

Intermolecular $^2hJ_{\text{NN}}$ -coupling in Multiply Hydrogen-bonded Ureidopyrimidinone Dimers in Solution

*Serge H. M. Söntjens, Marcel H. P. van Genderen, Rint P. Sijbesma**

*Department of Macromolecular and Organic Chemistry, Eindhoven University of Technology, P.O.
Box 513, 5600 MB Eindhoven, The Netherlands.*

Contents:

General Experimental Procedures	S2
Synthesis of compounds 2 , 3 , 4a , 5a .	S2-S4
^1H -NMR spectra of compound 5a (unlabeled)	S5
^{13}C -NMR spectrum of compound 5a (unlabeled)	S6
^1H -NMR 5a ^{15}N -labeled	S7
^{13}C -NMR spectrum of compound 5a (^{15}N -labeled)	S8
Comparison of ^{13}C NMR spectra of 5a (unlabeled) and 5a (^{15}N -labeled)	S9

General Experimental Procedures. ^1H and ^{13}C chemical shifts (δ) are reported in ppm relative to TMS. Solution ^{15}N -NMR experiments were recorded at 50.6 MHz, ^{15}N chemical shifts (δ) are reported in ppm relative to liquid NH_3 . Determination of J -coupling constants was performed by deconvolution of the spectra. S-Ethylthiuronium bromide was synthesized according to literature.¹

Guanidinium picrate- $^{15}\text{N}_1$ 2. S-Ethylthiuronium bromide (3.1 g, 20 mmol) was dissolved in 10 mL 2 N NaOH solution and was subsequently put under argon flow. The argon exiting the reaction vessel was passed through a double Drechsel bottle setup filled with 10% H_2O_2 , to oxidize any evolving ethanethiol in the subsequent reaction. To the reaction vessel a solution of ammonium chloride- ^{15}N (1.0 g, 19 mmol) in 8 mL of warm water was added, and the reaction mixture was heated to 70°C for 2 h. The production of ethanethiol was evident as mild gas evolution and showed the progress of the reaction. The reaction mixture was subsequently cooled, poured in a solution of picric acid in ethanol (100 mL, 0.272 M) and heated to reflux for 15 min. The yellow microcrystalline guanidinium picrate- $^{15}\text{N}_1$ which formed upon slow cooling of this solution was collected by filtration, washed with ethanol and dried *in vacuo* at 50°C to afford 4.0 g of crude compound. This crude product was used without further purification. ^1H -NMR (DMSO): δ 8.60 (s, 2H, picrate CH), 6.91 (d, 2H, $J = 91.2$ Hz, $^{15}\text{NH}_2$), 6.91 (s, 4H, $^{14}\text{NH}_2$). ^{13}C -NMR (DMSO): δ 166.3, 163.3 (d, $J = 19.8$ Hz), 147.2, 130.7, 129.9. ^{15}N -NMR (DMSO) δ 78.2 (triplet of quintets, $^1J_{\text{NH}} = 91.2$ Hz, $^3J_{\text{NH}} = 2.2$ Hz).

6-Tridecylisocytosine- $^{15}\text{N}_1$ 3. A solution of guanidinium picrate- $^{15}\text{N}_1$ (1.1 g, 3.5 mmol), ethyl-3-oxohexadecanoate (1.6 g, 1.5 eq), and KOH (220 mg, 1.1 eq) were heated to reflux temperature for 18 h in

(1) Brand, E.; Brand, F. C. In: *Org. Synth., Coll. Vol. 3*; John Wiley & Sons, Inc.: New York, 1955, p 440

50 mL ethanol. The reaction mixture was filtered at high temperature, to remove potassium picrate, and subsequently cooled to allow for the precipitation of the product as a tan paste, which was collected by filtration, recrystallized from ethanol and dried *in vacuo* at 50°C to afford 840 mg of the crude product (83%). ¹H-NMR δ 10.56 (s, 1H, OH), 6.40 (s+d, 2H, J = 89.0 Hz, ¹⁵NH₂ + ¹⁴NH₂), 5.34 (s, 1H, CH), 2.19 (t, 2H, C5-H₂), 1.50 (m, 2H, C6-CH₂CH₂), 1.2-1.3 (br. s, 20H), 0.83 (t, 3H, CH₃). ¹³C-NMR (DMSO) δ 170.5, 163.5, 156.2, 142.5 (impurity), 125.9 (impurity), 100.3, 39.9, 39.7, 37.7, 32.0, 29.7 (multiple peaks), 29.5, 29.4, 28.2, 22.8, 14.6. ¹⁵N-NMR δ 201.7, 151.1, 76.6.

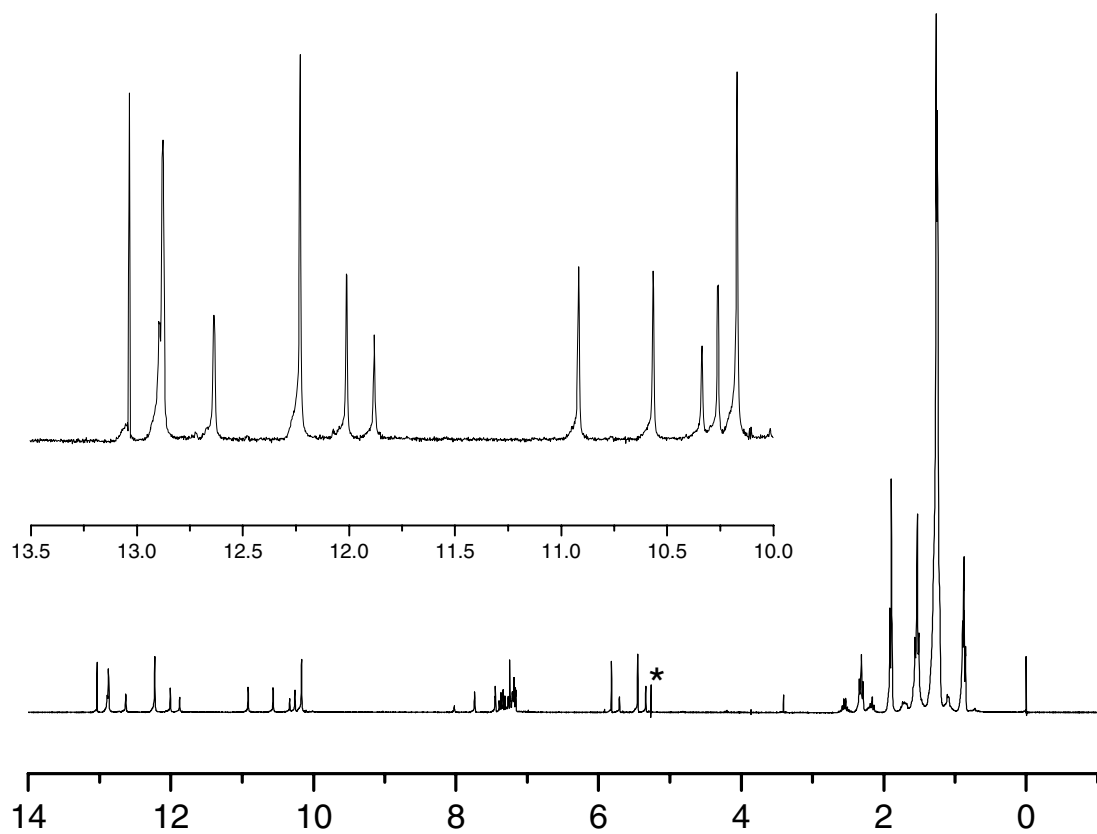
N-Butylaminocarbonyl-6-tridecyl-isocytosine-¹⁵N₁ 4a. Butyl isocyanate (0.1 g) was added to a solution of 6-tridecylisocytosine-¹⁵N₁ (300 mg, 1 mmol) in DMF (30 mL) at 90°C under an argon atmosphere. The reaction mixture was heated further for another 4½ h, after which it was cooled to 4°C to facilitate the crystallization of the product as a white microcrystalline material which was collected by filtration, washed with acetone and dried *in vacuo* at 50°C affording 330 mg of a 99% pure sample (85%). An analytically pure sample was obtained by recrystallization from acetic acid. mp 119°C. ¹H-NMR δ 13.18 (s+d, 1H, J = 93.0 Hz, N1-H), 11.88 (s+d, 1H, J = 91.2, C2-NH), 10.17 (t, 1H, J = 4.6 Hz, NHCH₂), 5.82 (s, 1H, C5-H), 3.25 (q, 2H, J = 6.6 Hz, NHCH₂), 2.45 (t, 2H, J = 7.5 Hz, C6-CH₂), 1.6 (br. m, 4H), 1.2 (br. m, 22H), 0.93 (t, 3H), 0.88 (t, 3H). ¹³C-NMR δ 173.2, 156.7, 154.8, 152.4, 105.9, 39.8, 32.7, 31.9, 31.6, 29.6 (multiple peaks), 28.8, 27.0, 22.7, 20.2, 14.1, 13.8. ¹⁵N-NMR δ 213, 133 (J_{NH} = 93.3 Hz), 117 (J_{NH} = 90.4 Hz). FTIR (cm⁻¹, enol): ν 3169, 3125, 2955, 2919, 2849, 2452, 1662, 1606, 1552, 1476, 1449, 1417, 1391, 1377. Elemental analysis: Calculated for C₂₂H₄₀N₃¹⁵N₁O₂ (MW 393.6): C 67.3; H 10.3; N 14.3; Found: C 67.1; H 10.0; N 14.0.

1,3-bis(1-methyl-1-(aminocarbonyl-6-tridecyl-isocytosine)ethyl)benzene 5a. 1,3-Bis(1-isocyanato-1-methyl-ethyl)benzene (0.33 g, 1.35 mmol) and 6-tridecylisocytosine (0.87 g, 2.97 mmol) were heated in dry pyridine (5mL) at 90 °C for 3h. The product was taken up in dichloromethane, washed with 1N aqueous HCl (3 × 50 mL), with brine, and the solution was dried over MgSO₄. The

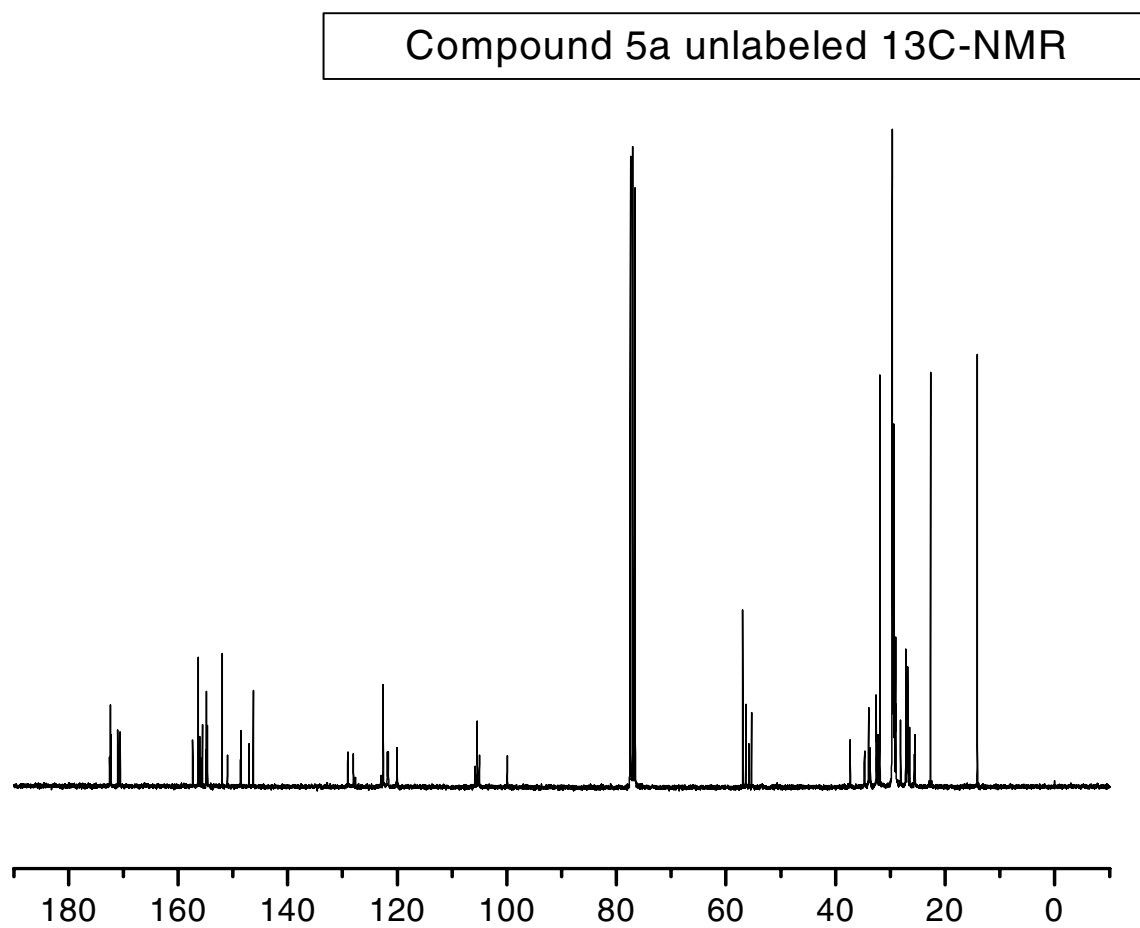
crude product was purified by column chromatography using dichloromethane/methanol 98:2 v/v as eluent to yield 0.66 g (60%) of **5a** as a white solid. ¹H-NMR (CDCl₃) 13.03 (s), 12.87 (s), 12.63 (s), 12.23 (s), 12.00 (s), 11.88 (s), 10.92 (s), 10.56 (s), 10.33 (s), 10.26 (s) 10.17 (s), 8.03 (s), 7.73 (s), 7.45 (s), 7.40-7.16 (multiple peaks), 5.82 (s), 5.71 (s), 5.45 (s), 5.34 (s), 2.53 (m), 2.29 (t), 2.16 (t), 1.89 (m), 1.71 (m), 1.53 (m), 1.10 (m), 0.88 (t). ¹³C-NMR (CDCl₃). 172.5, 172.4, 172.3, 171.0, 170.6, 157.3, 156.3, 156.0, 155.7, 154.9, 154.7, 151.9, 151.0, 148.6, 148.5, 147.1, 146.3, 129.0, 128.0, 122.8, 122.5, 121.8, 121.7, 121.6, 120.1, 105.8, 105.4, 105.0, 99.9, 56.9, 56.4, 55.9, 55.4, 37.3, 34.7, 34.0, 33.6, 32.6, 32.5, 32.3, 31.9, 29.6, 29.4, 29.3, 29.2, 29.0, 28.1, 27.2, 26.9, 26.8, 26.5, 25.6, 25.5, 22.7, 14.1 ppm. FTIR (neat, ATR): 3209, 2922, 2852, 1698, 1661, 1642, 1578, 1522, 1456, 1250 cm⁻¹.

1,3-bis(1-methyl-1-(aminocarbonyl-6-tridecyl-isocytosine-¹⁵N)ethyl)benzene 5a. Was prepared from 1,3-Bis(1-isocyanato-1-methyl-ethyl)benzene (26 mg, 0.1 mmol) and 6-tridecylisocytosine-¹⁵N₁ (74 mg, 0.26 mmol) in a similar way as the unlabeled material. The crude product was recrystallized from ethanol twice to afford 50 mg of the product as an off-white microcrystalline product (60%). ¹H-NMR (CDCl₃) 13.03 (s), 12.87 (s+d, J = 94 Hz), 12.63 (s+d, J = 94 Hz), 12.23 (s+d, 94 Hz), 12.00 (s+d, J = 91 Hz), 11.88 (s+d, J = 90 Hz), 10.92 (s+d, J = 91 Hz), 10.56 (s), 10.33 (s), 10.26 (s) 10.17 (s), 8.03 (s), 7.73 (s), 7.45 (s), 7.40-7.16 (multiple peaks), 5.82 (s), 5.71 (s), 5.45 (s), 5.34 (s), 2.53 (m), 2.29 (t), 2.16 (t), 1.89 (m), 1.71 (m), 1.53 (m), 1.10 (m), 0.88 (t). ¹³C-NMR (CDCl₃). 172.5 (br), 170.7 (br), 166.2 (br), 157.2 (br), 156.2 (br), 155.5 (br), 154.8 (br), 152.0, 148.6, 148.5, 147.1, 146.3, 129.0, 127.9, 122.8, 122.6, 121.70, 121.59, 121.53, 120.0, 105.8, 105.3, 104.9, 56.9 (d, J = 6 Hz), 56.3 (d, J = 5 Hz), 55.8 (d, J = 6 Hz), 55.3 (d, J = 5.7 Hz), 37.3, 34.6, 33.9, 33.6, 32.6, 32.5, 32.2, 31.9, 29.6, 29.4, 29.3, 29.2, 29.0, 28.1, 27.1, 26.8, 26.5, 25.6, 25.5, 22.7, 14.1. ppm. ESI-MS: 833.4 (M+H⁺), 855.4 (M+Na⁺), 871.4 ((M+K⁺)).

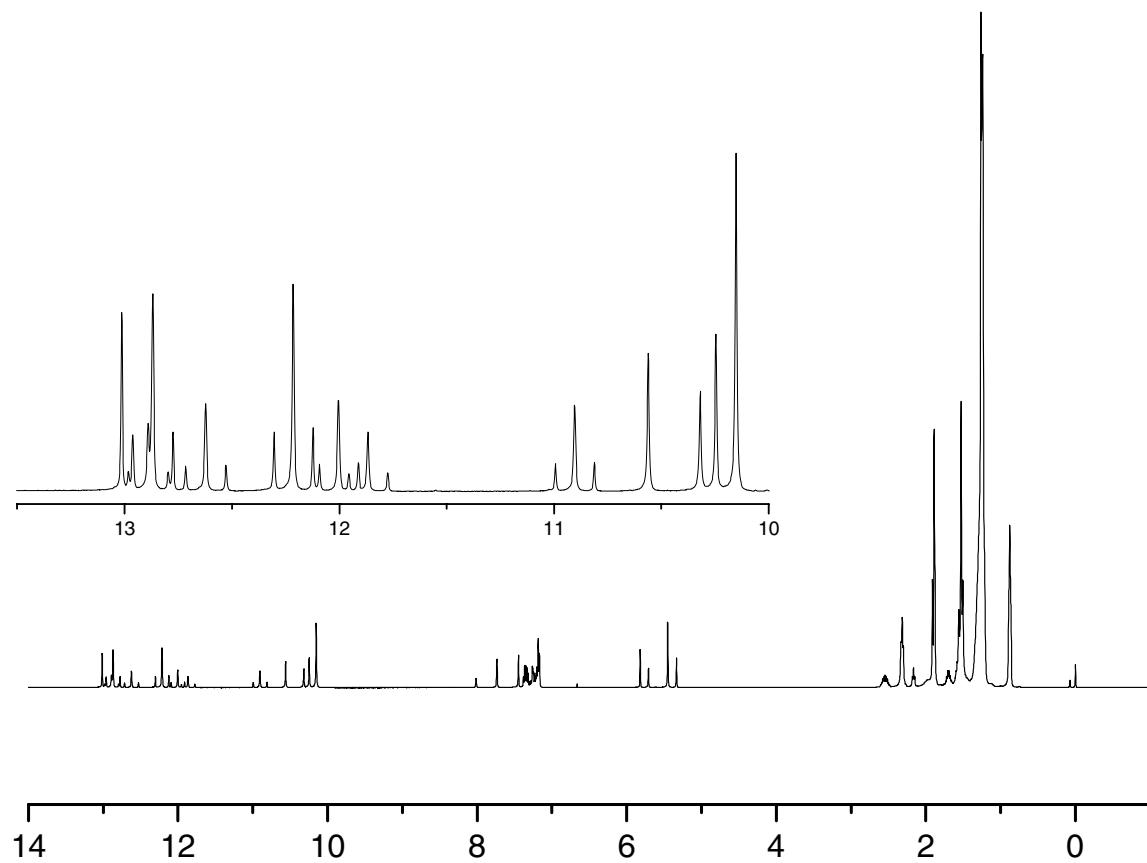
^1H -NMR spectra of compound **5a** (unlabeled)



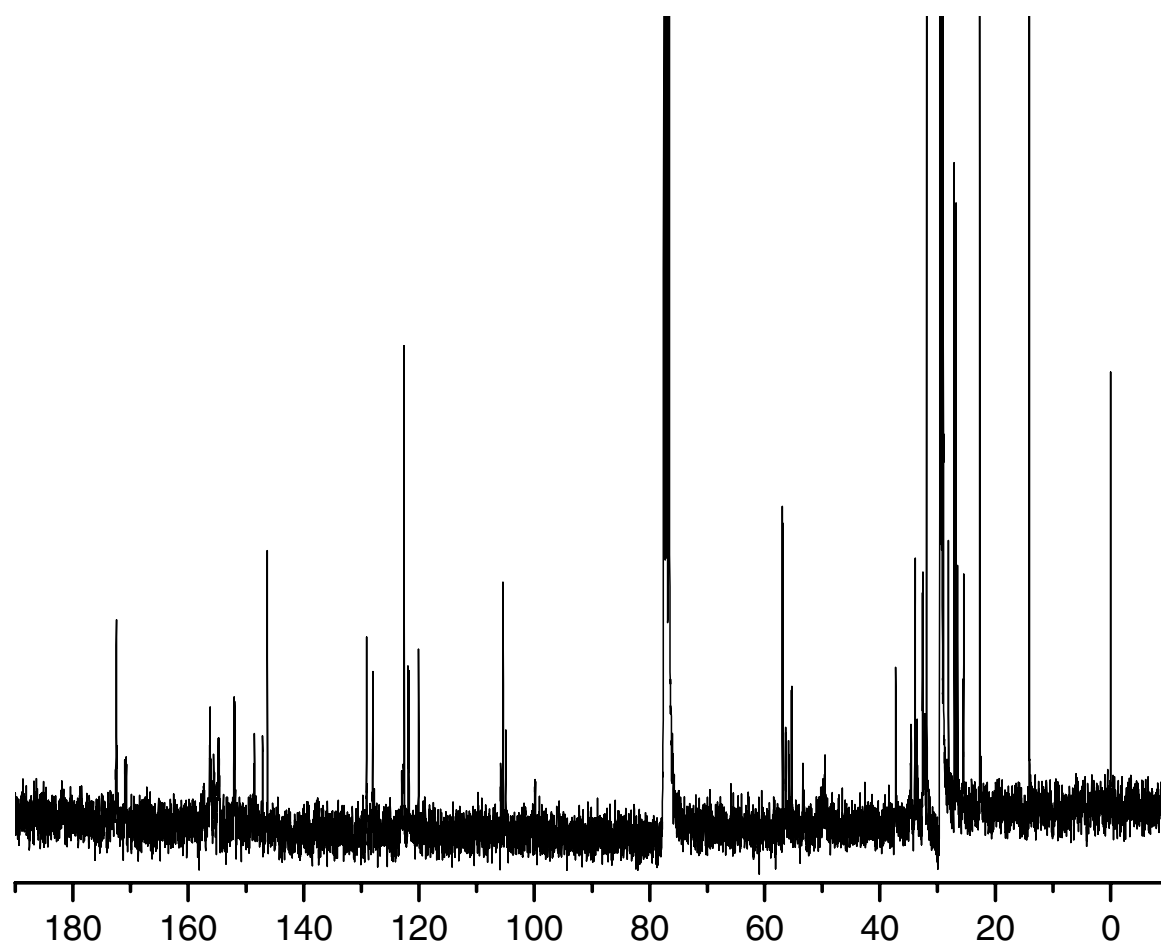
^{13}C -NMR spectrum of compound **5a** (unlabeled)



^1H -NMR **5a** ^{15}N labeled



^{13}C NMR **5a** (labeled)



Comparison of ^{13}C NMR spectra of **5a** (unlabeled) and **5a** (labeled)

