0.0565 \text{ [cm}^3/\text{min}]}$$

Table 1. Flow nitration of 2-ethylhexanol (**1a**) with DNP in liquid TFE.^a

Entry	Alcohol 1a rate			1a /DNP/NaOH molar ratio	DNP solution rate			Alkali solution rate		Reactor length (volume), m (cm ³)	Residence time, s	Conversion, % ^b
	mmol/min	mg/min	mL/min		mmol/min	mg/min	mL/min	mmol/min	mL/min			
1	0.362	47.1	0.0565	1 : 1.5 : 2.0	0.544	58.7	0.5435	1.087	0.54	2 (1)	100	100
2	0.725	94.2	0.1131	1 : 1.5 : 2.0	1.087	117.4	1.0870	2.174	1.09	2 (1)	50	100
3	1.449	188.4	0.2262	1 : 1.5 : 2.0	2.174	234.8	2.1740	4.348	2.17	2 (1)	25	100
4	0.478	62.1	0.0746	1 : 1.1 : 1.2	0.526	56.8	0.5256	0.631	0.32	2 (1)	100	99
5	0.478	62.1	0.0746	1 : 1.1 : 1.2	0.526	56.8	0.5256	0.631	0.32	1 (0.5)	50	93
6	0.478	62.1	0.0746	1 : 1.1 : 1.2	0.526	56.8	0.5256	0.631	0.32	0.5 (0.25)	25	90
7	0.956	124.2	0.1491	1 : 1.1 : 1.2	1.051	113.5	1.0512	1.261	0.63	2 (1)	50	98 ^c
8 ^d	0.510	66.2	0.0795	1 : 1.1 : 1.2	0.561	60.5	1.1210	0.673	0.34	2 (1)	50	99
9	0.519	67.5	0.0810	1 : 1.0 : 1.0	0.519	56.1	0.5190	0.519	0.26	2 (1)	100	90
10	0.519	67.5	0.0810	1 : 1.0 : 1.0	0.519	56.1	0.5190	0.519	0.26	1 (0.5)	50	87

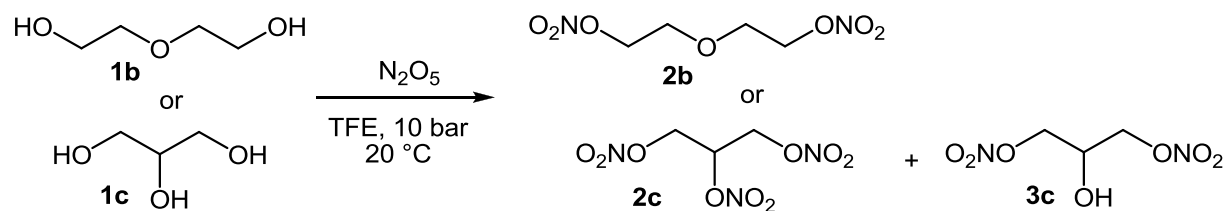
^a the reactions were performed at 10 bar, 20 °C and DNP concentration 1 mol/L;

^b the conversion was determined by ¹H NMR spectroscopy;

^c isolated yield of **2a** was 4.72 g per 30 min (94%);

^d DNP concentration was 0.5 mol/L.

Table 2. Flow nitration of diethylene glycol (**1b**) and glycerin (**1c**) with DNP in liquid TFE.^a



Entry	Alcohol	Substrate 1 rate			1a/DNP/NaOH molar ratio	DNP solution rate			Alkali solution rate		Reactor length (volume), m (cm ³)	Residence time, s	Conversion, % ^b
		mmol/min	mg/min	mL/min		mmol/min	mg/min	mL/min	mmol/min	mL/min			
1	1b	0.523	55.5	0.0496	1 : 2.2 : 2.4	1.151	124.3	1.1510	2.762	1.38	2 (1)	50	99 ^c
2		0.523	55.5	0.0496	1 : 2.2 : 2.4	1.151	124.3	1.1510	2.762	1.38	0.5 (0.25)	13	90
3	1c	0.356	32.8	0.0260	1 : 3.3 : 2.9	1.174	126.8	1.1740	3.405	1.70	2 (1)	50	96 (75:25) ^d
4		0.712	65.5	0.0520	1 : 3.3 : 2.9	2.348	253.6	2.3480	6.809	3.40	2 (1)	25	99 (91:9) ^d
5		1.067	98.3	0.0780	1 : 3.3 : 2.9	3.522	380.4	3.5220	10.214	5.11	2 (1)	17	100 (96:4) ^{d,e}
6		1.067	98.3	0.0780	1 : 3.3 : 2.9	3.522	380.4	3.5220	10.214	5.11	0.5 (0.25)	4	99 (91:9) ^d
7		0.975	89.8	0.0713	1 : 3.6 : 3.4	3.510	379.1	3.5100	11.934	5.97	0.5 (0.25)	4	99 (94:6) ^d

^a the reactions were performed at 10 bar, 20 °C and DNP concentration 1 mol/L;

^b the conversion was determined by ¹H NMR spectroscopy;

^c isolated yield of **2b** was 2.92 g per 30 min (95%);

^d **2c** / **3c** ratio (selectivity);

^e isolated yield of **2c** was 2.18 g per 10 min (90%).

4. Calculation of efficiency of batch and flow nitration of alcohols

The specific performances (P_s) of 2,2'-oxybis(ethane-2,1-diyl) dinitrate (**2b**) nitration processes in TFE medium were calculated to compare the efficacy of batch and flow modes.

The batch nitration of diethylene glycol (**1b**) in TFE medium was carried out using alcohol (0.85 g, 8.0 mmol) at 0–10 °C for 30 min in 22 cm³ steel autoclave.² The yield of **2b** was 1.55 g (99%).

$$P_s = \frac{m_{es}}{t_r \cdot V_a},$$

where m_{es} – mass of estery, V_a – autoclave volume, t_r – reaction time.

$$P_{sb} = \frac{1.55 \text{ g}}{30 \text{ min} \cdot 22 \text{ cm}^3} = 2.35 \cdot 10^{-3} \frac{\text{g}}{\text{min} \cdot \text{cm}^3}$$

In the flow nitration of diethylene glycol (**1b**) (0.523 mmol/min, 55.5 · 10⁻³ g/min, 0.0496 mL/min) in reactor of 2 m length and 1 cm³ volume the isolated yield of **2b** was 2.92 g per 30 min (95%) (Table 2, entry 1).

$$P_{sf} = \frac{2.92 \text{ g}}{30 \text{ min} \cdot 1 \text{ cm}^3} = 97.33 \cdot 10^{-3} \frac{\text{g}}{\text{min} \cdot \text{cm}^3}$$
$$\frac{P_{sf}}{P_{sb}} = \frac{97.33 \cdot 10^{-3}}{2.35 \cdot 10^{-3}} = 41.4$$

The flow nitration of diethylene glycol (**1b**) is 41 times more effective than its batch analog.

For propane-1,2,3-triyl trinitrate (nitroglycerin) (**2c**) with the yields 1.79 g (99%) in batch nitration² and 2.18 g per 10 min (90%) in flow one (Table 2, entry 5) specific performances equal

$$P_{sb} = \frac{1.79 \text{ g}}{30 \text{ min} \cdot 22 \text{ cm}^3} = 2.71 \cdot 10^{-3} \frac{\text{g}}{\text{min} \cdot \text{cm}^3}$$
$$P_{sf} = \frac{2.18 \text{ g}}{10 \text{ min} \cdot 1 \text{ cm}^3} = 2.18 \cdot 10^{-1} \frac{\text{g}}{\text{min} \cdot \text{cm}^3}$$
$$\frac{P_{sf}}{P_{sb}} = \frac{2.18 \cdot 10^{-1}}{2.71 \cdot 10^{-3}} = 80.1$$

The flow nitration of glycerol (**1c**) is 80 times more effective than its batch analog.

² Kuchurov, I.V.; Arabadzhi, S.S.; Zharkov, M.N.; Fershtat, L.L.; Zlotin, S.G. *ACS Sustainable Chem. Eng.*, **2018**, 6(2), 2535–2540.

5. Physical and Spectral data (IR, ¹H NMR, ¹³CNMR) of compounds 2a, 2b, 2c and 3c

2-Ethylhexyl nitrate (**2a**): b.p. 88 °C / 8 Torr; n_D^{20} 1.4305; FTIR ν 1625 (NO₂^{as}), 1275 (NO₂^s) cm⁻¹; ¹H NMR (CD₃COCD₃, 300 MHz) δ 4.46 (d, 2 H, CH₂ONO₂, J = 5.9 Hz), 1.73 (sep, 1 H, CH(CH₂)₃, J = 6.1 Hz); 1.48-1.31 (m, 8 H, 4 × CH₂); 0.96-0.88 (m, 6 H, 2 × CH₃); ¹³C NMR (CD₃COCD₃, 75 MHz) δ 76.9, 38.6, 31.1, 29.6, 24.5, 23.7, 14.4, 11.3; ¹⁴N NMR (CD₃COCD₃, 21.69 MHz) δ : -39.1 (ONO₂).

2,2'-Oxybis(ethane-2,1-diyl) dinitrate (**2b**): b.p. 140 °C / 7 Torr (Lit.³ 130 °C / 4 Torr); n_D^{20} 1.4522 (Lit.³ n_D^{20} 1.4518); FTIR ν 1620 (NO₂^{as}), 1272 (NO₂^s) cm⁻¹; ¹H NMR (CD₃COCD₃, 300 MHz) δ 4.72 (t, 4 H, CH₂ONO₂, J = 4.4 Hz), 3.85 (t, 4 H, CH₂O, J = 4.5 Hz); ¹³C NMR (CD₃COCD₃, 75 MHz) δ 72.1, 66.5; ¹⁴N NMR (CD₃COCD₃, 21.69 MHz) δ : -41.1 (ONO₂).

Propane-1,2,3-triyl trinitrate (**2c**): b.p. 86-87 °C / 0.16 Torr (Lit.⁴ 108-110 °C / 1 Torr]; n_D^{20} 1.4727 (Lit.⁴ n_D^{20} 1.473); FTIR ν 1632 (NO₂^{as}), 1265 (NO₂^s) cm⁻¹; ¹H NMR (CD₃COCD₃, 300 MHz) δ 5.96-5.89 (m, 1 H, CHONO₂), 5.16 (dd, 2 H, CH₂ONO₂, J_1 = 13.0 Hz, J_2 = 3.3 Hz); 4.98 (dd, 2 H, CH₂ONO₂, J_1 = 13.0 Hz, J_2 = 6.1 Hz); ¹³C NMR (CD₃COCD₃, 75 MHz) δ 75.9, 69.2; ¹⁴N NMR (CD₃COCD₃, 21.69 MHz) δ : -43.4 (ONO₂).

2-Hydroxypropane-1,3-diyl dinitrate (**3c**):

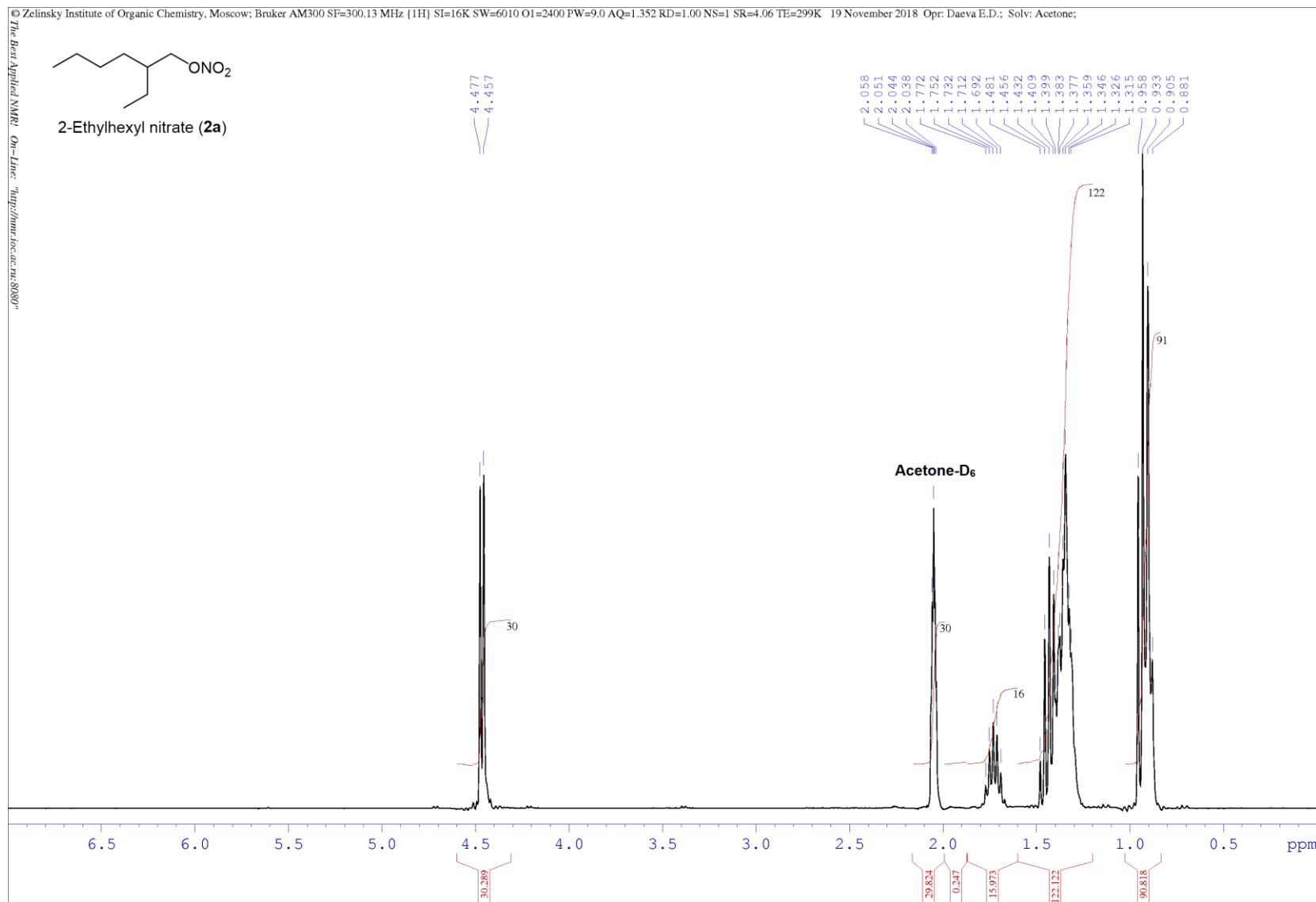
b.p. 78 °C / 0.14 Torr (Lit.⁵ 115-116 °C / 0.6 Torr]; n_D^{20} 1.4710 (Lit.⁵ n_D^{20} 1.4715); FTIR ν 1623 (NO₂^{as}), 1271 (NO₂^s) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.63 (dd, 2 H, CH₂ONO₂, J_1 = 11.6 Hz, J_2 = 4.5 Hz); 4.56 (dd, 2 H, CH₂ONO₂, J_1 = 11.7 Hz, J_2 = 6.0 Hz), 4.37-4.28 (m, 1 H, CH₂CHCH₂), 2.53 (br s, 1 H, CHOH); ¹H NMR (CD₃COCD₃, 300 MHz) δ 4.74 (dd, 2 H, CH₂ONO₂, J_1 = 11.2 Hz, J_2 = 4.3 Hz); 4.64 (dd, 2 H, CH₂ONO₂, J_1 = 11.5 Hz, J_2 = 6.3 Hz), δ 4.42-4.31 (m, 1 H, CH₂CHCH₂); ¹³C NMR (CD₃COCD₃, 75 MHz) δ 73.5, 64.7; ¹⁴N NMR (CD₃COCD₃, 21.69 MHz) δ -43.4 (ONO₂); HRMS (ESI+) m/z [M+Na]: calcd. 205.0067, found 205.0070.

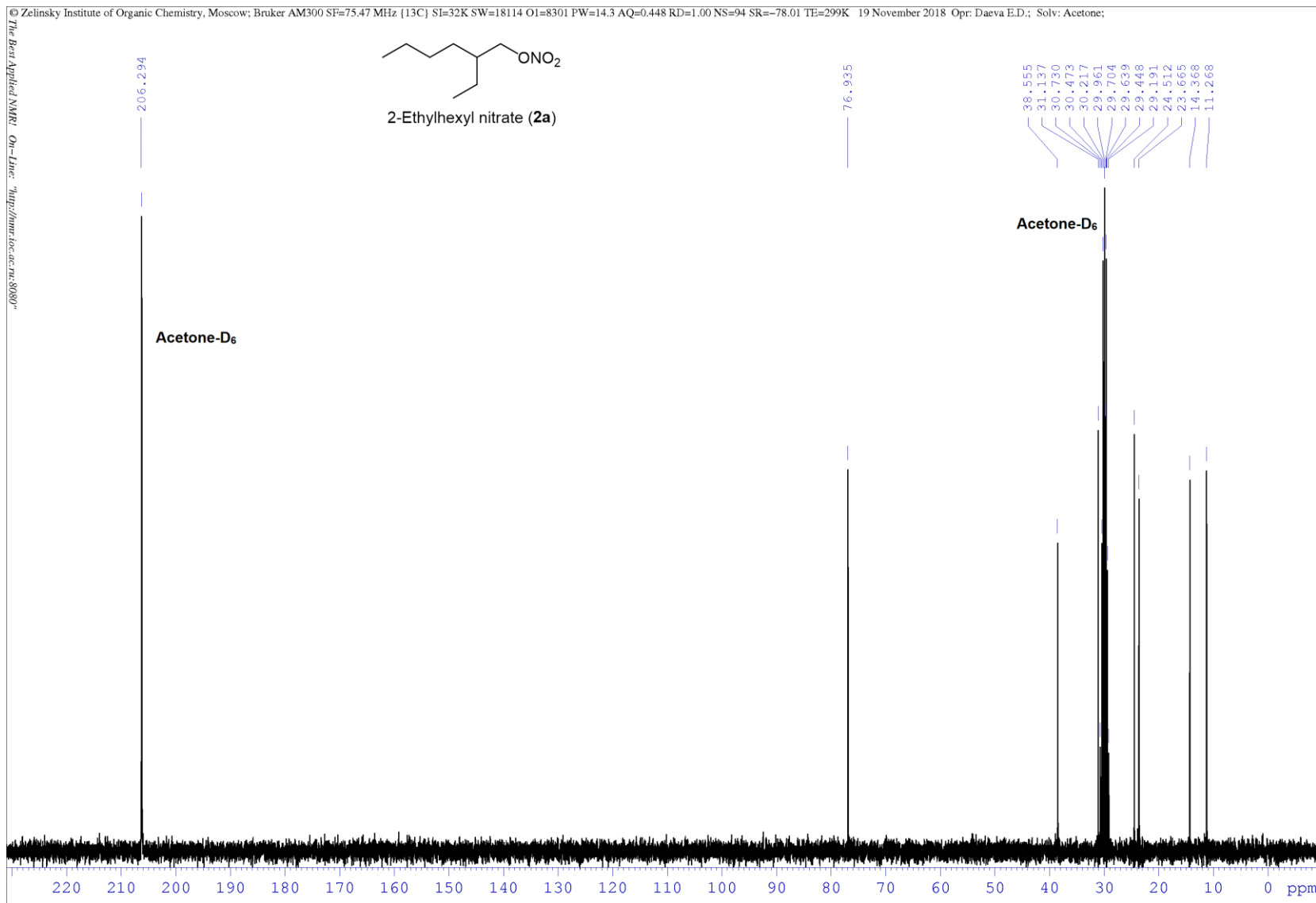
³ Urbański, T.; Witanowski, M. *Trans. Faraday Soc.* **1963**, 59, 1039–1045.

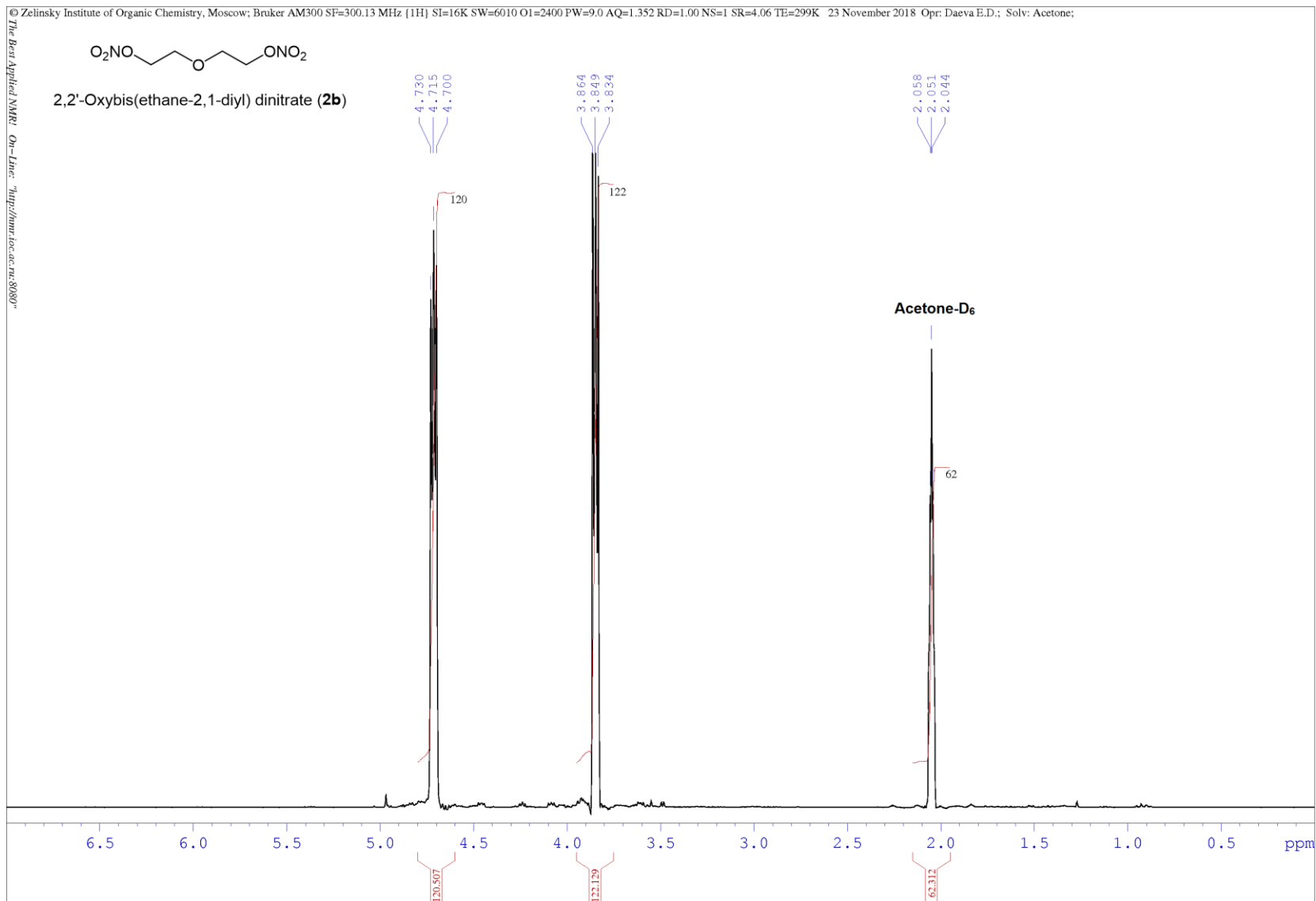
⁴ Fedorov, B. S.; Eremenko, L. T. *Russ. Chem. Bull.* **1997**, 46(5), 1022–1023.

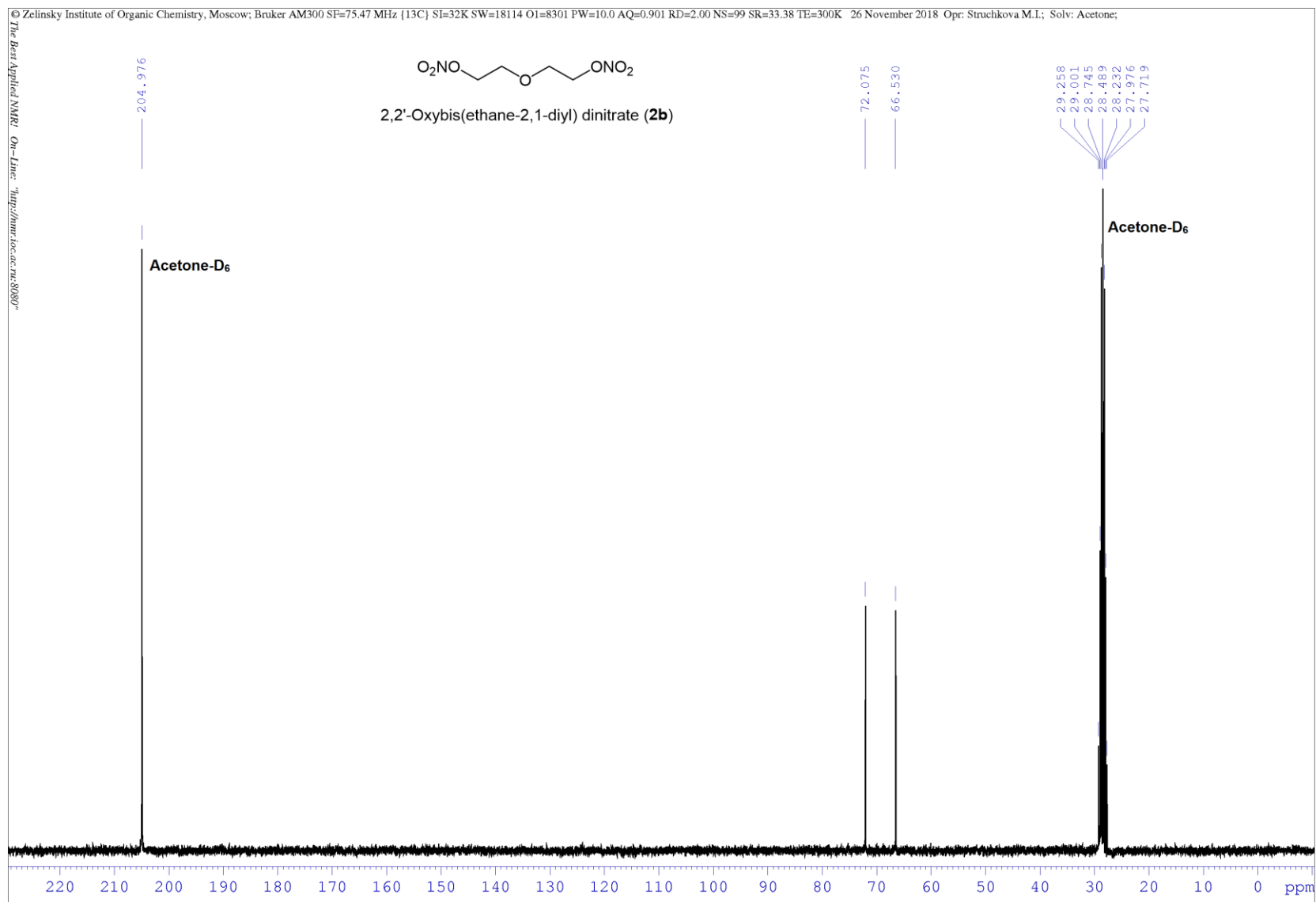
⁵ Dunstan, I.; Griffiths, J. V.; Harvey, S. A. *J. Chem. Soc.*, **1965**, 1319–1324.

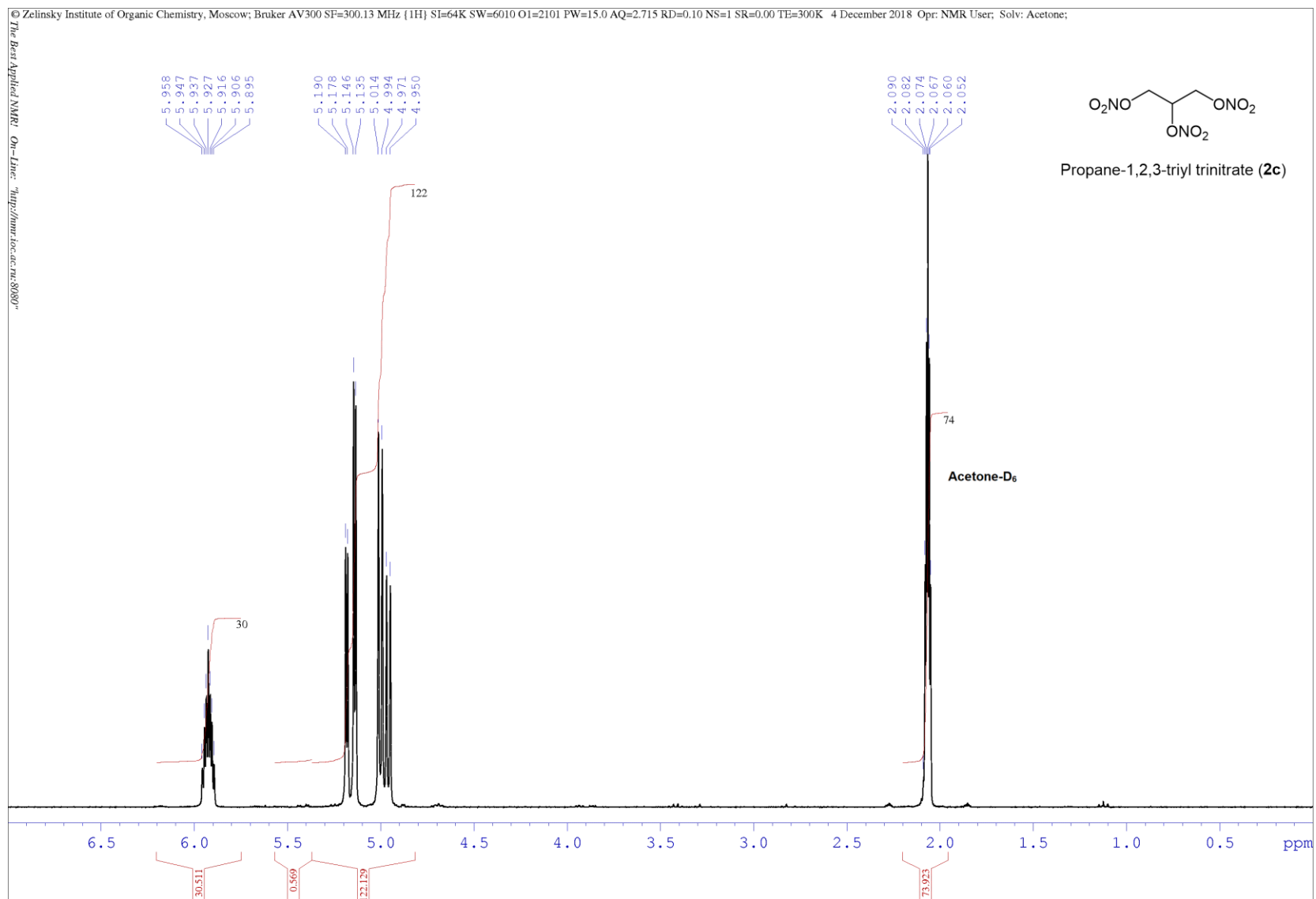
6. ^1H NMR and ^{13}C NMR spectra of compounds 2a, 2b, 2c and 3c

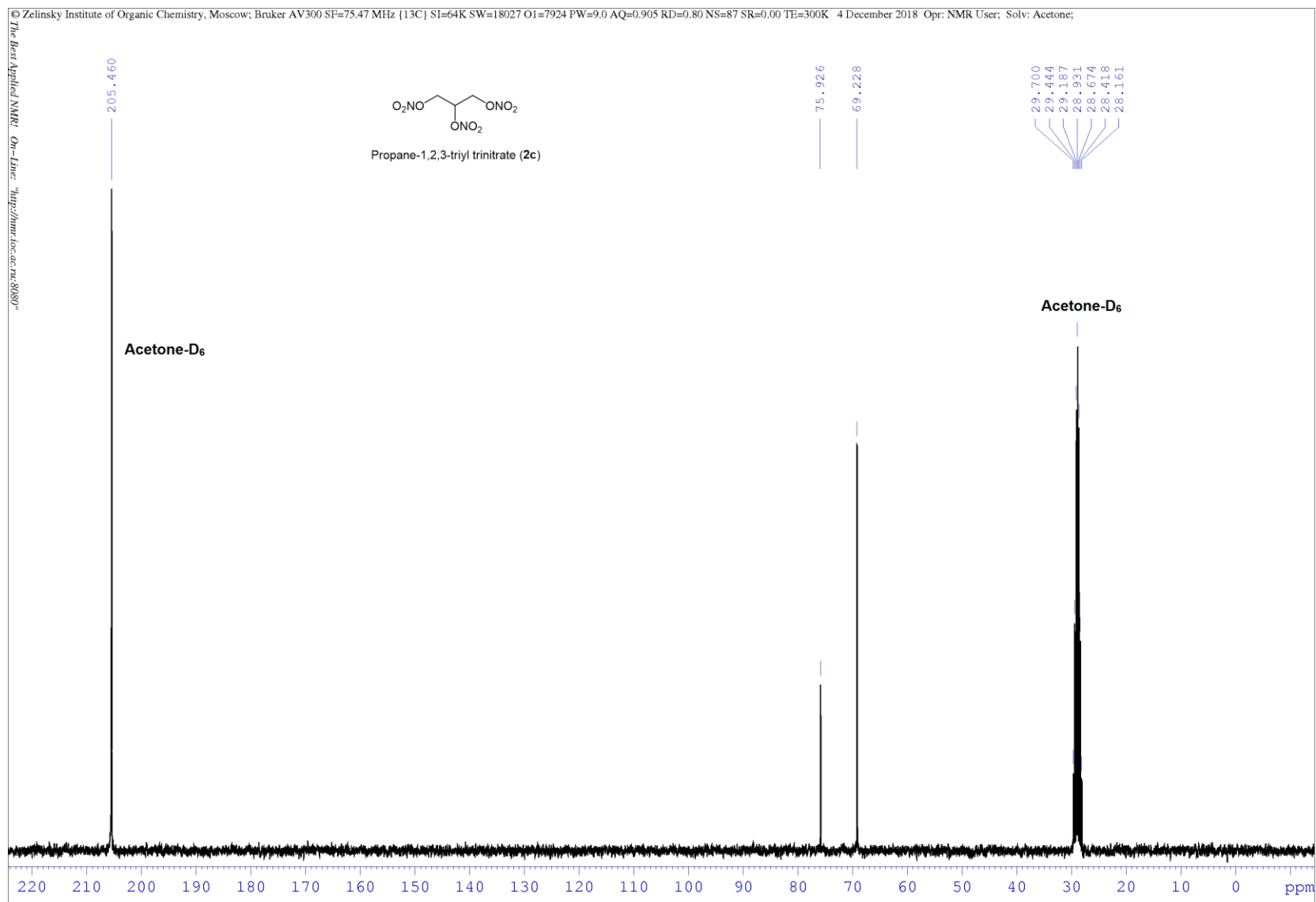


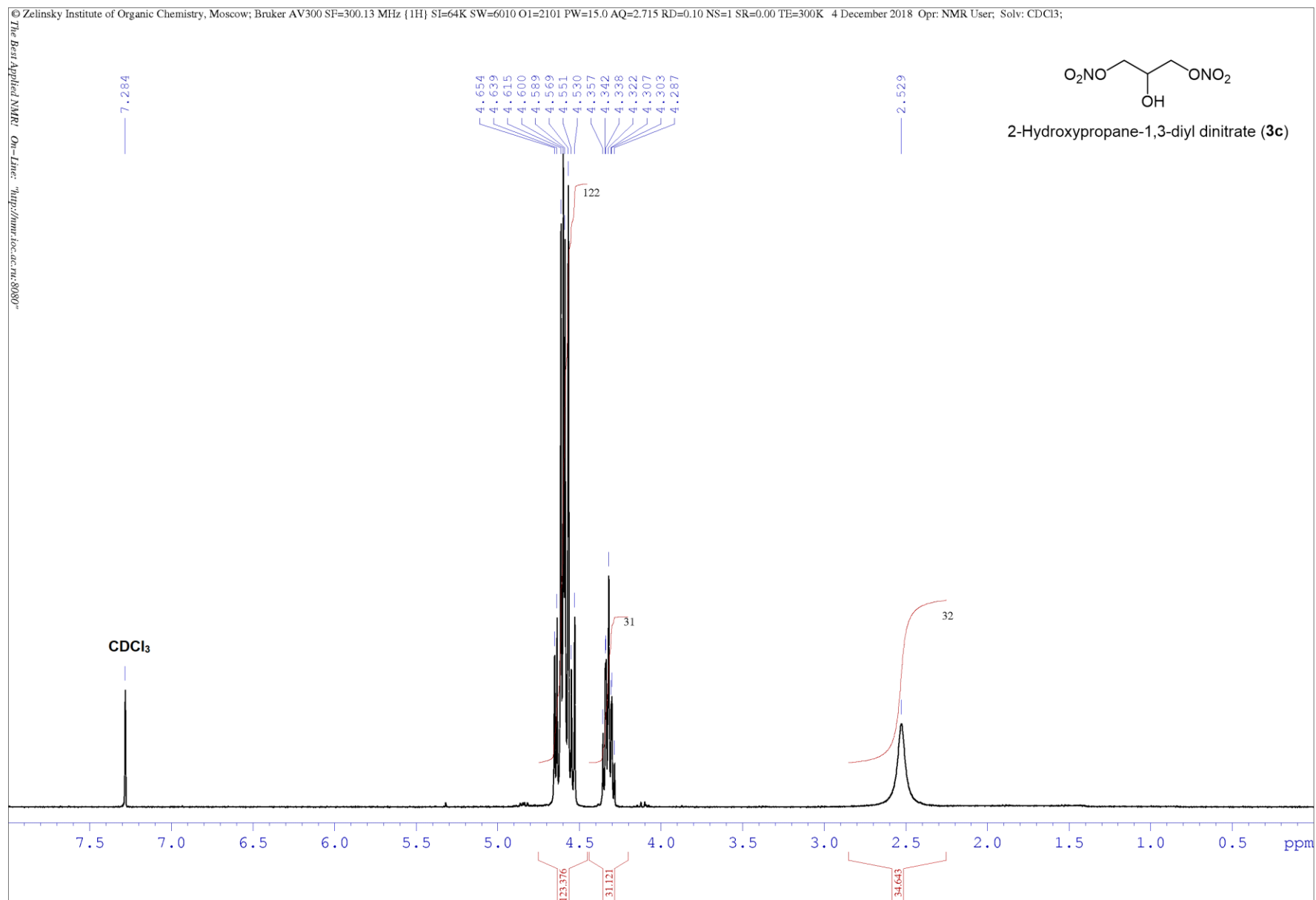




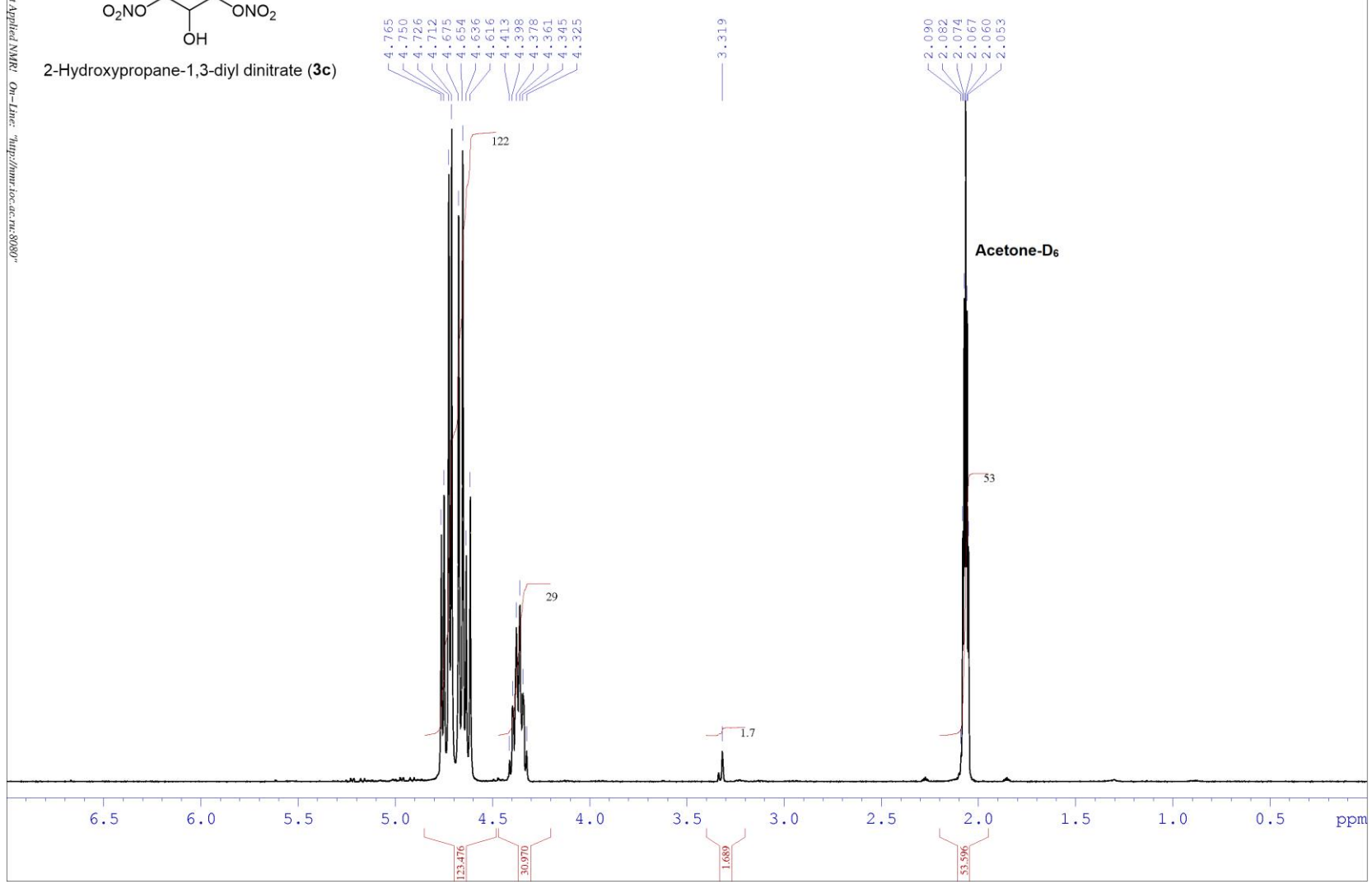
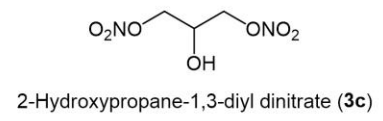


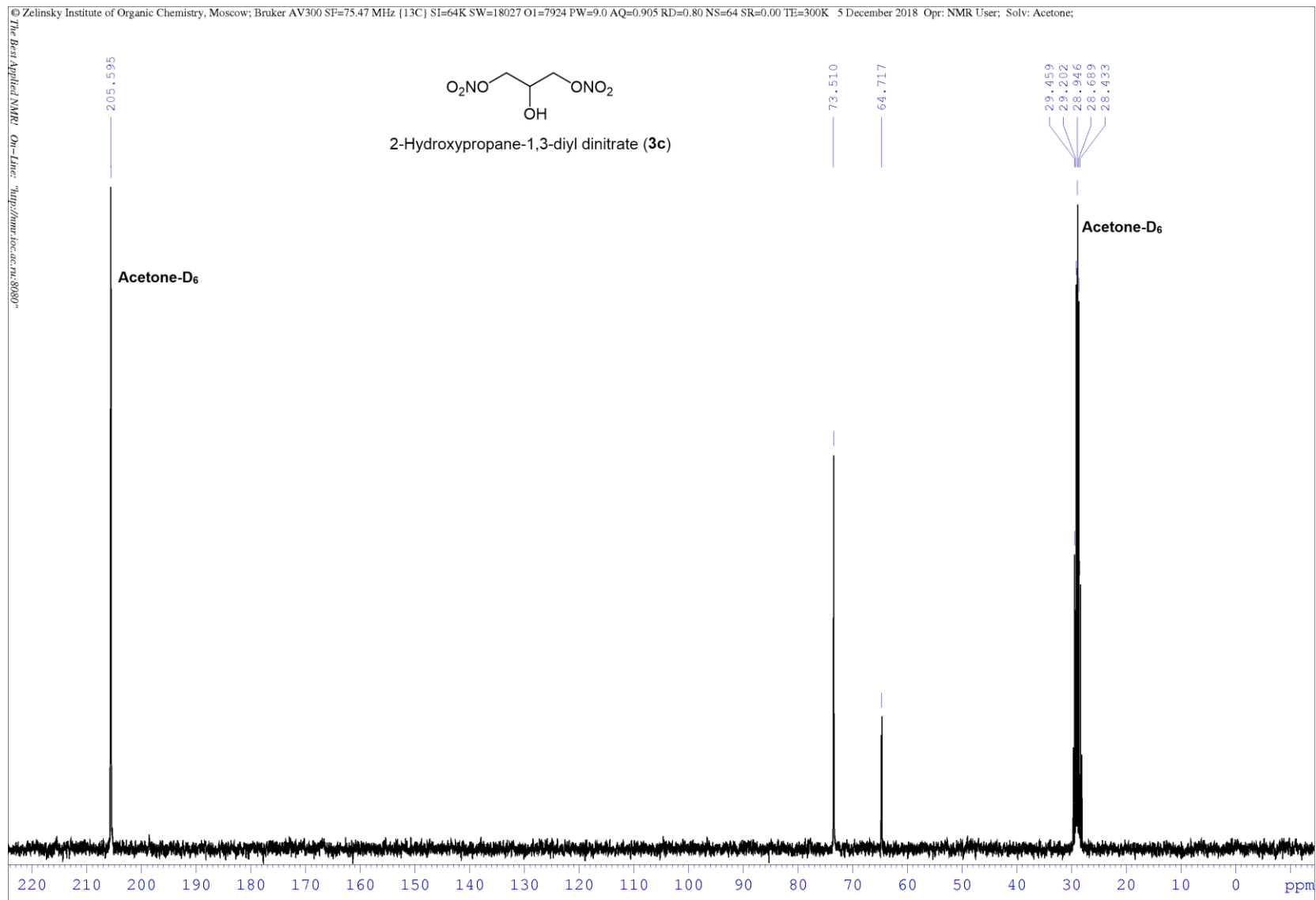




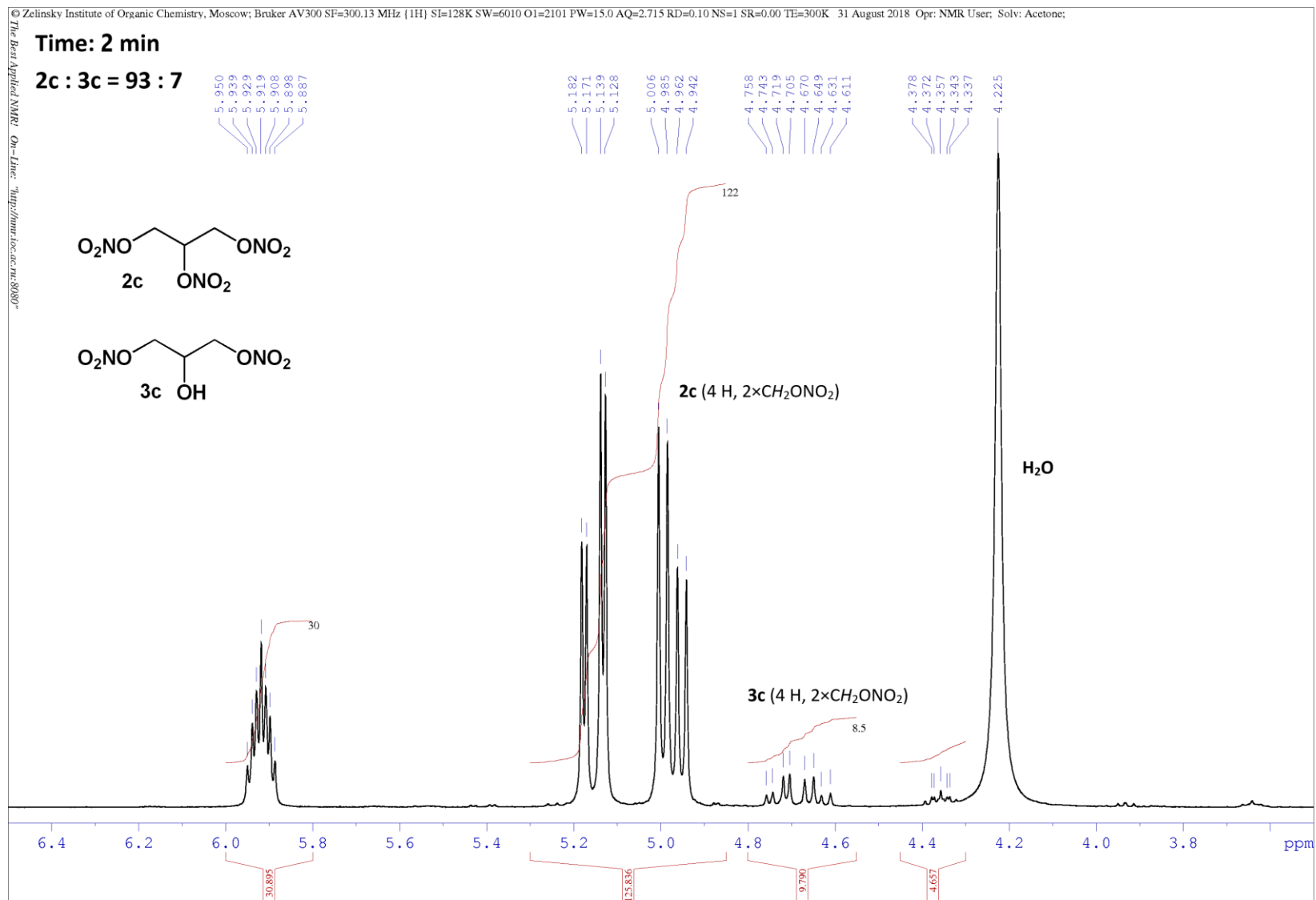


The Best Applied NMR On-Line: <http://nmr.ioc.ac.ru/8080/>



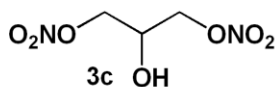
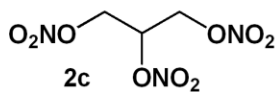


¹H NMR spectra of the reaction mixture 2c and 3c



Time: 5 min

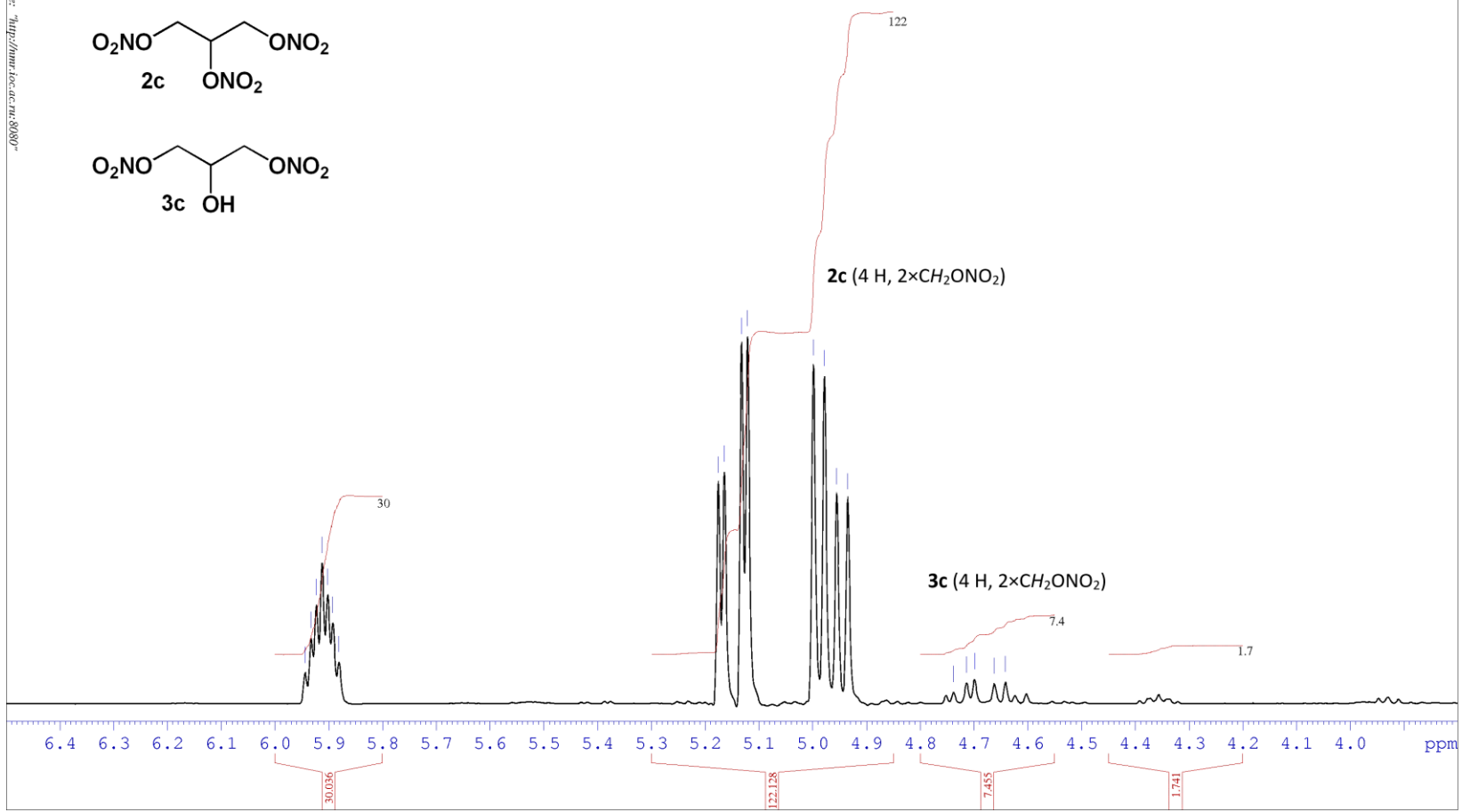
2c : 3c = 94 : 6

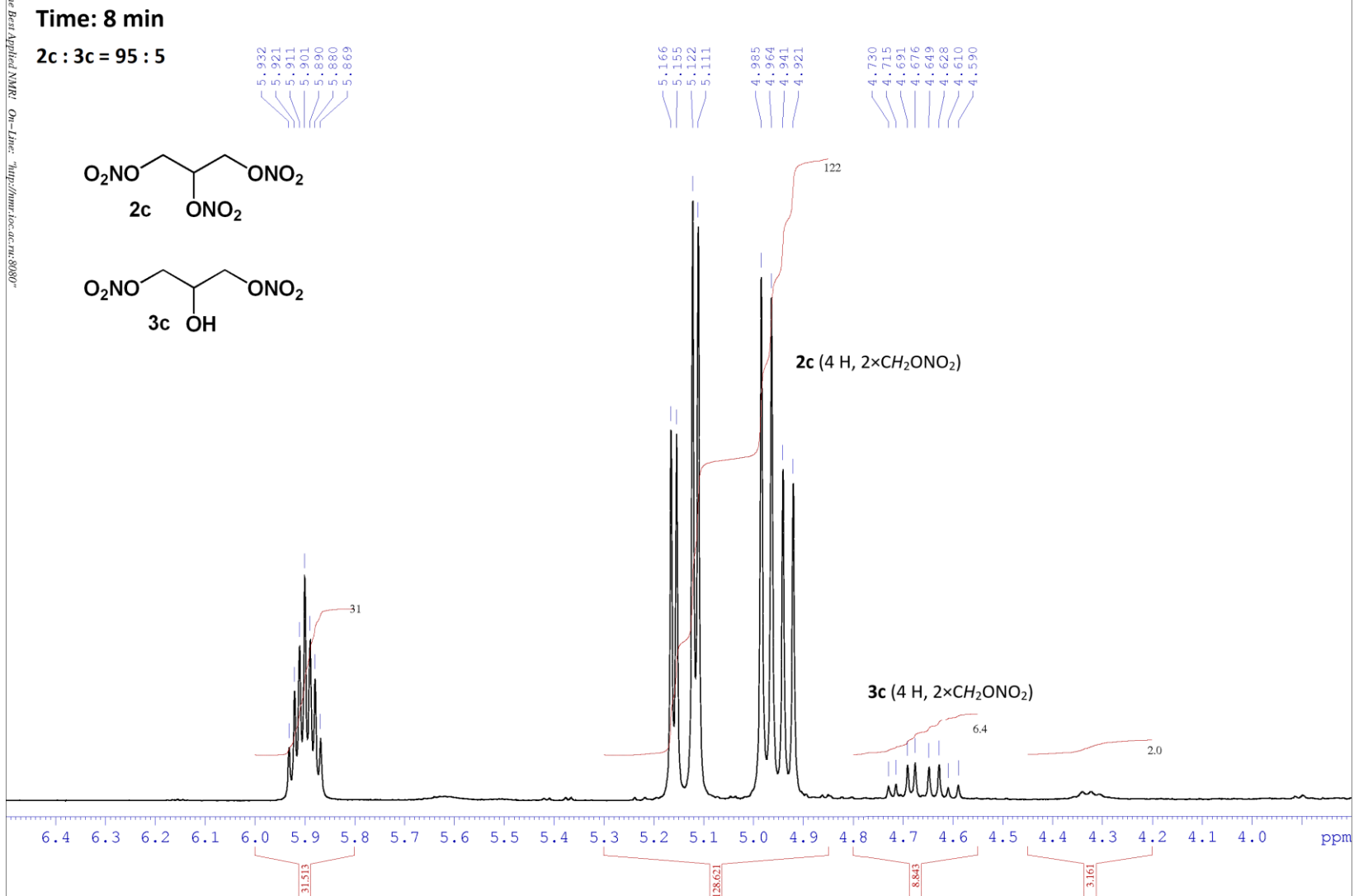


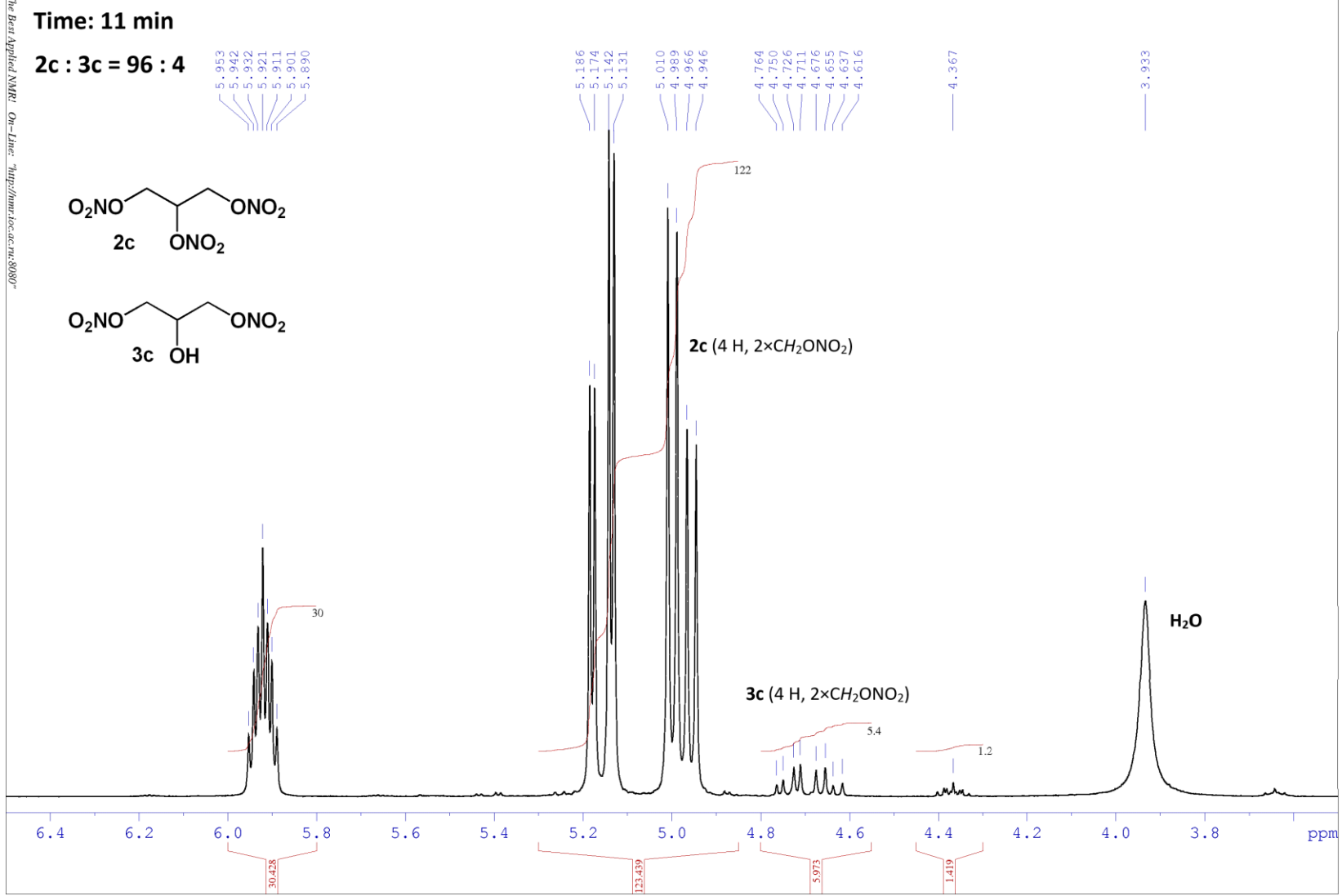
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5.913
5.902
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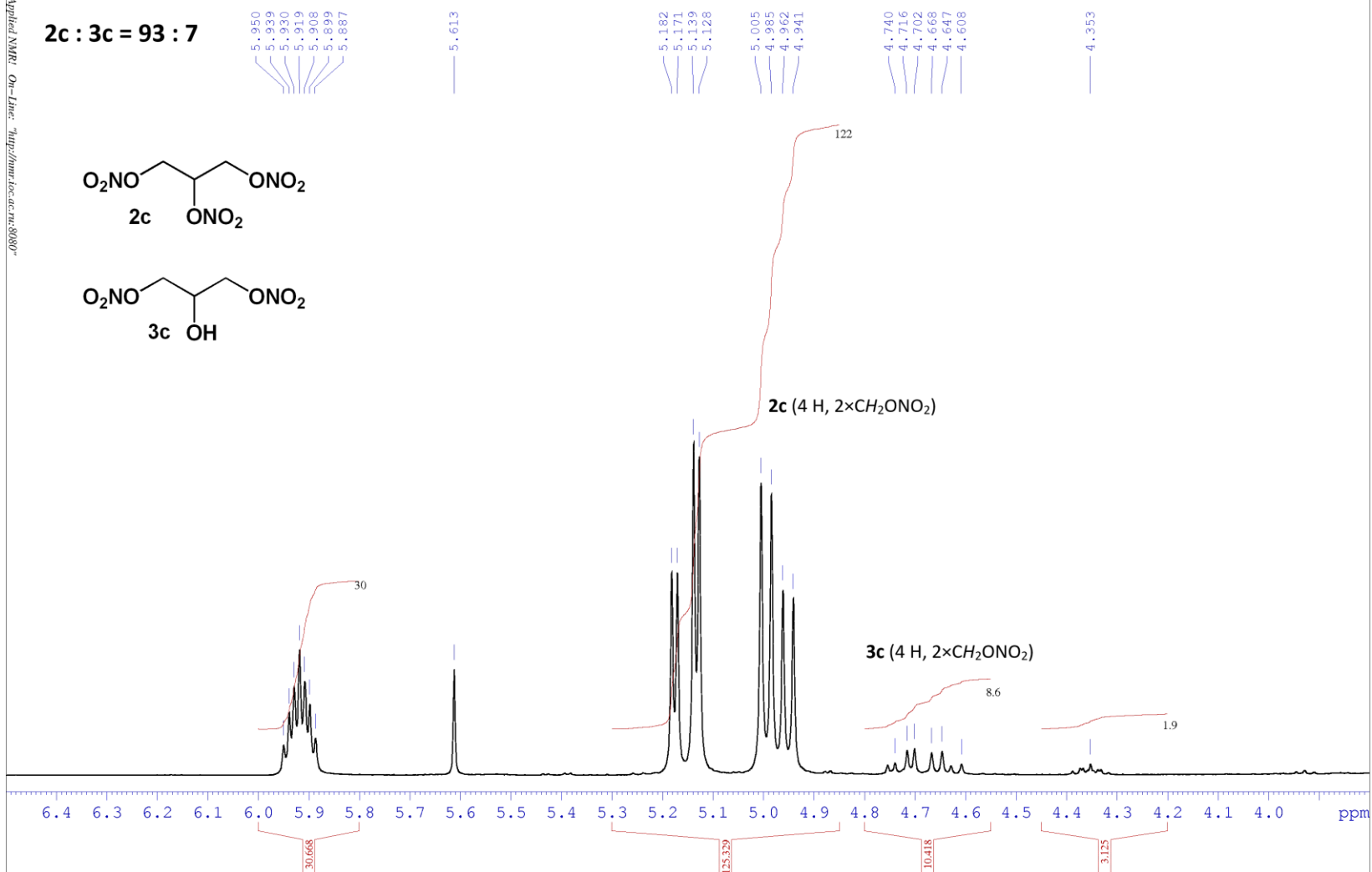
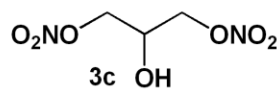
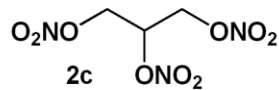




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Time: 14 min

2c : 3c = 93 : 7



7. IR spectra of compounds 2a, 2b, 2c and 3c

